Atlas and Synopsis of Lever’s Histopathology of the Skin

THIRD EDITION
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Introduction to the Pattern Classification System

In this atlas, diseases are classified not by the usual pathophysiologic classification but according to a pattern classification. In this pattern classification, the diseases are classified as listed below:

- **Location** in the skin—low power features—specified with Roman numerals (I, II, III, and so forth) and used as chapter titles throughout the book.
- **Morphologic patterns**—medium power features—specified with uppercase letters (A, B, C, and so forth) and red headings throughout the book.
- **Cell types**—high power features—specified with Arabic numerals (1, 2, 3, and so forth) and green headings throughout the book.
- **Representative disorders**—individual diagnoses are in blue headings throughout the book, with a clinical summary and histopathology given for each.

It is assumed that basic pathologic processes like suppuration, granulomatous inflammation, and neoplasia can be recognized by the reader.

In this atlas, the cutaneous diseases are listed in morphologic categories based on their location in the skin, their architectural patterns, and their cytology. The list of diseases in each morphologic category serves as a differential diagnosis for unknown disorders that present with the attributes of that category. The diseases are listed in rough order of their expected frequency in an average dermatopathology practice. In this atlas, representative disorders in each category are briefly described and illustrated. More detailed discussions of most of these and the other lesions in the lists can be found in the parent volume. For more information on the classification system, see the Introduction on page xxv.

Location

There are eight specified locations, which are assigned Roman numerals I through VIII, as follows:

I. Disorders Mostly Limited to the Epidermis and Stratum Corneum
II. Localized Superficial Epidermal or Melanocytic Proliferations
III. Disorders of the Superficial Cutaneous Reactive Unit
IV. Acantholytic, Vesicular, and Pustular Disorders
V. Perivascular, Diffuse, and Granulomatous Infiltrates of the Reticular Dermis
VI. Tumors and Cysts of the Dermis and Subcutis
VII. Inflammatory and Other Benign Disorders of Skin Appendages
VIII. Disorders of the Subcutis

When looking at a microscopic slide of an unknown disorder using this book, the first approach is to determine what part of the skin is primarily involved in that process.

Pattern

Next, the relevant sections of the book can be scanned in an effort to identify the predominant pattern of the abnormality. This can be done by scanning the table of contents, or by scanning the images in order to find ones that look similar to the image under the microscope. This process may seem difficult at first; however, this pattern recognition method has the potential to lead quite rapidly to the section that contains the disease in question. In these Roman numeral-designated sections, the various patterns that may occur in the various locations are designated by capital letters, A, B, C, and so forth. These patterns differ from one location to another. For example, within the very important group of inflammatory disorders of the superficial cutaneous reactive unit, the patterns include reactions involving the epidermis such as spongiosis, which is a basic pattern of the very common eczematous disorders; reactions involving these highly reactive superficial vessels such as perivascular lymphocytic inflammation, which is common in many diseases; reactions at the dermal epidermal interface such as vacuolar or lichenoid patterns, and changes in the interstitium such as sclerosis to name a few. All of these patterns have their own associations which are redundant and not specific. For

*Some of these "locations" also combine patterns where these have particularly broad significance. For example, “II Localized Superficial Epidermal or Melanocytic Proliferations,” “IV Epidermal Acantholytic, Vesicular, and Pustular Disorders,” “V Perivascular, Diffuse, and Granulomatous Infiltrates of the Reticular Dermis” are all terms that combine a location and one or more patterns, namely proliferations of cells to form plaques or superficial nodules (II), separation of epidermal cells either from each other or from the underlying dermis to form spaces termed vesicles, bullae, or pustules (IV), granulomas which are collections of epithelioid histiocytes (V) or tumors which are mass lesions formed by neoplastic cells (VI), and so on.
example, a lichenoid pattern, discussed in section IIIF can be shared by lichen planus (its prototypic disorder), a lichenoid drug reaction, a lichenoid actinic keratosis, and other conditions. As is often the case in dermatopathology, the term “lichenoid” is not intuitive histologically but is derived from the clinical appearance of the lesion and from clinical terminology.

**Cell Type**

The third level of classification is by cell type, designated by Arabic numerals 1, 2, 3, and so forth. The cell types in question in the same superficial inflammatory disorders discussed above include among others lymphocytes only (e.g., lichen planus which is section IIIF1), lymphocytes with eosinophils (e.g., lichenoid drug eruption IIIF2a), lymphocytes with plasma cells (e.g., syphilis IIIF2b), or in other patterns the cytologic choices might include neutrophils predominating (e.g., Sweet’s syndrome VC2), eosinophils predominating (e.g., Well’s syndrome VC6), and so on. Neoplasms also often have quite specific cytology. The addition of the cytologic classifier to the location and pattern classifiers can often lead to a very narrow differential diagnosis or even a specific diagnosis.

**Example**

As an example, in Example Figures 1, 2, and 3, a lesion is illustrated that was submitted with the history “subcutaneous nodule, rule out malignancy.”

At scanning magnification (Example Figure 1), an irregular mass is seen in the subcutis. At medium and high power (Example Figures 2 and 3), collections of epithelioid histiocytes constituting granulomas are recognized, and there are scattered giant cells. Epithelioid cell granulomas without necrosis and usually with giant cells are characteristically seen in sarcoidosis. However, other conditions such as tuberculosis and fungal infections should be excluded and diagnosis is therefore a clinicopathologic exercise. Turning to Section VIII “Disorders of the Subcutis,” granulomas involving the subcutaneous fat lobules are mentioned in Section C7 “Lobular Panniculitis Without Vasculitis,” and in Section D6 “Mixed Lobular and Septal Panniculitis, Granulomatous.” In Section C7, Subcutaneous Sarcoidosis is listed as the prototypic example, and the following conditions are listed in the differential diagnosis:

- erythema induratum/nodular vasculitis (if vasculitis is inapparent)
- subcutaneous granuloma annulare/pseudorheumatoid nodule
- rheumatoid nodules
- subcutaneous sarcoidosis
- mycobacterial, fungal, and other infections
Crohn's disease
epithelioid sarcoma

Consideration of this list, with reference if necessary to photomicrographs and descriptions of the listed entities elsewhere in the book (aided by the index or online search functions) suggests that sarcoidosis is the most likely diagnosis. A phone call to the clinician suggesting the possibility of sarcoidosis leads to further investigation, and the information that the patient has been coughing and has characteristic changes on a chest X-ray. Acid-fast stains are negative, and a presumptive diagnosis of sarcoidosis can be considered to be established. In this way, the recognition and accurate interpretation of histologic findings in an unknown case can lead to the establishment of the diagnosis of an important systemic disease.

Even if a specific diagnosis cannot be made, it is always useful to generate a differential diagnosis which can be correlated with the clinical impressions, often leading to a specific diagnosis based on clinicopathologic correlation. In this book, conditions that may be considered in the differential diagnosis are listed at the end of each section, and these lists may serve as the basis for writing a pathology report that considers, as completely as possible, the range of possibilities for any given case. The “prototypic” (i.e. most characteristic and often one of the most common) condition for each subsection is italicized in these lists, as an additional diagnostic reference point.

Advantages of Using the Pattern Classification System

We have found in practice that trainees who use this system can develop more comprehensive differential diagnoses as they preview cases for sign out with their teachers. Similarly, experienced dermatopathologists can use the book to ensure that their differential diagnostic considerations are complete, and also to illustrate to their trainees the range of lesions that can have morphology similar to that which is visualized under the microscope.

We hope and expect that using these principles will increase the value of the sign-out process as a learning experience, and ultimately may make itself redundant as the patterns become ingrained into the experience of the learner, who may then begin to recognize diseases like lichen planus, lupus profundus, bullous pemphigoid, superficial spreading melanoma, and so on in a flash of recognition or “gestalt,” similar to the manner in which old friends can be rapidly picked out of a crowd of otherwise generally similar human beings. When this stage is reached, our work can be considered to be done and a lifetime of continued learning, useful productivity, and fun, will follow.
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In this new edition, as in its predecessors, we have extensively updated the text, based on review of the recent literature, and also on material from the latest (tenth) edition of Lever’s Histopathology of the Skin. We have added more extensive discussions of a score or more diseases that were either not covered, or simply mentioned with little or no elaboration in the first edition. We have added more than 1000 new microscopic images, while aiming to keep this volume reasonably small, manageable, and affordable. We have retained and enhanced the overall organization and format of the book, for example, with color coding to enhance navigation through the chapters.

Most importantly, we have taken advantage of new technology to bring the quality of the images to the current state of the art. In most cases, we have used whole slide digital scans as the basis of the new images, which has resulted in stunning quality especially for the low power images. In cases where we did not have access to the slides, we have re-scanned the original transparencies at a much higher resolution, which has resulted in obvious improvements. More than 90% of the images have been improved in these ways, and are provided in an online image bank, for the reader’s convenience.

We have also adopted the inclusion of arrows and labels on the photomicrographs, adopting the style used in the excellent book Essential Dermatopathology by Sara Edward, published last year, and we thank her for this inspiration. In addition, we have added tables to each chapter to summarize the most salient diagnostic features of potential “look-alike” diseases.

As in the past, we acknowledge our gratitude to authors of all of the present and past editions of Lever, and these individuals are listed in the Acknowledgments.

As in the previous editions, we emphasize that this book is not intended to be a comprehensive discussion of all the details of the clinical and histologic features of skin disease. Nevertheless, we have found it to be a useful addition to our armamentarium of reference and teaching dermatopathology texts, particularly as an aid to the understanding of cutaneous reaction patterns and the development of differential diagnoses on the part of trainees, as well as more experienced observers. We hope that our readership will also find it of value in their practices and in their educational activities.

David E. Elder
Philadelphia
June, 2012
As defined by its title, this volume has been planned and executed as a synopsis and atlas of Lever’s Histopathology of the Skin. The histopathology of the skin, or dermatopathology, is an important subspecialty discipline of both dermatology and pathology, sharing the language and concepts of each of these major specialties. Comprehensive texts of dermatopathology are typically large and ponderous (both in literary style and in physical weight). These heavy texts serve as excellent references to the literature and provide comprehensive descriptions of a majority of the known classified diseases. However, the knowledge they contain is excessive, in many cases, for readers who may be studying for a nonspecialty board examination, or certainly for residents in the early period of learning their discipline. A more synoptic text can fill this gap by providing information that is selected to provide a framework for future learning, as well as a first step toward the development of basic diagnostic skills in the subject.

The synopsis presented in this book has been literally derived and shortened from the original text published as the eighth edition of Lever’s Histopathology of the Skin in 1997. Accordingly, we as editors acknowledge a debt of gratitude to the contributors to that edition, who are listed in the Acknowledgments of this book. In a few instances, we have used photomicrographs that were contributed by others to the eighth edition, and in these cases we have specifically acknowledged the contributor in the figure legends. Most of the color photomicrographs in this volume have been painstakingly prepared, to ensure consistency, by Michael Ioffreda. The case material used for these photomicrographs has been taken almost exclusively from cases seen by the Penn Cutaneous Pathology Section of the Department of Dermatology at the Hospital of the University of Pennsylvania, selected by Bernett Johnson*, Rosalie Elenitsas, and Michael Ioffreda**. Some of the material has been taken from the Course in Dermatopathology offered annually under the direction of Drs. Elenitsas and Johnson. Some additional cases have been identified from the files of the Section of Surgical Pathology at the Hospital of the University of Pennsylvania. Other new material in this volume includes an excellent series of clinical photographs of fine quality derived for the most part from the collections of our father-and-son colleagues, O. Fred Miller and Jeffrey J. Miller. These clinical images, which represent the gross pathology of the diseases, will no doubt be especially useful to those who may not be in regular contact with patients suffering from a large variety of common and uncommon skin diseases.

Traditionally, dermatopathology texts have been organized according to a classification of diseases by a combination of pathophysiologic and clinicopathologic criteria. As discussed in more detail in the Introduction, this approach may serve well as a compendium of multiple disease characteristics, but it does not truly parallel the way in which common reaction patterns may present in histopathologic material. These reaction patterns often appear similar in different diseases, which may therefore be difficult or impossible to distinguish from one another in a histology preparation. As a result, the reader of a traditional text will often have difficulty building a histologic differential diagnosis because the histologic look-alikes are covered in different chapters of the text. In this volume, the subject matter is organized according to the major patterns and cell types that may be involved in the morphologic expression of various disease entities in different levels of the skin and subcutaneous tissues. This organization should facilitate an understanding of the way in which different diseases may induce similar reaction patterns in the skin, and should aid in developing a more comprehensive differential diagnosis for a given case.

In selecting the materials to be covered in this volume, we have attempted to provide at least one important example of essentially all of the possible reaction patterns in the skin. For those diseases considered prototypic of particular reaction patterns, we have provided brief synopses of clinical aspects and histopathology. We have also attempted to illustrate the major entities in the differential diagnosis of the prototypes, usually with an associated text synopsis. In this manner, we have attempted to cover most of the important dermatologic diseases (e.g., those that might be covered in a board review course for dermatology residents) in one or more sections of the book. Of course, the book is not intended to provide coverage as comprehensive or exhaustive as that in the heavy texts.

This book is directed to all students of dermatopathology, including perhaps some medical students, but in particular pathology and dermatology residents and practicing dermatologists and pathologists. In addition, this book could benefit those family practitioners who do skin biopsies and would like to have a better understanding of the pathology reports that they receive from their laboratories. The particular contributions of this book to the educational experience or diagnostic armamentarium of...
of its readers should include an appreciation for the relationships between clinical and microscopic morphology of the common diseases of the skin, and for the manner in which different diseases may present with similar reaction patterns and thus simulate one another. This should result in an enhanced understanding of the process of differential diagnosis development for unknown skin lesions, and thus in greater diagnostic accuracy.

David E. Elder
Philadelphia, Pennsylvania
June, 1998
ACKNOWLEDGMENTS

This synopsis has been prepared in part from the eighth, ninth, and tenth editions of *Lever's Histopathology of the Skin*. Accordingly, we wish to acknowledge the contributors to those editions for their part in the development of the material that we have presented here in a considerably edited form. If any errors are present in this material, however, it is not attributable to these individuals, but to us.

Among the contributors listed alphabetically below, we wish to acknowledge first and foremost the contributions of the founding author of this text, Walter Lever, MD, and of his spouse and collaborator, Gundula Schaumberg-Lever, MD.

Others to whom we are grateful for assistance in the preparation of this work include many colleagues who have supported our effort, either in the form of helpful discussion, or by the provision of materials used in the book. These include our staff colleagues and the residents and fellows at Penn, Hershey and Geisinger. Several colleagues have graciously provided materials from their collections to complete our work. These colleagues are acknowledged in the text.

We are grateful to Liqat Ali, MD for invaluable work organizing slides to enable the replacement of most of the images in this edition with state of the art digital images.

The authors of the previous editions of *Lever* are listed below, as a token of our appreciation for their indispensable contributions to those works, and, in many instances, to this.
In this work, it is our goal to provide the reader with an expanded introduction to the concept of diagnosis of cutaneous disease by pattern analysis. This concept was developed by others in a body of work stretching back more than 30 years, and was adapted by us in an introductory form in Chapter 5 of the last three editions of Lever’s Histopathology of the Skin.

As we stated in those chapters, the diagnosis of disease concerns the ability to classify disorders into categories that predict clinically important attributes such as prognosis, or response to therapy. This permits appropriate interventions to be planned for particular patients. A complete understanding of this process would involve mastery of the stages of disease, the mechanisms of changes in morphology over time, and the molecular, cellular, gross clinical, and epidemiologic reasons for the differences among diseases. However, in practice, many diseases are successfully diagnosed using only a few of their distinguishing features or “diagnostic attributes.”

As there are hundreds of diseases, each having potentially scores of diagnostic attributes, it is evident that an efficient strategy must be employed to enable diagnoses to be considered, dismissed, or retained for further consideration. Observation of an experienced dermatopathologist reveals a rapidity of accurate diagnosis that precludes the simultaneous consideration of more than a few variables. The process of diagnosis by an experienced observer is quite different from that employed by the novice, and is based on the rapid recognition of combinations or patterns of criteria (1,2). Just as the recognition of an old friend occurs by a process that does not require the serial enumeration of particular facial features, this process of pattern recognition occurs almost instantly, and is based on broad parameters that do not, at least initially, require detailed evaluation.

In clinical medicine, patterns may present as combinations of symptoms and signs, or even of laboratory values, but in dermatopathology, the most predictive diagnostic patterns are recognized through the scanning lens of the microscope, or even before microscopy, as the microscopist holds the slide up to the light, to evaluate its profile and distribution of colors. Occasionally, a specific diagnosis can be made during this initial stage of pattern recognition, by a process of “gestalt” or instant recognition, but this should be tempered with a subsequent moment of healthy analytical scrutiny. More often, the scanning magnification pattern suggests a small list of possible diagnoses, a “differential diagnosis.” Then, features that are more readily recognized at higher magnification may be employed to differentiate among the possibilities. Put in the language of science, the scanning magnification pattern suggests a series of hypotheses, which are then tested by additional observations (1). The tests may be observations made at higher magnification, the results of special studies such as immunohistochemistry, or external findings such as the clinical appearance of the patient, or the results of laboratory investigations. For example, a broad plaque-like configuration of small blue dots near the dermal–epidermal junction could represent a lichenoid dermatitis, or a lichenoid actinic keratosis. At higher magnification, the blue dots are confirmed to be lymphocytes, and one might seek evidence of parakeratosis, atypical keratinocytes, and plasma cells in the lesion, a combination which would rule out lichen planus and establish a diagnosis of actinic keratosis.

Most diagnoses in dermatopathology are established either by the “gestalt” method, or by the process of hypothesis generation and testing (differential diagnosis and investigation) just described, but in either case the basis of the methods is the identification of simple patterns recognizable with the scanning lens that suggest a manageable short list of differential diagnostic considerations. This pattern recognition method was first developed in a series of lectures given in Boston by the late Wallace H. Clark (3), and has been refined since for inflammatory skin disease by Ackerman (4), for inflammatory and neoplastic skin disease by Mihm (5), and most recently by Murphy (6). The latter authors have published texts based more or less extensively on the pattern classification.

In the work on which this present Atlas and Synopsis is based, the classification of diseases was organized upon traditional lines, in which diseases were discussed on the basis of pathogenesis (mechanisms) or etiology as well as upon reaction patterns. This classification, in our opinion, has the significant advantage of placing disorders such as infections in a common relationship to one another, facilitating the description of their many common attributes. From a histopathologic point of view; however, the novice must learn that some infections, such as syphilis, can resemble disorders as disparate as psoriasis, as lichen planus, as a cutaneous lymphoma, or as a granulomatous dermatitis.

Since there is a limited number of reaction patterns in the skin, morphologic simulants of disparate disease processes are common in the skin, as elsewhere. For this reason, classification methods based on patterns and those based on pathogenesis are only loosely compatible with each other. An observer who is studying an unknown case
has available only the morphologic patterns under consideration. Not until the diagnosis is known can the pathogenesis of the disease be well understood. Thus, it is difficult to use a book based on a pathogenic classification as a guide to the diagnosis of an unknown case. To partially circumvent this problem, this book presents a pattern-based classification of cutaneous pathology based on location in the skin, on reaction patterns, and where applicable on cell type. The classification has been based on original lecture notes prepared by the late Wallace H. Clark, Jr., MD in 1965 (with permission), and on the published works cited above, especially that of Hood, Kwan, Mihm, and Horn (5). This book is also closely linked with the “big” Lever, and could in fact be used as a morphology-based index to that larger volume.

The classification is presented first in tabular form and is redundant, in that a particular disease entity may appear in several positions in the table, because of the morphologic heterogeneity of disease processes, which are often based on evolutionary or involutional morphologic changes as a disease waxes and wanes. Within each morphologic category, one or more disorders considered to be “prototypic” of that category are described and illustrated. For example, lichen planus is the “prototypic” lichenoid dermatitis. The “prototypic” member of each category is emphasized in the detailed descriptions, because such entities constitute the descriptive standard in a given category, and they are also the standard against which other entities are evaluated. For example, drug eruptions may adopt any of a number of morphologies as reflected by their appearance in the lichenoid category but also in the psoriasiform, perivascular, and bullous categories as well as elsewhere. A “naked” epithelioid cell granuloma may suggest sarcoidosis, the prototypic epithelioid cell granuloma, while the presence of lymphocytes and necrosis in addition to granulomas might suggest tuberculosis, plasma cells might suggest syphilis, and neutritis might suggest leprosy.

After discussion of the prototypic entity in each category, a list of differential diagnostic possibilities is presented. The order of presentation of particular entities in any given position in this list reflects the authors’ opinion of the relative frequency of the entities in the list, as encountered in a typical dermatopathology practice. For example, lichenoid drug eruption may be more common than lichen planus in most hospital-based practices. Some of these differential diagnostic possibilities are discussed in more detail because of their importance as diseases in their own right. For example, Spitz nevi are discussed in the section that also contains nodular melanoma, keratoacanthomas are discussed along with squamous cell carcinomas, and so on.

The classification tables may be used as the basis of an algorithmic approach to differential diagnosis, or as a guide to the descriptions in other books, including the VIIIth, IXth, and Xth editions of Lever’s Histopathology of the Skin, from which this book has been summarized. For example, a lichenoid dermatitis comprised of lymphocytes, could represent lichen planus, graft-versus-host disease, or mycosis fungoides, patch/plaque stage, whose descriptions are to be found in Chapters 7, 9, and 31 of the “Big Lever” respectively, but are discussed here in juxtaposition in Section IIIIF1. Terms such as “psoriasiform” and “lichenoid” are defined briefly in this book, and illustrated extensively, so that the reader may review more specific criteria for the distinctions among morphologic simulants. This system of hypothesis generating and testing should lead not only to more efficiency in the evaluation and diagnosis of an unknown case, but should also facilitate the development of pattern recognition skills as more subtle diagnostic clues are absorbed into the diagnostic repertoire to allow for “tempered gestalt” diagnosis in an increasing percentage of cases.

This book is intended as a guide to differential diagnosis but should not be construed as an infallible diagnostic tool. Diagnosis should be based not only on the diagnostic considerations presented here, but also on those discussed elsewhere in the literature, all considered in a clinical and epidemiologic context appropriate to the individual patient.

References
Disorders Mostly Limited to the Epidermis and Stratum Corneum

The stratum corneum is usually arranged in a delicate mesh-like or “basket-weave” pattern. It may be shed (exfoliated), or thickened (hyperkeratosis) with or without retention of nuclei (parakeratosis or orthokeratosis respectively). The granular layer may be normal, increased (hypergranulosis), or reduced (hypogranulosis). Usually, alterations in the stratum corneum result from inflammatory or neoplastic changes that affect the whole epidermis and, more often than not, the superficial dermis. Only a few conditions, mentioned in this section, show pathology mostly or entirely limited to the stratum corneum.

A. Hyperkeratosis With Hypogranulosis
   1. No Inflammation
      Ichthyosis Vulgaris

B. Hyperkeratosis With Normal or Hypergranulosis
   1. No Inflammation
      X-linked Ichthyosis
      Epidermolytic Hyperkeratosis
      Epidermodysplasia Verruciformis
   2. Scant Inflammation
      Lichen Amyloidosis and Macular Amyloidosis

C. Hyperkeratosis With Parakeratosis
   1. Scant or No Inflammation
      Dermatophytosis
      Granular Parakeratosis

D. Localized or Diffuse Hyperpigmentations
   1. No Inflammation
      Mucosal Melanotic Macules
      Ephelids (Freckles)
   2. Scant Inflammation
      Pityriasis (Tinea) Versicolor

E. Localized or Diffuse Hypopigmentations
   1. With or Without Slight Inflammation
      Vitiligo

References

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IA

HYPERKERATOSIS WITH HYPOGRANULOSIS

The stratum corneum is thickened, and the granular cell layer is absent or thinned.

IA1 No Inflammation

The dermis contains only the normal scattered perivascular lymphocytes, and there is no epidermal spongiosis or exocytosis. Ichthyosis vulgaris is the prototype.

Ichthyosis Vulgaris

CLINICAL SUMMARY. Ichthyosis includes a number of subtypes from congenital severe forms, such as harlequin ichthyosis, to mild non-congenital forms, such as ichthyosis vulgaris (IV), which is a common disorder that is usually first manifest in childhood and is inherited in an autosomal dominant fashion. Filaggrin gene mutations in IV cause keratohyalin granule deficiency, leading to hyperkeratosis and also to loss of barrier function, and increased susceptibility to atopic dermatitis (1). The skin shows scales that on the extensor surfaces of the extremities are large and adherent, resembling fish scales, and elsewhere are small. The flexural creases are spared.

HISTOPATHOLOGY. The characteristic finding is the association of moderate compact hyperkeratosis with loss of the normal “basket-weave” pattern of the keratin and a thin or absent granular layer. The hyperkeratosis often extends into the hair follicles, resulting in large keratotic follicular plugs. The dermis is normal.
I. Disorders Mostly Limited to the Epidermis and Stratum Corneum

IB

**HYPERKERATOSIS WITH NORMAL OR HYPERGRANULOSIS**

The stratum corneum is thickened, the granular cell layer is normal or thickened, and the dermis shows only sparse perivascular lymphocytes. There is no epidermal spongiosis or exocytosis.

1. No Inflammation
2. Scant Inflammation

**IB1 No Inflammation**

There is hyperkeratosis and the upper dermis contains only sparse perivascular lymphocytes.

**X-linked Ichthyosis**

**CLINICAL SUMMARY.** X-linked ichthyosis is recessively inherited, about 90% caused by gene deletion leading to steroid sulfatase deficiency which results in impaired hydrolysis of cholesterol sulfate leading to accumulation of cholesterol-3 sulfate in the epidermis (1,2). It is only rarely present at birth. Although female heterozygotes are frequently affected, males have a more severe form of the disorder. The thickness of the adherent scales increases during childhood. In contrast to ichthyosis vulgaris, the flexural creases may be involved.

**HISTOPATHOLOGY.** There is hyperkeratosis. The granular layer is normal or slightly thickened but not thinned as in dominant ichthyosis vulgaris. The epidermis may be slightly thickened.

**TABLE I.1. Three Prototypes of Ichthyosis (1)**

<table>
<thead>
<tr>
<th>Disease (severity)</th>
<th>Molecule</th>
<th>Locus of Disorder</th>
<th>Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV (mild)</td>
<td>Filaggrin</td>
<td>Keratohyaline (KH) granules</td>
<td>Hyperkeratosis (HK) without KH granules</td>
</tr>
<tr>
<td>XLI (moderate)</td>
<td>Steroid Sulphatase</td>
<td>Cornified Cell Envelope</td>
<td>HK with normal KH granules</td>
</tr>
<tr>
<td>HI (severe)</td>
<td>ABCA12</td>
<td>Intercellular lipid transport</td>
<td>HK with abnormal lamellar granules</td>
</tr>
</tbody>
</table>

IV, Ichthyosis vulgaris; HI, Harlequin Ichthyosis; XLI, X-linked ichthyosis.
**Epidermolytic Hyperkeratosis**

**CLINICAL SUMMARY.** This rather striking histologic reaction pattern is also known as granular degeneration of the epidermis. It is seen in some linear epidermal nevi and in bullous congenital ichthyosiform erythroderma. The disease results from mutations in the K1 and K10 keratin genes (chromosomes 12 and 17, respectively), which encode the keratins in the suprabasal epidermis. These mutations cause faulty assembly of keratin tonofilaments and impair their insertion into desmosomes. These flaws prevent normal development of the cytoskeleton, resulting in epidermal “lysis” and a tendency to form vesicles (3). Similar changes are also seen as one of the reaction patterns in Grover’s disease, and the same pattern is commonly observed as an incidental finding, when it may be referred to as “focal acantholytic dyskeratosis” (4).

**HISTOPATHOLOGY.** The salient histologic features are (1) perinuclear vacuolization of the cells in the stratum spinosum and in the stratum granulosum; (2) peripheral to the vacuolization, irregular cellular boundaries; (3) an increased number of irregularly shaped, large keratohyalin granules; and (4) compact hyperkeratosis in the stratum corneum.

**Epidermodysplasia Verruciformis**

**CLINICAL SUMMARY.** Epidermodysplasia verruciformis (EV) is a genetic disease characterized by HPV infection with types not seen in otherwise healthy individuals.

---

Clin. Fig. IB1.a. **X-linked ichthyosis.** Large “dirty” scales on the ankle are characteristic.

Fig. IB1.a. **X-linked ichthyosis.** At scanning power, the epidermis appears normal, except for uniform thickening of the stratum corneum.

Fig. IB1.b. **X-linked ichthyosis, medium power.** The thickened stratum corneum (arrow) contains no parakeratotic nuclei, constituting orthokeratosis.

Fig. IB1.c. **X-linked ichthyosis, high power.** A granular layer is present, visible as a thin blue line in the upper epidermis (arrow).
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Clin. Fig. IB1.b. *Epidermolytic hyperkeratosis in bullous congenital ichthyosiform erythroderma*: (a). Popliteal flexures are involved with keratotic, almost verrucous, malodorous scale. Erosions appear in sites of bullae.

Clin. Fig. IB1.c. *Bullous congenital ichthyosiform erythroderma*. The sole of the same patient’s foot shows characteristic symptomatic yellow keratoderma. The patient’s son shares this autosomal dominant condition.

Fig. IB1.d. *Epidermolytic hyperkeratosis, low power*. The epidermis is thickened and there is papillomatosis (these changes are not usually seen in focal acantholytic dyskeratoses). There is compact hyperkeratosis in the stratum corneum.

Fig. IB1.e. *Epidermolytic hyperkeratosis, medium power*. The epidermis shows vacuolated keratinocytes with large keratohyalin granules. There is compact hyperkeratosis in the stratum corneum.

Fig. IB1.f. *Epidermolytic hyperkeratosis, high power*. There is ortho-keratotic hyperkeratosis. The epidermis shows vacuolated keratinocytes with large keratohyalin granules. The keratohyalin granules are irregular and cell borders are ill-defined (arrows).
Hyperkeratosis With Normal or Hypergranulosis

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It usually begins in childhood and is characterized by a generalized infection by certain subtypes of HPV (referred to as “EV HPVs”), frequent association with cutaneous carcinomas, and abnormalities of cell-mediated immunity. Two forms of EV are recognized. One is induced by HPV-3 and HPV-10 and characterized by a persistent widespread eruption resembling verrucae planae with a tendency toward confluence into plaques. Some of the cases are familial. There is no tendency to malignant transformation in this form. The second form is primarily related to HPV-5. There is often a familial history with an autosomal recessive or X-linked recessive inheritance. In addition to the plane warts, irregularly outlined, slightly scaling macules of various shades of brown, red, and white, tinea versicolor-like lesions, and seborrheic keratosis like lesions have been noted. Development of Bowen’s disease (squamous cell carcinoma in situ) within lesions in exposed areas is a common occurrence, and invasive lesions of squamous cell carcinoma are occasionally found. The oncogenic potential is highest for HPV-5 and HPV-8. EV-like lesions can develop in renal transplant patients and in HIV-infected persons. Two known EV susceptibility loci, EV1 and EV2, which belong to the transmembrane channel-like (TMC) gene family, may serve as restriction factors for EV HPVs. In EV individuals, these genes are mutated and malfunctioning, causing a defective cell-mediated immune mechanism against certain types of viruses.

HISTOPATHOLOGY. The epidermal changes, although similar to those observed in verruca plana, often differ by being more pronounced and more extensive. Affected keratinocytes are swollen and irregularly shaped. They show abundant, slightly basophilic blue-gray cytoplasm and some contain numerous round, basophilic keratohyalin granules. A few dyskeratotic cells may be seen in the lower part of the epidermis. Although some nuclei appear pyknotic, others appear large, round, and empty owing to marginal distribution of the chromatin. In immunocompromised patients, EV often lacks the histologic features of verruca planae; a focally thickened granular layer is a marker for viral detection, and the risk for dysplasia in such lesions is much higher than in epidermodysplasia verruciformis not associated with acquired immunosuppression.
Conditions to consider in the differential diagnosis:
- lamellar ichthyosis
- X-linked ichthyosis
- epidermolytic hyperkeratosis
- epidermolytic acanthoma
- oculocutaneous tyrosinosis (tyrosinemia)
- acanthosis nigricans
- large cell acanthoma
- epidermodysplasia verruciformis
- hyperkeratosis lenticularis perstans (Flegel’s disease)

IB2 Scant Inflammation

There is hyperkeratosis, and lymphocytes are minimally increased about the superficial plexus. There may be a few neutrophils in the stratum corneum.

Lichen Amyloidosis and Macular Amyloidosis

CLINICAL SUMMARY. Lichen amyloidosis (7) and macular amyloidosis are best considered as different manifestations of the same disease process. Lichen amyloidosis is characterized by closely set, discrete, brown-red pruritic often somewhat scaly papules and plaques that are most commonly located on the legs, especially the shins. The plaques often have verrucous surfaces and then resemble hypertrophic lichen planus or lichen simplex chronicus. It is assumed by some that the pruritis leads to damage of keratinocytes by scratching and to subsequent production of amyloid.

HISTOPATHOLOGY. Lichen and macular amyloidosis show deposits of amyloid that are limited to the papillary dermis. Most of the amyloid is situated within the dermal papillae. Although the deposits usually are smaller in macular amyloidosis than in lichen amyloidosis, differentiation of the two on the basis of the amount of amyloid is not possible. The two conditions actually differ only in the appearance of the epidermis, which is hyperplastic and hyperkeratotic in lichen amyloidosis. Occasionally, the amount of amyloid in macular amyloidosis is so small that it is missed, even when special stains are used on frozen sections. In such instances, more than one biopsy may be necessary to confirm the diagnosis.

Fig. IB2.a

Fig. IB2.b

Fig. IB2.c
Clin. Fig. IB2.a. *Lichen amyloidosis*. Patient presented with pruritic papules on the pretibial areas.

Clin. Fig. IB2.b. *Lichen amyloidosis*. Pigmented discrete papules result from deposition of amyloid derived from keratinocytes.

**Fig. IB2.d.** *Lichen amyloidosis, low power.* In contrast to macular amyloidosis, lichen amyloidosis reveals irregular acanthosis, papillomatosis, and hyperkeratosis. The papillary dermis is expanded by amorphous eosinophilic material (arrows) and there is a mild perivascular inflammatory infiltrate.

**Fig. IB2e.** *Lichen amyloidosis, high power.* At higher magnification the amorphous deposits of amyloid are seen in the papillary dermis associated with pigment laden macrophages.
Conditions to consider in the differential diagnosis of this category:

- dermatophytosis
- lichen amyloidosis and macular amyloidosis

**HYPERKERATOSIS WITH PARAKERATOSIS**

The stratum corneum is thickened, the granular cell layer is reduced, there is parakeratosis. The dermis may show only sparse perivascular lymphocytes, although some of the conditions listed here in other instances may show more substantial inflammation. There is no epidermal spongiosis or exocytosis. Most examples of dermatoses associated with parakeratosis have significant inflammation in the dermis (see Sections IIIA–E). Some neoplastic disorders (e.g., actinic keratoses) present with parakeratosis, usually also associated with epidermal thickening, and inflammation in the dermis (see Section IIA).

**IC1 Scant or No Inflammation**

Lymphocytes are minimally increased about the superficial plexus. There may be a few lymphocytes and/or neutrophils in the stratum corneum. Dermatophytosis is prototypic (8). However, many examples of dermatophytosis have significant inflammation, simulating one or another of the superficial inflammatory dermatoses (see Section III).

**Clin. Fig. IC1**  
*Tinea pedis.* A leading edge of scale and erythema in a moccasin distribution characterizes this infection, most commonly caused by the dermatophyte Trichophyton rubrum.

**Fig. IC1.a**  
*Dermatophytosis, medium power.* At this magnification, the epidermis may appear normal, slightly thickened as here, spongiotic, and/or psoriasiform. There is slight uniform thickening of the stratum corneum.

**Fig. IC1.b**  
*Dermatophytosis, high power.* At high magnification, there is mixed ortho-keratotic hyperkeratosis often “sandwiched” above a layer of parakeratosis. The granular layer is normal. Hyphal forms may be appreciable even in the H&E section (arrows).

**Fig. IC1.c**  
*Dermatophytosis, high power—Grocott stain for fungi.* A PAS or a Grocott stain highlights fungal hyphae in the stratum corneum. These are likely to be most numerous in areas away from any neutrophils.
Disorders Mostly Limited to the Epidermis and Stratum Corneum

Hyperkeratosis With Parakeratosis

**CLINICAL SUMMARY.** Fungal infections of seven anatomical regions are commonly recognized: tinea capitis (including tinea favosa or favus of the scalp), tinea barbae, tinea faciei, tinea corporis (including tinea imbricata), tinea cruris, tinea of the hands and feet, and tinea unguium. *Tinea corporis* may be caused by any dermatophyte, but by far the most common cause in the United States is *T. rubrum*, followed by *M. canis* and *T. mentagrophytes*. In *T. rubrum* infection, there are large patches showing central clearing and a polycyclic scaling border, which may be quite narrow and thread-like.

**HISTOPATHOLOGY.** Fungi may present as filamentous hyphae, arthrospores, yeast forms, or pseudohyphae. Hyphae are thread-like structures that may be septate or nonseptate. Arthrospores are spores formed by fragmentation of septate hyphae at the septum, usually appearing as rounded, box-like, or short cylindrical forms. Yeasts are single-celled forms that appear as round, elongated, or ovoid bodies; they grow by budding, and their progeny may adhere to each other and form elongated chains called pseudohyphae. If fungi are present in the horny layer, they usually are “sandwiched” between two zones of cornified cells, the upper being orthokeratotic and the lower consisting partially of parakeratotic cells. This “sandwich sign” should prompt the performance of a stain for fungi for verification. The presence of neutrophils in the stratum corneum is another valuable diagnostic clue. In the absence of demonstrable fungi, the histologic picture of fungal infections of the glabrous skin is not diagnostic. Depending on the degree of reaction of the skin to the presence of fungi, there may be histologic features of an acute, a subacute, or a chronic spongiotic dermatitis.

Granular Parakeratosis

**CLINICAL SUMMARY.** Granular parakeratosis was initially described as “axillary granular parakeratosis” because all of the original patients presented with lesions confined to the axillae. Subsequent reports described lesions in inguinal creases, inframammary folds, and other non-intertriginous areas (9). It occurs in both men and women with predominance in the female gender. The characteristic clinical findings are erythematous or hyperpigmented plaques that may be crusted or verrucous. There may be associated pruritus or burning. The total number of lesions is usually small and there are no oral lesions. Because of the clinical presentation, the clinical differential diagnosis usually includes Hailey–Hailey disease, Darier’s disease, acanthosis nigricans, or contact dermatitis. In the original descriptions, an unusual contact reaction to deodorants was hypothesized, however, with subsequent reports, this is felt to be less likely. The current hypothesis is that granular parakeratosis is a disorder of keratinization, possibly an abnormality of filaggrin processing.

**HISTOPATHOLOGY.** The histopathology of granular parakeratosis is distinctive. There is a markedly thickened stratum corneum with parakeratosis and retention of

---

**Fig. IC1.d.** Granular parakeratosis, low power. There is acanthosis of the epidermis with little to no spongiosis. There is a markedly thickened and compacted stratum corneum. The superficial dermis reveals mild perivascular inflammation.

**Fig. IC1.e.** Granular parakeratosis, high power. The stratum corneum is markedly thickened and compacted. It is basophilic in appearance. Within the thickened stratum corneum, there is retention of the basophilic granules of the granular cell layer (arrow).
multiple basophilic granules. The epidermis may be normal or slightly thickened. The dermis shows either absent inflammation or either mild perivascular mononuclear cell infiltrate. Except for one reported case of granular parakeratosis associated with tinea, special stains for fungi are negative.

**Conditions to consider in the differential diagnosis of this category:**
- dermatophytosis
- granular parakeratosis
- pityriasis rubra pilaris
- ichthyosis
- seborrheic dermatitis
- acanthosis nigricans
- scurvy
- vitamin A deficiency
- pellagra (niacin deficiency)
- Hartnup disease
- acrokeratosis neoplastica (Bazex syndrome)
- epidermal dysmaturation (cytotoxic chemotherapy-variable keratin alterations)
- epidermolytic hyperkeratosis

**LOCALIZED OR DIFFUSE HYPERPIGMENTATIONS**

Increased melanin pigment is present in basal keratinocytes, without melanocytic proliferation.

1. No Inflammation
2. Scant Inflammation

**ID1 No Inflammation**

The upper dermis contains only sparse perivascular lymphocytes. Mucosal melanotic macule (melanosis) is the prototype (10).

**Clin. Fig. ID1.a**  
*Labial melanotic macule*. A benign acquired macule with irregular borders and uniform brown pigmentation developed near the vermilion border in a middle-aged female. Melanoma is considered in the differential diagnosis.

**Fig. ID1.a**  
*Labial lentigo, low power*. At this magnification, the epidermis may appear completely normal, unless the difference in melanin pigment content between the lesion and the adjacent skin can be appreciated. Often, however, there is slight acanthosis as in this example. There may be patchy lymphocytes and melanophages in the papillary dermis, or inflammatory cells may be completely absent, as here.

**Fig. ID1.b**  
*Labial lentigo, high power*. There is increased brown melanin pigment in basal keratinocytes (arrows). Melanocytes may be slightly increased, but there is no contiguous melanocytic proliferation as in nevi and melanomas. A few melanophages are present in the papillary dermis.
Localized or Diffuse Hyperpigmentations

**Mucosal Melanotic Macules**

**CLINICAL SUMMARY.** These benign lesions present as a pigmented patch on a mucous membrane. Common locations include the vermilion border of the lower lip, the oral cavity, the vulva, and, less often, the penis. The lesions may be synonymously referred to as “mucosal lentigo” or “mucosal melanotic macule.” In the common location on the vulva (“vulvar lentigo”), this process may present as a broad, irregular, and asymmetric patch of brown to blue-black hyperpigmentation, resembling a melanoma. The lesions are entirely macular, unlike most invasive melanomas. The so-called “labial lentigo” (“labial melanotic macule”), a hyperpigmented macule of the lower lip, is uniformly pigmented brown, usually completely macular, and usually less than about 6 mm in diameter.

**HISTOPATHOLOGY.** At first glance, a biopsy specimen may appear normal. The findings include mild acanthosis without elongation of rete ridges, and hyperpigmentation.

![Clin. Fig. ID1.b](image1)  
**Clin. Fig. ID1.b.** *Ephelis.* Fair complexioned male has prominent brown macule which darkens in sunlight.

![Clin. Fig. ID1.c](image2)  
**Clin. Fig. ID1.c.** *Ephelis, low power.* At this magnification, the epidermis may appear completely normal, unless the difference in melanin pigment content between the lesion and the adjacent skin can be appreciated.

![Clin. Fig. ID1.d](image3)  
**Clin. Fig. ID1.d.** *Ephelis, medium power.* There is increased melanin pigment in basal keratinocytes. Melanocytes are not increased in number.

![Clin. Fig. ID1.b](image4)  
**Clin. Fig. ID1.b.** *Cafe au lait macule.* Evenly tan-colored macules can be seen in normal individuals. Multiple cafe au lait changes raise suspicion for neurofibromatosis.

![Clin. Fig. ID1.c](image5)  
**Clin. Fig. ID1.c.** *Becker’s nevus:* Teenage male acquired an enlarging tan macule with scalloped borders on his shoulder and chest. Hypertrichosis may develop.
I. Disorders Mostly Limited to the Epidermis and Stratum Corneum

of basal keratinocytes, recognized in comparison with surrounding epithelium, with scattered melanophages in the dermis. Although melanocytes may be normal in number, in most instances the number is slightly increased. Because of this slight increase in the number of melanocytes, the term “genital lentiginosis” has recently been proposed for these lesions. Although these lesions may simulate melanoma clinically, histologically there is no contiguous melanocytic proliferation and no significant atypia. Occasionally, especially in the penile and vulvar lesions, there are prominent dendrites of melanocytes ramifying among the hyperpigmented keratinocytes. There may be associated mild keratinocytic hyperplasia, and patchy lymphocytes with scattered melanophages in the papillary dermis may account for the blue-black color that may simulate melanoma clinically.

Ephelids (Freckles)

CLINICAL SUMMARY. Freckles, or ephelids, are small, brown macules scattered over skin exposed to the sun. Exposure to the sun deepens the pigmentation of freckles.
Disorders Mostly Limited to the Epidermis and Stratum Corneum

Localized or Diffuse Hypopigmentations

Melanin pigment is reduced in basal keratinocytes, with (vitrilgo) or without (early stages of chemical depigmentation) a reduction in the number of melanocytes.

**IE1** With or Without Slight Inflammation

Lymphocytes may minimally increased about the dermal–epidermal junction, as in the active phase of vitiligo, or may be absent, as in albinism. Vitiligo is the prototype (13,14).

**Vitiligo**

**CLINICAL SUMMARY.** Vitiligo is an acquired, disfiguring, patchy, total loss of skin pigmentation. Stable patches often have an irregular border but are sharply demarcated from the surrounding skin. In expanding lesions, there may rarely be a slight rim of erythema at the border and a thin zone of transitory partial depigmentation.

**HISTOPATHOLOGY.** The central process in vitiligo is the destruction of melanocytes at the dermo–epidermal junction. With silver stains or the dopa reaction, well-established lesions of vitiligo are totally devoid of melanocytes. The periphery of expanding lesions that are hypopigmented rather than completely depigmented still show a few dopa-positive melanocytes and some melanin granules in the basal layer. In the outer border of patches of vitiligo, melanocytes are often prominent and demonstrate long dendritic processes filled with melainin granules. Rarely, a superficial perivascular and somewhat lichenoid mononuclear cell infiltrate with vacuolar change is observed at the border of the depigmented areas.

**Conditions to consider in the differential diagnosis:**
- vitiligo
- chemical depigmentation
- idiopathic guttate hypomelanosis
- albinism
- tinea versicolor
- piebaldism
- Chediak–Higashi syndrome
- hypopigmented mycosis fungoides

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**IE** LOCALIZED OR DIFFUSE HYPOPIGMENTATIONS

Scant Inflammation

Lymphocytes are minimally increased about the superficial plexus. There may be a few lymphocytes and/or neutrophils in the stratum corneum. Melanophages may be present in the papillary dermis. Pityriasis (tinea) versicolor is the prototype (12).

**Pityriasis (Tinea) Versicolor**

**CLINICAL SUMMARY.** The frequently used term “tinea versicolor” is not accurate since the causative organism, *Malassezia furfur*, is not a dermatophyte. Pityriasis versicolor usually affects the upper trunk, where there are multiple pink to brown papules that may appear hyper- or hypopigmented. On gentle scraping, the surface of the discolored areas is finely scaled.

**HISTOPATHOLOGY.** In contrast to other fungal infections of the glabrous skin, the horny layer in lesions of pityriasis versicolor contains abundant amounts of fungal elements, which can often be visualized in sections stained with hematoxylin–eosin as faintly basophilic structures. *Malassezia (Pityrosporum)* is present as a combination of both hyphae and spores, often referred to as “spaghetti and meatballs.” The inflammatory response in pityriasis versicolor is usually minimal, although there may occasionally be slight hyperkeratosis, slight spongiosis, or a minimal superficial perivascular lymphocytic infiltrate.

**Conditions to consider in the differential diagnosis:**
- pityriasis (tinea) versicolor
- lichen amyloidosis
- post-inflammatory hyperpigmentation
- erythema dyschromicum perstans
- pretibial pigmented patches in diabetes
Clin. Fig. IE.1. Vitiligo. Acquired depigmented, well-demarcated patches often appear with striking symmetry.

Fig. IE1.a. Vitiligo, low power. The epidermis may appear completely normal at scanning magnification, unless it is appreciated that melanin pigment is reduced compared to surrounding skin.

Fig. IE1.b. Vitiligo, high power. At high magnification, in the left panel, a careful search reveals the absence of melanocytes from the basal lamina region. In the right panel, from the periphery of the area of the depigmentation, there is often a subtle lymphocytic infiltrate, as here.

Fig. IE1.c. Vitiligo, Fontana stain, medium power. A Fontana stain reveals, in the left panel, the absence of melanin pigment in basal layer keratinocytes, changes typical of vitiligo. In the right panel, from the adjacent skin, there is melanin in the basal layer of the skin, a normal distribution.

Fig. IE1.d. Vitiligo, Melan A stain, medium power. Similarly, the left panel shows a region of vitiligo in which melanocytes are absent, compared to the normal skin in which the distribution of Melan A positive melanocytes (arrows) is normal.
References

## Localized Superficial Epidermal or Melanocytic Proliferations

Localized superficial epithelial and melanocytic proliferations may be reactive but are often neoplastic. The epidermis (keratinocytes) may proliferate without extension into the dermis, extend into the dermis and may be squamous or basaloid. Melanocytes within the epidermis may proliferate with or without cytologic atypia (nevi, dysplastic nevi, melanoma in situ), in a proliferative epidermis (superficial spreading melanoma in situ, Spitz nevi) or an atrophic epidermis (lentigo maligna); they can also extend into the dermis as proliferative infiltrates (invasive melanoma with or without vertical growth phase). There may be an associated variably cellular often mixed inflammatory infiltrate, or inflammation may be essentially absent.

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IIA1 Localized Epidermal Proliferations

The epidermis is thickened secondary to a localized proliferation of keratinocytes (acanthosis). The proliferation can be cytologically atypical, as in squamous cell carcinoma in situ, or bland, as in eccrine poroma. It may be papillary as in seborrheic keratoses and verrucae, or highly irregular as in pseudoeotheptelialomatous hyperplasia. Actinic keratoses and squamous cell carcinoma are prototypic examples. Clear cell acanthoma may also be included in this category, or may mimic an inflammatory condition.

Actinic Keratosis

CLINICAL SUMMARY. Actinic keratoses (1) are usually seen as multiple lesions in sun-exposed areas of the skin in persons in or past middle life who have fair complexions. Usually, the lesions measure less than 1 cm in diameter. They are erythematous, are often covered by adherent scales, and barely palpable except in their hypertrophic form. Actinic keratoses may be regarded conceptually as local keratinocytic neoplastic proliferations characterized by architectural abnormalities and cytologic atypia, whose histopathology spans a spectrum from mild dysplasia to carcinoma in situ (2).

HISTOPATHOLOGY. Five types of actinic keratoses can be recognized histologically: hypertrophic, atrophic, bowenoid, acantholytic, and pigmented. In the hypertrophic type, hyperkeratosis is pronounced and is intermingled with areas of parakeratosis. The epidermis is thickened in most areas and shows irregular downward proliferation that is limited to the uppermost dermis and does not represent frank invasion. Keratinocytes in the lower portion of the epidermis show a loss of polarity and thus a disorderly arrangement. Some of these cells show crowding, pleomorphism, and atypicality of their nuclei, which appear large, irregular, and hyperchromatic, and some of the cells are dyskeratotic or apoptotic, and there may be increased mitotic activity sometimes with abnormal mitoses. The degree of cytologic atypia and architectural disorder (i.e., dysplasia) can be graded as mild, moderate, or severe and has been correlated with cell cycle marker expression (3). In contrast to the epidermal keratinocytes, the cells of the hair follicles and eccrine ducts that penetrate the epidermis within actinic keratoses retain their normal appearance and keratinize normally, giving rise to the characteristic alternating columns of hyperkeratosis and orthokeratosis.

Atrophic actinic keratoses lack the hypertrophic epithelial proliferation seen in the hypertrophic type; bowenoid keratoses are characterized by high grade atypia that approaches full thickness (squamous cell carcinoma in situ); acantholytic keratoses show dysshesion of lesional cells that may simulate a glandular pattern; and pigmented keratoses resemble any of the other forms but contain increased melanin pigment.

In all five types of actinic keratoses, the upper dermis usually shows a fairly dense, chronic inflammatory
infiltrate composed predominantly of lymphoid cells but often also containing plasma cells. The upper dermis usually shows solar or basophilic degeneration.

**Eccrine Poroma**

**CLINICAL SUMMARY.** Eccrine poroma (4) is a fairly common solitary tumor, found most commonly on the sole or the sides of the foot, and next in frequency on the hands and fingers, but also in many other areas of the skin, such as the neck, chest, and nose. Eccrine poroma generally arises in middle-aged persons. The tumor has a rather firm consistency, is raised and often slightly pedunculated, is asymptomatic, and usually measures less than 2 cm in diameter. In eccrine poromatosis, more than 100 papules are observed on the palms and soles.

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**Clin. Fig. IIA1.a.** Actinic keratosis. Scaly erythematous macules and papules with a "sandpaper" texture appear commonly on face and dorsal hands, areas subject to chronic sun exposure.

**Fig. IIA1.a.** Hypertrophic actinic keratosis, low power. There is hyperkeratosis alternating with parakeratosis, and irregular thickening of the epithelium. In the dermis, there are patchy lymphocytes and plasma cells.

**Fig. IIA1.b.** Hypertrophic actinic keratosis, medium power. The normal epidermal maturation pattern is disturbed, with increased thickness of the basal layer.

**Fig. IIA1.c.** Hypertrophic actinic keratosis, high power. Basal keratinocytes show attributes of dysplasia or *in situ* malignancy—nuclear crowding, enlargement, hyperchromatism, and pleomorphism. Note the orthokeratotic column above the hyperplastic follicular infundibulum in the center of the image. (continues)
II. Localized Superficial Epidermal or Melanocytic Proliferations

Fig. IIA1.d. *Actinic keratosis, low power.* This lesion demonstrates striking alternating columns of hyperkeratosis and parakeratosis. The epithelium is irregularly thickened.

Fig. IIA1.e. *Actinic keratosis, low power.* Columns of orthokeratotic keratin extend above the hyperplastic epithelium of skin adnexa (sweat ducts in this instance). Parakeratotic keratin extends above the full-thickness dysplastic epithelium. Atypia is full thickness (Bowenoid actinic keratosis/squamous cell carcinoma *in situ*).

Fig. IIA1.f. *Eccrine poroma, scanning magnification.* There is a well-defined epidermal proliferation which is sharply circumscribed from the adjacent skin.

Fig. IIA1.g. *Eccrine poroma, high magnification.* At higher magnification, this lesion is composed of a uniform, bland-appearing epithelial cells. These lesions are often associated with formation of small ducts lined by an eosinophilic cuticle similar to that of the native eccrine duct.

Fig. IIA1.g1. *Eccrine poroma, high magnification.* Additional image showing ducts at high magnification.
HISTOPATHOLOGY. In its typical form, eccrine poroma arises within the lower portion of the epidermis, from where it extends downward into the dermis as tumor masses that often consist of broad, anastomosing bands. The tumor cells are smaller than squamous cells, have a uniform cuboidal appearance and a round, deeply basophilic nucleus, and are connected by intercellular bridges. They show no tendency to keratinize within the tumor, except on the surface. Although the border between tumor formations and the stroma is sharp, tumor cells located at the periphery show no palisading. As a characteristic feature, the tumor cells contain significant amounts of glycogen, usually in an uneven distribution. In most but not in all eccrine poromas, narrow ductal lumina and occasionally cystic spaces are found within the tumor, lined by an eosinophilic, PAS-positive, diastase-resistant cuticle similar to that lining the lumina of eccrine sweat ducts and by a single row of luminal cells.

Squamous Cell Carcinoma in Situ & Bowen's Disease

CLINICAL SUMMARY. Bowen's disease usually consists of a solitary lesion manifested as a slowly enlarging erythematous patch of sharp but irregular outline, within which there are generally areas of scaling and crusting. It may occur on exposed or on unexposed skin and in pigmented or poorly pigmented skin. It may be caused on exposed skin by exposure to the sun (“Bowenoid actinic keratoses”) and on unexposed skin by the ingestion of arsenic. Some cases, especially in immunosuppressed patients and in genital and periangual sites, may be associated with oncogenic viruses including human papilloma virus (HPV) (5), and merkel cell polyoma virus (6).

HISTOPATHOLOGY. Bowen's disease (7) is an intraepidermal squamous cell carcinoma referred to also as squamous cell carcinoma in situ. When full-thickness atypia is present in an actinic keratosis, the term squamous cell carcinoma in situ may also appropriately be applied. The Bowenoid type of actinic keratosis is histologically indistinguishable from Bowen's disease. As in Bowen's disease, there is within the epidermis considerable disorder in the arrangement of the nuclei, as well as clumping of nuclei and dyskeratosis. The epidermis is acanthotic and the cells lie in complete disorder, resulting in a “windblown” appearance. Many cells are highly atypical, with large, hyperchromatic nuclei and, frequently, multiple clustered nuclei. The horny layer usually is thickened and consists largely of parakeratotic cells with atypical, hyperchromatic nuclei. In contrast to actinic keratoses where the adnexal epithelium is hyperplastic, the infiltrate of atypical cells in Bowen's disease frequently extends into follicular infundibula and causes replacement of the follicular epithelium by atypical cells down to the entrance of the sebaceous duct. In a small percentage of cases of Bowen's disease, (about 3%–5%), an invasive squamous cell carcinoma develops.
Bowenoid Papulosis

**CLINICAL SUMMARY.** As recently reviewed (8), Bowenoid papulosis presents as papules and plaques that frequently regress and relapse in vulvar and penile skin. It is best regarded as a form of squamous cell carcinoma in situ that carries a low risk of transformation to invasive carcinoma. The lesions are contagious and likely transmitted via sexual contact or vertical transmission in the peripartum period. Various high-risk HPV types, including types 16 and 18, have been linked to the disease.

**HISTOPATHOLOGY.** As in Bowen's disease, the lesions are characterised by psoriasiform epidermal hyperplasia, hyperkeratosis, and focal parakeratosis. There is full-thickness epidermal dysplasia with crowding of keratinocytes and loss of architecture. The lesional cells are large, with hyperchromatic, pleomorphic nuclei, and demonstrate loss of cellular polarity, and abnormal maturation. Mitoses, some atypical, are often seen. Partially vacuolated koilocyte-like cells are often present, and small, rounded, eosinophilic, inclusion-like bodies with a surrounding halo are sometimes present in the stratum corneum and granulosum. In comparison to Bowen's disease, histologic changes of BP are less pronounced and more focal. There may be a lymphocytic infiltrate in the dermis. Immunoperoxidase staining has demonstrated the presence of papillomavirus antigen in the nuclei of superficial epidermal cells.
IIA. Localized Irregular Thickening of the Epidermis

**CLINICAL SUMMARY.** This not uncommon tumor (9) typically occurs as a solitary lesion on the legs, as a slowly growing, sharply delineated, red nodule or plaque 1 to 2 cm in diameter, covered with a thin crust and exuding some moisture. A collarette is often seen at the periphery. The lesion appears stuck on, like a seborrheic keratosis, and is vascular, like a pyogenic granuloma.

**HISTOPATHOLOGY.** Within a sharply demarcated area of the epidermis, the epidermal cells, with the exception of those of the basal cell layer, appear strikingly clear and slightly enlarged. Their nuclei appear normal. Staining with the periodic acid–Schiff (PAS) reaction reveals large amounts of glycogen within the cells. The rete ridges are elongated and

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**Clear Cell Squamous Cell Carcinoma in Situ**

See Fig. IIA.p.

**Clear Cell Acanthoma**

**CLINICAL SUMMARY.** This not uncommon tumor (9) typically occurs as a solitary lesion on the legs, as a slowly growing, sharply delineated, red nodule or plaque 1 to 2 cm in diameter, covered with a thin crust and exuding some moisture. A collarette is often seen at the periphery. The lesion appears stuck on, like a seborrheic keratosis, and is vascular, like a pyogenic granuloma.

**HISTOPATHOLOGY.** Within a sharply demarcated area of the epidermis, the epidermal cells, with the exception of those of the basal cell layer, appear strikingly clear and slightly enlarged. Their nuclei appear normal. Staining with the periodic acid–Schiff (PAS) reaction reveals large amounts of glycogen within the cells. The rete ridges are elongated and
II. Localized Superficial Epidermal or Melanocytic Proliferations

may be intertwined. The surface is parakeratotic with few or no granular cells. The acrosyringia and acrotrichia within the tumor retain their normal stainability. A conspicuous feature in most lesions is the presence throughout the epidermis of numerous neutrophils, many with fragmentation of their nuclei, often forming microabscesses in the parakeratotic horny layer. Slight spongiosis is present between the clear cells. Dilated capillaries are seen in the elongated papillae and often also in the dermis underlying the tumor. In addition, there is a mild to moderately severe lymphoid infiltrate in the dermis. Some clear cell acanthomas appear papillomatous, with the configuration of a seborrheic keratosis.

Conditions to consider in the differential diagnosis:

No Cytologic Atypia
- seborrheic keratosis
- verrucae
- dermatosis papulosa nigra
- stucco keratosis
- large cell acanthoma
- clear cell acanthoma
- epidermal nevi
- eccrine poroma
- hidroacanthoma simplex
- oral white sponge nevus
leukoeema of the oral mucosa
v verrucous hyperplasia of oral mucosa (oral florid papillomatosis)

**With Cytologic Atypia**
- actinic keratosis
- arsenical keratosis
- squamous cell carcinoma in situ
- Bowen's disease
- erythroplasia of Queyrat
- erythropoikia of the oral mucosa
- Bowenoid papulosis

**Pseudoepitheliomatous Hyperplasia**
- halogenoderemas
- deep fungal infections
- epidermis above granular cell tumor
- Spitz nevus
- verrucous melanoma

### IIA Superficial Melanocytic Proliferations

The epidermis may be thickened (acanthosis) and is associated with a proliferation of single or nested melanocytic cells. The proliferation can be malignant as in superficial spreading melanoma or benign as in nevi. These are the prototypes.

**Superficial Melanocytic Nevi and Melanomas**

**CLINICAL SUMMARY.** Melanocytic nevi (10,11) vary considerably in their clinical appearance. Five clinical types can be recognized: (1) flat lesions which for the most part are histologically junctional nevi, and compound nevi which include (2) slightly elevated lesions often with raised centers and flat peripheries many of which are histologically dysplastic nevi, (3) dome-shaped lesions, (4) papillomatous lesions, and (5) pedunculated lesions. The first two types are usually pigmented and are superficial at the histologic level (confined to the epidermis and papillary dermis); the latter three may or may not be pigmented, and may involve the reticular dermis. Most small, flat lesions represent either a lentigo simplex or a junctional nevus; flat lesions or lesions with flat peripheries greater than 5 mm in diameter with irregular indefinite borders and pigment variegation are clinically dysplastic nevi. Dysplastic nevi are most important as simulants and markers of increased risk for melanoma. Although about one-third of melanomas may arise in a dysplastic nevus, dysplastic nevi are vastly more common than melanomas and therefore the risk of progression of any one lesion is very low (12).

Melanomas are neoplastic proliferations of cytologically malignant melanocytes (13). Two major steps or phases of melanoma development can be distinguished. The first is the nontumorigenic or radial growth phase (RGP) which presents clinically as an irregular patch or plaque of variegated pigmentation. Histologically in this step the melanomas may be in situ or microinvasive but are non-tumorigenic (there are no dermal mitoses). In the next step, the vertical growth phase (VGP), the lesional cells have acquired the capacity for proliferation in the dermis. A clinically evident tumor mass is usually formed (tumorigenic melanoma which may be mitogenic or non-mitogenic), often within the confines of an antecedent RGP constituting a tumor within a plaque. In occasional cases the lesion is nontumorigenic but there are dermal mitoses (mitogenic but nontumorigenic melanoma). Tumorigenic or mitogenic melanomas may have competence for metastasis, while this is extraordinarily rare in the nontumorigenic nonmitogenic RGP melanomas (14). The RGP plaque is seen histologically at the edges of the VGP tumor as a “lateral” or “horizontal” component. Three major clinicopathologic types of cutaneous radial growth phase in situ or microinvasive melanoma are recognized: the (1) superficial spreading or pagetoid, (2) lentigo maligna, and (3) acral lentiginous types. A fourth type of melanoma is defined by the lack of a discernible adjacent radial growth phase component. This is termed (4) nodular melanoma, and is discussed in Section VI B.3. Similar lesions occur in mucosal sites; when a radial growth phase is present it is commonly lentiginous.

**HISTOPATHOLOGY.** Melanocytic nevi are defined and recognized by the presence of nevus cells, which, even though they are melanocytes, differ from ordinary melanocytes by being arranged at least partially in clusters or “nests,” by having a tendency toward rounded rather than dendritic cell shape, and by a propensity to retain pigment in their cytoplasm rather than to transfer it to neighboring keratinocytes. Although a histologic subdivision of nevi into junctional, compound, and intradermal nevi is generally accepted, it should be realized that these are transitional stages in the “life cycle” of nevi, which start out as junctional nevi and, after having become intradermal nevi, undergo involution, likely through a process of senescence (15). The lentigo simplex is regarded as an early or evolving form of melanocytic nevus. It has the clinical appearance of a small lenticulate or lens-shaped pigmented spot (hence the term “lentigo”), and is characterized histologically by the presence of single melanocytes arranged in contiguity along elongated rete ridges. The lack of nests at the histologic level distinguishes a lentigo from a nevus. The lentiginous pattern is seen in the common lentiginous junctional nevus, in which nevus cells in nests are present in combination with the “lentiginous pattern” just described. Dysplastic nevi also exhibit a partially lentiginous, but predominantly nested architecture. They are larger (greater than 5 mm in histologic section diameter) and there is cytologic atypia affecting randomly scattered nevus cells. Individuals with clinically and/or histologically dysplastic nevi are at increased risk of developing melanoma (16–18).

The lentiginous pattern of proliferation is also seen in the “lentiginous” forms of melanoma, in which in contrast to nevi the lesional cells are uniformly atypical, and
the pattern is less well organized than in nevi, often with haphazard proliferation of keratinocytes resulting in irregular thickening and thinning of the epidermis. In the most common form of melanoma, the superficial spreading type, the pattern of proliferation is termed “pagetoid” with lesional cells extending singly and in groups up into the keratinocytic epithelium, which as in lentiginous melanomas tends to be irregularly thickened and thinned. Some degree of pagetoid proliferation, often slight, is usually present in the lentiginous melanomas as well, and pagetoid proliferation may also be seen on occasion in benign nevi, especially Spitz nevi (sections IID2 and VIB3), and pigmented spindle cell nevi (see below). The lentiginous, pagetoid and nested patterns, as well as the degree of pigmentation, and the presence of actinic elastosis and also other readily recognizable histologic, clinical, and epidemiologic factors have been linked to the prevalence of mutations of BRAF and NRAS in melanomas (19); other oncogenes are in the process of categorization, and may be amenable to targeted therapy for metastatic melanoma.

Junctional nevi including dysplastic nevi may exhibit an irregularly thickened epidermis but more often they tend to have regularly elongated rete ridges and are discussed in a later section (IIC.1). The pigmented spindle cell nevus of Reed is a lesion that often has a rather irregularly thickened rete pattern, and is discussed here as a prototype. In situ or microinvasive melanomas of the superficial spreading and acral lentiginous types also tend to have an irregularly thickened and thinned epidermis. The former is discussed in the section on pagetoid proliferations (IID.2), while the latter is discussed below.

**Pigmented Spindle Cell Nevus**

**CLINICAL SUMMARY.** The pigmented spindle cell nevus (60), first described by Richard Reed, may be regarded as a variant of the classical Spitz nevus. The lesions are usually 3 to 6 mm in diameter, deeply pigmented, and either flat or slightly raised dome-shaped lesions. Most patients are young adults, and the most common location is on the lower extremities. Because of the heavy pigment and the history of sudden appearance, a clinical diagnosis of melanoma is often suspected clinically. The lesions are generally stable after a relatively sudden appearance and a short-lived period of growth.

**HISTOPATHOLOGY.** The lesion is characterized by its relatively small size and its symmetry, and by a proliferation of uniform, narrow, elongated, spindle-shaped, often heavily pigmented melanocytes at the dermal-epidermal junction. The epidermis tends to be irregularly thickened, and there is hyperkeratosis often with conspicuous melanin pigment in the stratum corneum. The nests of spindle cells are vertically oriented, and tend to blend with adjacent keratinocytes rather than forming clefts as in Spitz nevi. Kamino bodies may be present as in Spitz nevi. In the papillary dermis, the nevus cells lie in a compact cluster pattern, pushing the connective tissue aside. Involvement of the reticular dermis, common in Spitz nevi, is unusual in pigmented spindle cell nevi. Some lesions may show upward epidermal extension of junctional nests of melanocytes, or of single cells in a “pagetoid pattern.” In contrast to superficial spreading melanomas, pigmented spindle cell nevi are smaller, symmetrical, and show sharply demarcated lateral margins. The tumor cells appear strikingly uniform “from side to side.” If lesional cells descend into the papillary dermis, they mature along nevus lines in pigmented spindle cell nevi, in contrast to melanomas. Mitoses may be present in the epidermis in either lesion, but are uncommon in the dermis in pigmented spindle cell nevi. Abnormal mitoses are very uncommon indeed.

**Acral Lentiginous Melanoma**

**CLINICAL SUMMARY.** Acral lentiginous melanoma (ALM) occurs on the hairless skin of the palms and soles and in the ungual and periungual regions, the soles being the most common site (20). In groups such as Asians, Hispanics, Polynesians, and blacks, for whom the overall incidence of melanoma is low, most melanomas are of the acral type. However, the absolute incidence of acral melanoma in these groups is similar to that in Caucasians who have a much higher overall incidence of melanoma. In addition, the genetic profile differs from that of the more common superficial spreading type of melanoma, with cyclin D amplification being a common finding (21, 22). Mutations of Kit are also relatively common having been described in 39% of mucosal, 36% of acral, and 28% of melanomas on chronically sun-damaged skin, but not in any (0%) melanomas on skin without chronic sun damage (23). These considerations suggest that different etiologic factors, probably not involving sunlight, are operative in acral than in other sites. Although the survival rate of patients with acral melanomas in most series is poor, this is probably a result of their typically advanced microstage and/or stage at diagnosis.

Clinically, *in situ* or microinvasive ALM shows uneven pigmentation with an irregular, often indefinite border. The soles of the feet are most commonly involved. If the tumor is situated in the nail matrix, the nail unit may show a longitudinal pigmented band (longitudinal melanonychia), and the pigment may extend onto the nail fold (Hutchinson’s sign). Tumorigenic vertical growth may be heralded by the onset of a nodule, with development of ulceration. However, some acral melanomas may be deeply invasive while remaining quite flat, because the thick stratum corneum acts as a barrier to exophytic growth.

**HISTOPATHOLOGY.** The lesions are termed “lentiginous” because majority of the lesional cells are single and
IIA. Localized Irregular Thickening of the Epidermis

 localized near the dermal–epidermal junction, especially at the periphery of the lesion. Usually, however, some tumor cells can be found in the upper layers of the epidermis, especially near areas of invasion in the centers of the lesions. The histologic picture differs from that of lentigo maligna, because of irregular acanthosis, the lack of elas-tosis in the dermis, and the frequently dendritic character of the lesional cells. Early in situ or microinvasive lesions may show, especially at the periphery, a deceptively benign histologic picture consisting of an increase in basal melanocytes and hyperpigmentation with only focal atypia of the melanocytes. However, in the centers of the lesions, uniform, severe cytologic atypia is usually readily evident. There may be a lichenoid lymphocytic infiltrate that may largely obscure the dermal–epidermal junction, and in some cases this may be so dense as to simulate an inflammatory process. In most of the lesions, both spindle-shaped and rounded tumor cells are observed, and, in many cases, pigmented dendritic cells are prominent. Pigmentation is often pronounced, resulting in the presence

Clin. Fig. IIA2.a. Pigmented spindle cell nevus. A well-circumscribed symmetrical, small, uniformly pigmented lesion which appeared rapidly on the thigh of a young woman, but then remained stable. The dark blue-black color differs from the pink or tan color of most classic Spitz nevi, and may suggest the possibility of melanoma clinically. (W. Witmer).

Fig. IIA2.a. Pigmented spindle cell nevus, low power. These lesions may be entirely within the epidermis (junc-tional) or they may be compound. In the latter case, they tend to be confined to the papillary dermis. In this scanning magnification, the lesion is well circumscribed; there is an abundance of brown pigment, both within the thickened epidermal layer and within the superficial dermis.

Fig. IIA2.b. Pigmented spindle cell nevus, medium power. At higher magnification, this nevus is composed of a proliferation of single and nested uniform melanocytes which contain an abundance of melanin pigment. The nests tend to blend with the surrounding keratinocytes in contrast to the clefting artifact that characterizes classic Spitz nevi.

Fig. IIA2.c. Pigmented spindle cell nevus, high power. The melanocytes are spindled in form and frequently oriented perpendicular to the skin surface. The keratinocytes and the stratum corneum also contain an abundance of melanin pigment and there are numerous melanophages in the superficial dermis.
Clin. Fig. IIA2.b. Acr al lentiginous melanoma. There is an irregular patch of variegated hyperpigmentation in acral skin, including shades of tan, brown, gray-white, red, and blue-black. Although much of this lesion represents the non-tumorigenic radial growth phase, there was an invasive component that extended into the reticular dermis to a depth of 1.4 mm. (W. Witmer).

Fig. IIA2.d. Acr al lentiginous melanoma, low power. This punch biopsy of acral skin could be from the periphery of a lesion of the type illustrated above. A thickened stratum corneum is typical of this site. There is a melanocytic proliferation within the epidermis associated with slight inflammation in the superficial dermis.

Fig. IIA2.e. Acr al lentiginous melanoma, medium power. Within the epidermis, there is a disorganized proliferation of predominantly single but focally clustered heavily pigmented melanocytic cells. Orderly nests are not present in this proliferation. Within the superficial dermis, there often may be a lymphocytic infiltrate and numerous melanophages (not prominent here).

Fig. IIA2.f. Acr al lentiginous melanoma, high power. Higher magnification reveals that the proliferation is almost exclusively of single atypical often dendritic melanocytes mostly in the lower third of the epidermis. This histologic appearance is relatively subtle and may be readily missed; for example, if specimen is examined only at scanning magnification.
of melanophages in the upper dermis and of large aggregates of melanin in the broad stratum corneum. As in lentigo maligna, when tumorigenic vertical growth phase is present, it is often of the spindle cell type and not uncommonly desmoplastic and/or neurotropic. In other instances, the invasive and tumorigenic cells in the dermis may be deceptively differentiated along nevus lines.

Conditions to consider in the differential diagnosis:

1. Junctional nevi
2. Recurrent melanocytic nevi
3. Pigmented spindle cell nevi
4. Junctional and superficial compound Spitz nevi
5. Compound or dermal nevi, papillomatous
6. Junctional or superficial compound dysplastic nevi

In situ or microinvasive melanoma, superficial spreading type
In situ or microinvasive melanoma, acral lentiginous type

IIB. Localized Lesions With Thinning of the Epidermis

A thinned epidermis is characteristic of aged or chronically sun-damaged skin. The epidermis is thinned secondary to diminished number and to decreased size of keratinocytes.

1. With Melanocytic Proliferation
2. Without Melanocytic Proliferation

IIB1. With Melanocytic Proliferation

The epidermis is thinned (atrophic) and there is proliferation of single or small groups of atypical melanocytes, resulting in the localization of melanocytes in contiguity with one another, in the basal layer of the epidermis. Lentigo maligna is a prototypic example.

Clin. Fig. IIB1.a

Clin. Fig. IIB1.b

Fig. IIB1.a

Clin. Fig. IIB1.a. Lentigo maligna melanoma. An elderly woman had a many-year history of an enlarging macule on the ear, with varying shades of brown and irregular borders.

Clin. Fig. IIB1.b. Lentigo maligna melanoma. A longstanding enlarging lesion on the temple region shows variegated colors, large size, a papular component and irregular borders.

Fig. IIB1.a. Lentigo maligna, low power. At scanning magnification, this lesion is very broad and poorly circumscribed, the epidermis is atrophic and many areas show a flattened rete ridge architecture. This lesion has an invasive and tumorigenic component in the right side of the image. (continues)
II. Localized Superficial Epidermal or Melanocytic Proliferations

**Fig. IIB1.b.** Lentigo maligna, medium power. In the basal cell zone, there is a lentiginous proliferation of predominantly single, uniformly atypical melanocytes which locally grow in a confluent or “contiguous” manner. The underlying dermis reveals a broad zone of solar elastosis.

**Fig. IIB1.c.** Lentigo maligna, high power. Higher magnification reveals enlarged, hyperchromatic, and irregular nuclei of the majority of the lesional melanocytic cells (“uniform cytologic atypia”).

**Fig. IIB1.d,e.** Lentigo maligna, medium power. There is a tumorigenic component comprising uniformly atypical cells, quite heavily pigmented in this instance.

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**Lentigo Maligna Melanoma, in Situ or Microinvasive**

**CLINICAL SUMMARY.** Lentigo maligna melanoma (LMM) (24) accounts for about 10% of all melanomas and typically occurs on the chronically exposed cutaneous surfaces of the elderly, most commonly on the face. The genetic mechanisms of development of these lesions appear to be different from those operating in the more common superficial spreading melanomas, often involving NRAS rather than BRAF (33). The lesion evolves slowly over many years, starting as an unevenly pigmented macule that gradually extends peripherally and may attain a diameter of several centimeters. It has an irregular border and, as long as it remains in situ or microinvasive, is not indurated. The color is variegated ranging from light brown to brown, with dark brown, black or gray-white flecks. Fine reticulated lines are usually also present and are helpful in distinguishing the lesions from actinic lentigines.

**HISTOPATHOLOGY.** Although the earliest stages may be subtle, fully evolved lentigo maligna is characterized by contiguous proliferation of lesional melanocytes, occurring in an atrophic, flattened epidermis. This epidermal architectural pattern is in contrast to SSM, where it is irregularly thickened and thinned, or to actinic lentigines and dysplastic nevi, where there is elongation of the rete. Some lesions, termed “nevoid lentigo maligna,” may overlap histologically with dysplastic nevi and are discussed in section IIC. Cytologically, the lesional cells in classic LMM tend to be nevoid to epithelioid and sometimes elongated and spindle-shaped. Their nuclei are atypical, being slightly to moderately, or sometimes more severely enlarged, hyperchromatic, and pleomorphic. This atypia is “uniform” (i.e., present in a majority of the lesional cells), in contrast to dysplastic nevi. Frequently, atypical melanocytes extend along the basal cell layer of hair follicles, often for a considerable distance and frequently extending to the
Localized Superficial Epidermal or Melanocytic Proliferations

II

IIB. Localized Lesions With Thinning of the Epidermis

base of a shave biopsy specimen. There is usually some upward pagetoid extension of atypical melanocytes. Although single cells predominate, some nesting of melanocytes in the basal layer may be observed. The atypical melanocytes within the nests usually retain their spindle shape, and they often “hang down” like raindrops from the interface. The upper dermis, which almost always shows severe elastotic solar degeneration, contains numerous melanophages and a rather pronounced, often bandlike, inflammatory infiltrate. Microinvasion may be demonstrable in these areas of dermal inflammation.

The differential diagnosis of LMM includes lentiginous junctional nevi and dysplastic nevi, and actinic lentigines. All of these lesions are characterized by lentiginous elongation of rete ridges (section IIC), in contrast to the solar atrophy that characterizes the epidermis in the classic pattern of LMM. Junctional nevi exhibit little or no cytologic atypia, and dysplastic exhibit mild to moderate atypia, in contrast to the uniform moderate to severe atypia that characterizes most examples of LMM. Some examples of lesions thought to be in the general category of LMM have preserved rete ridges. These have been termed “nevus lentigo maligna” or “lentiginous melanoma” and are discussed in Section IIC.

Recurrent (“Persistent”) Nevus, Lentiginous Patterns

Clinical Summary. First described by Kornen and Ackerman as “pseudomelanoma,” this relatively common...
phenomenon often follows shave biopsy of a nevus (25). Clinically recurrent hyperpigmentation on biopsy may show histologic changes suggestive of melanoma. Recurrence may follow incomplete removal of a nevus, particularly by a shave biopsy or electrodesiccation, or the nevus may apparently have been completely excised. The pigmentation in recurrent nevi is confined to the region of the scar, and typically presents within a few weeks of the surgical procedure. After this rapid appearance, the pigment is stable. In contrast, recurrent melanoma does not respect the border of the scar, and extends over time into the adjacent skin. Paradoxically, recurrent melanoma occurs more slowly, over months or years, but progresses inexorably.

**HISTOPATHOLOGY.** Although most recurrent nevi are not cytologically atypical, in a few instances they contain atypical melanocytes, both singly and in nests, arranged mainly along the epidermal–dermal junction, but occasionally also extending into the upper dermis and also into the epidermis in a pagetoid pattern (see IID2) (26). The junctional nests are often composed of pigmented epithelioid melanocytes forming irregular nests possibly the result of their growth within an atrophic epidermal layer that interfaces with scar tissue. Deep remnants of the nevus may be seen in the reticular dermis beneath the scar (27). A lymphocytic infiltrate with melanophages may be seen in the upper dermis. Nevus cells in the dermis tend to show evidence of maturation, and the Ki-67 proliferation rate is low (28). However, mitotic figures may occasionally be observed. Distinction from melanoma may be difficult without a pertinent history. However, the presence of fibrosis in the upper dermis and often of remnants of a melanocytic nevus beneath the zone of fibrosis, as well as the sharp lateral demarcation, usually make a correct diagnosis possible. As is true clinically, the recurrent nevus is confined to the epidermis above the scar, while recurrent melanoma may extend into the adjacent epidermis. However, persistent nevus, after a partial biopsy, may also involve skin adjacent to a scar. In this instance, ordinary criteria for the distinction between melanomas and nevi apply. In any problematical case in which the diagnosis is in doubt, the original biopsy should be obtained for review.

**Superficial Atypical Melanocytic Proliferations of Uncertain Significance, Lentiginous Patterns**

Superficial atypical melanocytic proliferations of uncertain significance (SAMPUS) is a descriptive term that may be applied to lesions that exhibit conflicting or borderline features between melanoma and its benign simulants, such as actinic lentigines with atypia, or dysplastic nevi with focal areas of confluent or continuous basal lentiginous proliferation insufficient for a more definitive diagnosis. A differential diagnosis should always be given, so that appropriate definitive therapy can be planned. Lesions that are entirely intraepidermal may be termed “Intraepidermal melanocytic proliferations of uncertain significance” (“IAMPUS”). The term “SAMPUS” is used to reflect the fact that invasion of the dermis, if not accompanied by tumorigenic and/or mitogenic proliferation in the dermis, is not associated with competence for metastasis (14). See also IID2, Page 49. The differential diagnosis for the lesion illustrated below includes a dysplastic nevus or an evolving LMM. Because of the locally recurring potential of the latter, complete

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**Fig. IIB1.h.** **SAMPUS, lentiginous pattern.** There is a lentiginous and nested melanocytic proliferation in sun-damaged skin. The rete ridge patterns are incompletely effaced and focally exaggerated.

**Fig. IIB1.i.** **SAMPUS, lentiginous pattern.** There are increased single cells near the dermal–epidermal junction, with some cells rising above it.
Fig. IIB1.j. SAMPUS, lentiginous pattern. Nested and single cells are present; however, the basal proliferation is not continuous.

Fig. IIB1.k. SAMPUS, lentiginous pattern. In another area, there is a suggestion of continuous and focal pagetoid proliferation. Cytologic atypia is moderate, but relatively uniform.

Fig. IIB2.a. Atrophic actinic keratosis, low power. There is hyperkeratosis with patchy parakeratosis. The underlying epidermis is thin.

Fig. IIB2.b. Atrophic actinic keratosis, medium power. There is slight atypia of basal keratinocytes, with patchy to bandlike lymphocytes usually with plasma cells in the papillary dermis (not seen in this example), and actinic elastosis.

excision is indicated. Because of the risk marker significance of either diagnosis, the patient should be considered for surveillance, especially if there are other clinically atypical nevi or a family or personal history of melanoma.

Conditions to consider in the differential diagnosis:
- melanoma in situ (lentigo maligna type)
- actinic lentigo (atrophic lesions)
- recurrent nevus

IIIB Without Melanocytic Proliferation

The epidermis is thinned without proliferation of keratinocytes or melanocytes. Each melanocyte is separated from the next by several keratinocytes. Atrophic actinic keratosis and porokeratosis (29) are prototypic examples.

Atrophic Actinic Keratosis

(See also IIA.1). Atrophic actinic keratoses lack the epidermal proliferation seen in most lesions, especially in the hypertrophic type.

Porokeratosis

CLINICAL SUMMARY. Porokeratosis (30) is characterized by a distinct peripheral keratotic ridge that corresponds histologically to the cornoid lamella. Although five different forms can be distinguished, disseminated superficial actinic
porokeratosis is by far the most common type. The lesions often are most pronounced in sun-exposed areas and may be exacerbated by exposure to the sun. They present as small patches surrounded only by a narrow, slightly raised, hyperkeratotic ridge without a distinct furrow.

**HISTOPATHOLOGY.** The peripheral, raised, hyperkeratotic ridge shows a keratin-filled invagination of the epidermis. In the prototypic plaque type of porokeratosis, the invagination extends deeply downward at an angle, the apex of which points away from the central portion of the lesion.

Clin. Fig. IIB2.a

Fig. IIB.2.c

Fig. IIB.2.d

**Clin. Fig. IIB2.a.** *Disseminated superficial actinic porokeratosis.* Illustrated here are two of many oval plaques and papules with slightly raised keratotic rims and atrophic centers that developed on sun exposed legs.

**Fig. IIB.2.c.** *Porokeratosis, low power.* On each end of this shave biopsy specimen, there are two cornoid lamellae which can be seen at scanning magnification as discrete foci of parakeratosis. Parakeratotic columns lean toward the center of the lesion.

**Fig. IIB.2.d.** *Porokeratosis, medium power.* The cornoid lamella is characterized by a well-defined stack of parakeratotic keratin which overlies an invagination of the epidermis. Beneath the parakeratotic column, there is focal loss of the granular cell layer and dyskeratosis.

**Fig. IIB.2.e.** *Porokeratosis, high power.* Porokeratosis may be associated with a patchy to bandlike lichenoid mononuclear cell infiltrate in the superficial dermis, though not in this example.
In the center of this keratin-filled invagination rises a parakeratotic column, the so-called cornoid lamella, representing the most characteristic feature of porokeratosis of Mibelli. In the epidermis beneath the parakeratotic column, the keratinocytes are irregularly arranged, and some cells possess an eosinophilic cytoplasm as a result of premature keratinization. Usually no granular layer is found at the site at which the parakeratotic column arises, but elsewhere the keratin-filled invagination of the epidermis has a well-developed granular layer. The histologic changes in disseminated superficial actinic porokeratosis are similar but less pronounced, the central invagination being rather shallow.

**Conditions to consider in the differential diagnosis:**

- atrophic actinic keratosis
- porokeratosis

### LOCALIZED LESIONS WITH ELONGATED RETE RIDGES

Elongation of the rete ridges without melanocytic proliferation in a localized lesion is termed papillomatosis in which each papilla may be likened to a glove of epidermis covering a finger of stroma. Elongated rete with melanocytic proliferation and predominance of single cells over nests is termed a “lentiginous” pattern. This pattern may be seen in lentiginous junctional and compound nevi, in dysplastic nevi and in the “lentiginous” melanomas. However, in melanomas, the epidermal rete pattern is more often irregularly thickened and thinned than regularly elongated.

1. With Melanocytic Proliferation
2. Without Melanocytic Proliferation

#### IIC1 With Melanocytic Proliferation

The epidermal rete ridges are elongated, and within these rete, there is melanocytic proliferation. Actinic lentigo, lentigo simplex, lentiginous junctional nevus, and dysplastic nevus are prototypic (31).

**Actinic Lentigo**

**CLINICAL SUMMARY.** Lentigines are macular hyperpigmentations in which histologically the number of epidermal melanocytes is increased, but the nests of melanocytes that define nevus cells are not present. In actinic lentigo, which arises most frequently in older

![Clin. Fig. IIC1.a](image1.png)

**Clin. Fig. IIC1.a.** Actinic lentigo. A 1 cm, rather irregular patch of slightly variegated hyperpigmentation in a background of chronic solar damage.

![Fig. IIC1.a](image2.png)

**Fig. IIC1.a.** Actinic lentigo, low power. At scanning magnification, there is uniform elongation of rete ridges with hyperpigmentation. Significant inflammation is not present.

![Fig. IIC1.b](image3.png)

**Fig. IIC1.b.** Actinic lentigo, medium power. Melanocytes are slightly increased in number, but in contrast to lentigo maligna, the rete ridges are elongated and there is no contiguous proliferation of uniformly atypical melanocytes.
adults, there are usually multiple lesions with a predilection to areas of sun exposure. They are relatively large compared to simple lentigines (usually about 5 mm but with some lesions greater than 1 cm), rather asymmetrical, and poorly-circumscribed macules that are variably pigmented in shades of brown usually without black. When the asymmetry and pigmented variegation are more prominent, biopsy may be necessary to distinguish these lesions from lentigo maligna. Actinic lentigines are the prototypic “freckles” in individuals with severe solar damage; they are important markers of melanoma risk and (like simple ephelids) are associated with polymorphisms of the MC1R gene which has been termed the “freckle gene” and is involved in regulation of melanin synthesis (32). They may also be associated with mutations of genes that are also involved in seborrheic keratoses, supporting the notion that there may be relationships between these conditions (33).

**HISTOPATHOLOGY.** The findings include, in a relatively large lesion, slight or moderate elongation of the rete ridges, with an obvious increase in the amount of melanin in both the melanocytes and the basal keratinocytes, and often with the presence of melanophages in the upper dermis. In some instances, melanin is also present in the upper layers of the epidermis and stratum corneum. Melanocytes usually appear somewhat increased in number, as has been demonstrated in careful quantitative studies.

**Lentigo Simplex**

**CLINICAL SUMMARY.** Lentigines are macular hyperpigmentations in which histologically the number of epidermal melanocytes is increased, but the nests of melanocytes that define nevus cells are not present. In lentigo simplex, which arises most frequently in childhood, there are usually only a few scattered lesions without predilection to areas of sun exposure. They are small (usually 2–3 mm), symmetrical, and well-circumscribed macules that are evenly pigmented but vary individually from brown to black. The definition is a histologic one, and clinically, lentigo simplex is indistinguishable from a junctional nevus.

**HISTOPATHOLOGY.** The findings include, in a small lesion usually 2 to 3 mm or less in diameter, a slight or moderate elongation of the rete ridges, an increase in the concentration of melanocytes in the basal layer, an increase in the amount of melanin in both the melanocytes and the basal keratinocytes, and the presence of melanophages in the upper dermis. In some instances, melanin is also present in the upper layers of the epidermis and stratum corneum. Because of the existence of these transitional forms, the lentigo simplex is regarded as a form of evolving melanocytic nevus. In a recent study, lentigo simplex lesions lacked the BRAF mutations that characterize most nevi, challenging but not necessarily refuting this presumption (34).

**Lentiginous Junctional Nevus**

**CLINICAL SUMMARY.** The term “lentigo” derives from the clinical appearance of a small lenticulate or lens-shaped pigmented spot. The prototype of the lentiginous pattern is seen in the lentigo simplex which regarded as an early or evolving form of melanocytic nevus. In lesions otherwise clinically characteristic of lentigo simplex, small nests of nevus cells may be present at the epidermal–dermal junction, especially at the lowest pole of rete ridges.

Clin. Fig. IIC1.b  
**Clin. Fig. IIC1.b.** *Lentigo simplex.* A 2 to 3 mm uniform patch of brown or dark brown to black hyperpigmentation, in normal or sun-damaged skin.

Fig. IIC1.c  
**Fig. IIC1.c.** *Lentigo simplex, medium power.* In contrast to actinic lentigo, melanocytes are obviously increased at the dermal–epidermal junction and are at least focally contiguous with one another. In contrast to a dysplastic nevus or a lentigo maligna, the lesion is small and there is no significant cytologic atypia.
These lesions then combine features of a lentigo simplex and a junctional nevus (lentiginous junctional nevus, or “jentigo”). If nevus cells are also present in the dermis but there is a junctional component that extends beyond the dermal component, the term “lentiginous compound nevus” may be used. Lentiginous junctional and compound nevi are typically in the 2- to 5-mm size range; lesions larger than 5 mm are often dysplastic nevi.

**HISTOPATHOLOGY.** Although the term “lentigo” is originally of clinical derivation, it has taken on a histologic connotation defined by the presence of single melanocytes arranged in contiguity about elongated rete ridges, as in the lentigo simplex. The lack of nests at the histologic level distinguishes a lentigo from a nevus. In a lentiginous junctional nevus, nevus cells lie in well-circumscribed nests either entirely within the lower epidermis or bulging downward into the dermis but still in contact with the epidermis. In addition, varying numbers of diffusely arranged single nevus cells are seen in the lowermost epidermis, especially in the basal cell layer. The rete ridges tend to be uniformly elongated, completing the “lentiginous” pattern. Dysplastic nevi also exhibit a lentiginous architecture, but they are larger (greater than 4–5 mm in histologic section) and there is cytologic atypia affecting randomly scattered nevus cells. Lesions smaller than 4 mm that exhibit lentiginous architecture and cytologic atypia are occasionally encountered. We sign these lesions out descriptively, with a note that additional evaluation of the patient may be indicated to rule out the possibilities of other clinically atypical nevi, or of a family or personal history of melanoma. If these or other risk factors for melanoma are found, then periodic surveillance of the patient may be indicated, depending on the magnitude of the risk as judged clinically.

**Nevus Spilus**

**CLINICAL SUMMARY.** The *speckled lentiginous nevus*, or *nevus spilus*, consists of a light brown patch or band present from the time of birth that in childhood becomes dotted with small, dark brown macules.

**HISTOPATHOLOGY.** The light brown patch or band shows basal hyperpigmentation of keratinocytes similar to a cafe au lait macule. The speckled areas show junctional nests of nevus cells at the lowest poles of some of the rete ridges and diffuse junctional activity and dermal aggregates of nevus cells, similar to a lentigo simplex.

**Junctional or Superficial Compound Dysplastic Nevi**

**CLINICAL SUMMARY.** Dysplastic nevi (35) form, clinically and histologically, a continuum extending from a common nevus to a superficial spreading melanoma. They may be located anywhere on the body but are most common on the trunk. A clinically dysplastic nevus is defined...
II. Localized Superficial Epidermal or Melanocytic Proliferations

by (1) the presence of a macular component either as the entire lesion or surrounding a papular center; (2) large size, exceeding 5 mm; (3) irregular or ill-defined “fuzzy” border; and (4) irregular pigmentation within the lesion. Dysplastic nevi are most important as markers of individuals at increased risk for melanoma (30,36); they are also potential precursors of melanoma; however, most are stable lesions and wholesale excision of them for prevention of melanoma is not recommended. Most dysplastic nevi are excised in order to rule out melanoma histologically. The latter are arranged as single cells and in nests whose long axes tend to lie parallel to the epidermal surface and that tend to form “bridges” between adjacent rete. The melanocytes in the junctional nests are frequently spindle-shaped, but they may be large and epithelioid with abundant cytoplasm containing fine, dusty melanin particles. If the lesion is compound, nests of melanocytes in the papillary dermis show evidence of maturation with descent into the dermis. In these compound dysplastic nevi, the

Clin. Fig. IIC1.d. Nevus spilus. This usually congenital lesion presents as a light brown patch in which speckled brown macules appear in childhood.

Fig. IIC1.f. Nevus spilus, low power. Scanning magnification may seem to show only a single small melanocytic lesion confined to the epidermis, or to the epidermis and papillary dermis. Depending on the size of the biopsy (which may be submitted to rule out melanoma), there may be more than one of these small lesions. Between the lesions, the epidermis is hyperpigmented, but this may not be apparent histologically unless the normal skin at the edge of the lesion is included for comparison.

Fig. IIC1.g. Nevus spilus, medium power. In the focal lesions, there is elongation of rete ridges and a very sparse superficial lymphocytic infiltrate. The appearances are identical to a lentiginous nevus.

Fig. IIC1.h. Nevus spilus, high power. Higher magnification reveals a lentiginous proliferation of single and nested melanocytes along the dermal–epidermal junction. Atypia of melanocytes is not seen.

HISTOPATHOLOGY. Architectural features include a “lentiginous” pattern of elongation of the rete ridges with an increase in the number of melanocytes. The latter are arranged as single cells and in nests whose long axes tend to lie parallel to the epidermal surface and that tend to form “bridges” between adjacent rete. The melanocytes in the junctional nests are frequently spindle-shaped, but they may be large and epithelioid with abundant cytoplasm containing fine, dusty melanin particles. If the lesion is compound, nests of melanocytes in the papillary dermis show evidence of maturation with descent into the dermis. In these compound dysplastic nevi, the
Localized Lesions With Elongated Rete Ridges

intraepidermal component extends by definition beyond the lateral border of the dermal component, forming a “shoulder” to the lesion histologically, and a “targetlike” or “fried-egg” pattern clinically. A patchy lymphocytic infiltrate is present in the dermis. “Pagetoid” extension of melanocytes into the epidermis is absent or slight and is limited to the lowermost layers. Cytologically, in addition to the lentiginous melanocytic hyperplasia, melanocytic nuclear atypia is required for the diagnosis, characterized by irregularly shaped, large, hyperchromatic nuclei in some melanocytes. Most atypical melanocytes lie singly or in small groups, and the atypia involves only a minority of the lesional cells (“random” cytologic atypia). Focal extension of atypical-appearing melanocytes into the lower spinous layer may occur, but if this is prominent, transformation into melanoma in situ may have occurred.

Nevoid Lentigo Maligna

CLINICAL SUMMARY. This term may be attributed to Kossard who described in 1997 a group of cases of nevoid melanomas characterized by small cells and a nevoid appearance (37). Rete ridges tend to be preserved, and nesting may be prominent, at least in the centers of these lesions. Similar lesions have been more recently described as “lentiginous melanoma,” emphasizing that this is a histologic pattern of melanoma to be distinguished from lentiginous nevus (38). In yet another useful study, 43% of

Clin. Fig. IIC1.e

Clin. Fig. IIC1.f

Fig. IIC1.i

Clin. Fig. IIC1.e. Dysplastic nevus. This pigmented lesion fulfills criteria for a dysplastic nevus: (a) macule with indefinite edge; (b) size >5 mm; (c) irregular border; and (d) irregular pigmentation.

Clin. Fig. IIC1.f. Dysplastic nevi. This young patient has been followed since childhood. She developed multiple dysplastic nevi around the age of puberty, since this picture was taken she has developed several primary melanomas, all in the curable non-tumorigenic or radial growth phase stage of evolution.

Fig. IIC1.i. Compound dysplastic nevus, low power. At scanning magnification, there is a broad compound nevus. Near the center of the lesion the nevus is compound with both an epidermal and dermal component. The “shoulders,” at each periphery of the lesion, are composed only of a junctional component.

Fig. IIC1.j. Compound dysplastic nevus, low power. The epidermal rete ridges are uniformly elongated. Nests of melanocytes form “bridges” between these elongated rete. The dermal component of the lesion is at the left of this image, and the junctional component extends to the right, forming the “shoulder.”
II. Localized Superficial Epidermal or Melanocytic Proliferations

in situ lentigo maligna lesions had predominant dysplastic nevus-like features (39). It was concluded that large pigmented lesions on sun-damaged skin and elderly individuals should warrant consideration of LMM diagnosis even in the setting of dysplastic nevus like features histologically. Biopsies especially from the centers of the lesions could lead to a mistaken diagnosis of a dysplastic nevus, leading to the possibility of residual melanoma in situ, which could persist, recur, and progress to a more significant lesion. At least at the periphery, the pattern may be predominantly that of single cells in a continuous distribution along the dermoepidermal junction, more typical of lentigo maligna.

Conditions to consider in the differential diagnosis:
- lentigo simplex
- nevus spilus
Localized Superficial Epidermal or Melanocytic Proliferations

IICT. Localized Lesions With Elongated Rete Ridges

Fig. IIC1.o  Nevoid lentigo maligna, low power. This lesion is comparatively broad, variably cellular, and is located in skin with moderate to severe actinic elastosis.

Fig. IIC1.p  Nevoid lentigo maligna, low power. At the left of this image, the lesion is comprised of small cells, arranged about the tips and sides of elongated rete ridges, without continuous proliferation between the rete at least in all areas. To the right, there is a larger cell type which is uniformly atypical and predominantly nested.

Fig. IIC1.q  Nevoid lentigo maligna, low power. At the far periphery of the lesion, to the right of the image, there are two nests which tend to “hang down” from the interface in a “droplet-like” pattern. Elsewhere, similar nests are unevenly scattered along the interface, admixed with some single cells.

Fig. IIC1.r  Nevoid lentigo maligna, low power. A high-power view of the periphery of the lesion, demonstrating moderate to severe uniform atypia in the cells within the nests.

Fig. IIC1.s  Nevoid lentigo maligna, high power. The nests are somewhat more closely packed, and cytologic atypia is again demonstrated. It might be tempting to consider a field such as this to represent some form of dysplasia; however, a cautious approach is appropriate in sun-damaged skin of an elderly subject. The most appropriate diagnosis for this case, in our opinion, is nevoid lentigo maligna (melanoma in situ, lentigo maligna type); however, alternatively it might be designated as an “intraepidermal atypical melanocytic proliferation of uncertain significance,” with a differential diagnosis including in situ melanoma, and a recommendation for appropriate management. This lesion was narrowly re-excised but nevertheless recurred locally 3 years later.
II. Localized Superficial Epidermal or Melanocytic Proliferations

lentiginous junctional nevus
junctional nevus
dysplastic nevus
Meyerson’s nevus
nevoid lentigo maligna
acral lentiginous melanoma
mucosal-lentiginous melanoma

IIC2 Without Melanocytic Proliferation

The epidermis is thickened (acanthotic). Melanocytes are normal as are keratinocytes. The only change is acanthosis. Epidermal nevi are prototypic (40). The differential diagnosis includes acanthosis nigricans.

Epidermal Nevus

CLINICAL FEATURES. Epidermal nevi, or verrucous nevi (“nevus verrucosus”), may be either localized or systematized. In the localized type, which is present usually but not invariably at birth, only one linear lesion is present, often referred to as nevus unius lateris. It consists of closely set, papillomatous, hyperkeratotic papules. In the systematized type, papillomatous hyperkeratotic papules often in a linear configuration are present as many lesions. These lesions are often linear in a parallel arrangement, particularly on the trunk. The term ichthyosis hystrix is occasionally used, perhaps unnecessarily, for instances of extensive bilateral lesions. Linear epidermal nevi may occasionally be associated with skeletal deformities and central nervous system deficiencies, such as mental retardation, epilepsy, and neural deafness, and, rarely, with basal or squamous cell carcinoma. They may also be associated with the distinctive pattern of epidermolytic hyperkeratosis (see also IB1). Various epidermal nevus syndromes exist and have been recently reviewed in terms of their molecular pathogenesis (41).

HISTOPATHOLOGY. Nearly all cases of the localized type of linear epidermal nevus and some cases of the systematized type show the histologic picture of a benign papilloma. One observes considerable hyperkeratosis, papillomatosis, and acanthosis with elongation of the rete ridges resembling seborrheic keratosis, except that the lesions are usually considerably larger. In other instances, papillomatosis may be inconspicuous and orthokeratotic hyperkeratosis may be the major finding.

Seborrheic Keratoses

See also Section IIE2

Acanthosis Nigricans

CLINICAL SUMMARY. There are eight types of acanthosis nigricans malignant (42); benign inherited, obesity-associated, and syndromic which are often associated with insulin resistance syndromes (43), acral, unilateral, drug-induced, and mixed. Clinically, acanthosis nigricans presents papillomatous brown patches, predominantly in the intertriginous areas such as the axillae, the neck, and the genital and submammary regions. In extensive cases of the malignant type, mucosal surfaces, such as the mouth, the vulva, and the palpebral conjunctivae, may be involved. In the acral type, there is velvety hyperpigmentation of the dorsa of the hands and feet.

HISTOPATHOLOGY. The lesions show hyperkeratosis and papillomatosis but only slight, irregular acanthosis and usually no hyperpigmentation. Thus, the term
Localized Lesions With Elongated Rete Ridges

**Acanthosis nigricans** has little histologic justification. In a typical lesion, the dermal papillae project upward as fingerlike projections. The valleys between the papillae show mild to moderate acanthosis and are filled with keratotic material. Horn pseudocysts can occur in some cases. The epidermis at the tips of the papillae and often also on the sides of the protruding papillae appears thinned. Slight hyperpigmentation of the basal layer is demonstrable with silver nitrate staining in some cases but not in others. The brown color of the lesions is caused more by hyperkeratosis than by melanin.

**Conditions to consider in the differential diagnosis:**
- epidermal nevi
- psoriasis
- lichen simplex chronicus
- acanthosis nigricans
- actinic lentigo

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**Fig. IIC2.b.** *Epidermal nevus, medium power.* The epidermis shows varying degrees of acanthosis and papillomatosis with hyperkeratosis. Frequently, there is pseudohorn cyst formation resembling a seborrheic keratosis.

**Fig. IIC2.c.** *Epidermal nevus, high power.* Epidermal maturation is essentially normal. Pigment is variable. The papillary dermis may show fibroplasia with little or no inflammation.

**Fig. IIC2.d.** *Seborrheic keratosis, low power.* Compared to epidermal nevi, seborrheic keratoses tend to be more sharply circumscribed lesions that lie above the plane of the adjacent epidermal surface.

**Fig. IIC2.e.** *Seborrheic keratosis, medium power.* Seborrheic keratoses are composed of basaloid cells that show squamous differentiation only near the surface. In an epidermal nevus, the pattern of normal keratinocytic maturation from a single basal layer is more closely maintained (Figures IIC2.b & c).
II. Localized Superficial Epidermal or Melanocytic Proliferations

LocEDILsIThPAGETID1ePIThELIAL 

A neoplastic proliferation of one cell type distributed as single cells or nests within a benign epithelium is termed “Pagetoid” after Paget’s disease of the breast (mammary carcinoma cells proliferating in skin of the nipple).

1. Keratinocytic Proliferations
2. Melanocytic Proliferations
3. Glandular Epithelial Proliferations
4. Lymphoid Proliferations

IID1 Keratinocytic Proliferations

The epidermis has atypical keratinocytes scattered within mature epithelium at all or multiple levels; there is loss of normal maturation. Mitoses are increased and there may be individual cell necrosis. Pagetoid squamous cell carcinoma in situ is a prototypic example.

Pagetoid Squamous Cell Carcinoma in Situ

(See also IIA1). An occasional finding in squamous cell carcinoma in situ [Bowen’s disease (21)] is vacuolization of the cells, especially in the upper portion of the epidermis. Also, in exceptional cases, multiple nests of atypical cells are scattered through a normal epidermis, sometimes with sparing of the basal cell layer.

Clonal Seborrheic Keratosis

In the clonal, or nesting, type of seborrheic keratosis, well-defined nests of cells are located within the epidermis (44). In some instances, the nests resemble foci of basal cell epithelioma, since the nuclei appear small and dark-staining and intercellular bridges are seen in only a few areas. In other instances of clonal seborrheic keratosis, the nests are composed of fairly large cells showing distinct intercellular bridges, with the nests separated from one another by strands of cells exhibiting small, dark nuclei.

Clin. Fig. IIC2.b. Acanthosis nigricans. An elderly woman had an explosive development of velvety, hyperpigmented plaques in the intertriginous areas. She had metastatic endometrial carcinoma.

Fig. IIC2.f. Acanthosis nigricans, medium power. There is papil-lomatosis with prominent hyperkeratosis which is predomi-nantly orthokeratotic.

Fig. IIC2.g. Acanthosis nigricans, high power. In contrast to a seborrheic keratosis, acanthosis nigricans fails to reveal signifi-cant acanthosis of the epidermis.
Localized Superficial Epidermal or Melanocytic Proliferations

Fig. IID1.a. Pagetoid squamous cell carcinoma in situ, low power. The epidermis is irregularly thickened and thinned, with effaced rete ridges, and a parakeratotic scale-crust. There is a dense bandlike lympho-plasmacytic infiltrate in the dermis.

Fig. IID1.b. Pagetoid squamous cell carcinoma in situ, medium power. Large pale cells are present among more compact eosinophilic keratinocytes.

Fig. IID1.c. Pagetoid squamous cell carcinoma in situ, high power. At high magnification, a search for desmosomes will usually reveal their presence between the neoplastic cells and their less atypical neighbors, establishing the diagnosis of squamous cell carcinoma in situ, and ruling out melanoma and Paget's disease.

Fig. IID1.d. Clonal seborrheic keratosis, low power. In contrast to a squamous cell carcinoma in situ, this lesion shows uniform acanthosis of the epidermis with a predominantly basket-weave stratum corneum.

Fig. IID1.e. Clonal seborrheic keratosis, medium power. Within a thickened epidermal layer, there are "clones" composed of aggregates of bland-appearing epithelial cells clustered within the epidermis.

Fig. IID1.f. Clonal seborrheic keratosis, medium power. Lack of features such as cytologic atypia, mitotic figures, and an atypical parakeratotic scale help differentiate this lesion from a squamous cell carcinoma in situ with a clonal pattern.
II. Localized Superficial Epidermal or Melanocytic Proliferations

Conditions to consider in the differential diagnosis:
- pagetoid squamous cell carcinoma in situ
- clonal seborrheic keratosis
- intra-epithelial epithelioma (Borst-Jadassohn)

Melanocytic Proliferation

Atypical melanocytes are seen at all levels within the otherwise mature but often hyperplastic epidermis. Melanoma in situ or microinvasive (superficial spreading type) is prototypic (45). Pigmented spindle cell nevus (46) is an important differential.

**Melanoma in Situ or Microinvasive, Superficial Spreading Type**

**CLINICAL SUMMARY.** The lesions may occur on exposed skin but are rather more commonly found on intermittently exposed skin and are rare on unexposed skin. The most frequently involved sites are the upper back, especially in men, and the lower legs in women. The lesions are slightly or definitely elevated, with palpable borders and irregular, partly arciform outlines. There is often variation in color that includes not only tan, brown, and black, but also pink, blue, and gray. Gray-white areas may be observed at sites of spontaneous regression.

 Clin. Fig. IID2.a

**Clinical Fig. IID2.a.** Melanoma in situ, superficial spreading type. A slowly enlarging pigmented lesion on the chest of a middle-aged male. The asymmetry, irregular notched border, color variegation, and size raise suspicion for melanoma.

**Fig. IID2.a.** Superficial spreading melanoma in situ, medium power. There is a broad and poorly circumscribed lesion characterized by an increased number of uniformly enlarged melanocytes in the epidermis. Strictly in situ lesions such as this may have little or no dermal inflammation.

**Fig. IID2.b.** Superficial spreading melanoma in situ, medium power. There is extensive pagetoid (or “buckshot”) scatter of lesional cells into the epidermis. The cells have a uniform appearance (“uniform cytologic atypia”).

**Fig. IID2.c.** Superficial spreading melanoma in situ, high power. Cytologic atypia, characterized here by nuclear enlargement, hyperchromatism, and irregularity, may be moderate, as here, or severe.
Fig. IID2.d. *Superficial spreading melanoma, invasive, low power.* The epidermis is irregularly thickened with distortion of the rete ridge pattern. There is a perivascular to diffuse lymphocytic infiltrate in the papillary dermis.

Fig. IID2.e. *Superficial spreading melanoma, invasive, medium power.* Enlarged epithelioid melanocytes are scattered in a “pagetoid” or “buckshot scatter” pattern among keratinocytes. A few clusters of lesional cells are seen in the papillary dermis, constituting invasion.

Fig. IID2.f. *Superficial spreading melanoma, invasive, high power.* The lesional cells are large, with abundant cytoplasm and, often, finely-divided cytoplasmic melanin pigment. Their nuclei are uniformly enlarged, somewhat hyperchromatic, and have prominent nucleoli.

Fig. IID2.g. *Recurrent nevus phenomenon, lentiginous and pagetoid pattern, low power.* At scanning magnification, one can see a flattened rete ridge architecture, a feature which is a clue to previous trauma or biopsy. There is a proliferation of melanocytes in the epidermis which does not extend beyond the lateral border of the scar.

Fig. IID2.h. *Recurrent nevus phenomenon, lentiginous and pagetoid pattern, medium power.* At the dermal–epidermal interface, there is a lentiginous and focally pagetoid proliferation of single and nested, heavily pigmented melanocytes, which overlie a zone of scar tissue in the superficial dermis. The lesional cells may be large with enlarged nuclei and prominent nucleoli, single cells may be prominent, and there may be cells extending above the dermal–epidermal junction. These features taken together may suggest melanoma, but the proliferation does not extend beyond the lateral border of scar, and the pre-existing nevus on review is benign. (continues)
II. Localized Superficial Epidermal or Melanocytic Proliferations

Microinvasion may be clinically inapparent, but the onset of tumorigenic vertical growth is indicated by the development of a papule followed by nodularity and sometimes ulceration, the latter usually being a late feature.

**Histopathology.** Architectural pattern features include the large diameter of the lesions, poor circumscription (the last cells at the edge of the lesion are often small, single, and scattered), and asymmetry (one half of the lesion does not mirror the other half). The epidermis is irregularly thickened and thinned with distortion of the rete ridge pattern. Rather uniformly rounded, large melanocytes are present near the dermo-epidermal junction and usually also scattered in a pagetoid pattern.

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**Fig. IID2.i** Junctional Spitz nevus, low power. In contrast to malignant melanoma, this lesion is small and symmetrical.

**Fig. IID2.j** Junctional Spitz nevus, high power. Pagetoid proliferation of melanocytes is not uncommon in Spitz nevi, especially in young patients. Globoid eosinophilic globules (Kamino bodies) are characteristic of classic Spitz nevi, especially when confluent as here. They may occasionally be seen also in melanomas.

**Fig. IID2.k** Junctional Spitz nevus, high power. Clefting artifact between the nests of Spitz nevus cells and the adjacent keratinocytes is a characteristic feature.

**Fig. IID2.l** Junctional Spitz nevus, high power. The Spitz nevus is composed of large nevoid melanocytes with abundant amphophilic cytoplasm and large nuclei with prominent eosinophilic nucleoli.
Localized Lesions With Pagetoid Epithelial Proliferation

**Fig. IID2.m.** SAMPUS, pagetoid pattern. This lesion, from the wrist of a 15-year-old girl, is relatively small but not especially well circumscribed or symmetrical at scanning magnification.

**Fig. IID2.n.** SAMPUS, pagetoid pattern. At the periphery of the lesion, the last cells are single rather than nested (poor circumscription).

**Fig. IID2.o.** SAMPUS, pagetoid pattern. The lesional cells are large spindle and/or epithelioid cells, with abundant amphophilic cytoplasm, characteristic of the cells of Spitz tumors/nevi. However, there are no Kamino bodies.

**Fig. IID2.p.** SAMPUS, pagetoid pattern. There is pagetoid extension of the lesional cells focally to the stratum corneum, raising the question of melanoma in situ (MIS), superficial spreading type. However, the differential diagnosis also includes a pagetoid Spitz tumor or even a severely dysplastic nevus. This lesion should be managed taking into consideration the locally recurring potential of MIS and also the risk marker significance of a dysplastic nevus or melanoma. Thus, a re-excision should be considered and the patient's other risk factors should be considered for evaluation of the need for follow-up of her nevi.
throughout the epidermis. The large cells lie in nests and singly. The nests tend to vary a good deal in size and shape. As previously discussed, the pagetoid and nested patterns in this form of melanoma tend to be associated with the presence of mutations of the BRAF oncogene (33). Dermal melanophages and a dermal infiltrate are usually present except in some strictly in situ lesions. The lymphocytic infiltrate is typically dense and bandlike, especially in invasive lesions. Cytologically, the lesional cells are rather uniform and have atypical, hyperchromatic nuclei and abundant cytoplasm containing varying amounts of melanin that often consists of small, “dusty” particles. This “uniform cytologic atypia” is of considerable diagnostic importance and contrasts with the random atypia of dysplastic nevi. Distinction from a dysplastic nevus is based on greater size, asymmetry, and cellularity, the presence of high-level and extensive pagetoid proliferation or of contiguous basilar proliferation of uniformly atypical cells, the presence of moderate to severe and uniform cytologic atypia, and the presence of lesional cell mitoses in some melanomas.

**Recurrent Nevus (Pseudomelanoma), Pagetoid Patterns**

The atypical proliferation in these lesions may be lentigous, simulating a lentiginous melanoma as discussed in section IIB1, or pagetoid, simulating superficial spreading melanoma.

**Junctional Spitz Tumor (Nevus) With Pagetoid Proliferation**

Although most Spitz tumors are compound nevi that involve the reticular dermis (discussed in section VIB3), junctional examples are also not uncommonly observed, especially in young children but also occasionally in adults. Some cases are associated with pagetoid proliferation of the lesional cells in the epidermis (47). When this is present, the differential diagnosis of melanoma should always be considered and multiple histologic attributes should be evaluated including size, symmetry, age of the patient, presence of eosinophilic globules (Kamino bodies, depicted in Figure IID2.i) and predominance of nests or single cells. Occasionally in adults, and more commonly in children, pagetoid proliferation of Spitz nevus cells in the epidermis may be seen.

**Superficial/Intraepidermal Atypical Melanocytic Proliferations of Uncertain Significance, Pagetoid Patterns**

SAMPUS is a descriptive term that may be applied to lesions that exhibit conflicting or borderline features between melanoma and its benign simulants, such as pagetoid Spitz nevi, or dysplastic nevi with a few pagetoid cells insufficient for a more definitive diagnosis. A differential diagnosis should always be given, so that appropriate definitive therapy can be planned. See also IIB1, page 32. The term “SAMPUS” is used to reflect the fact that invasion of the dermis, if not accompanied by tumorigenic and/or mitogenic proliferation in the dermis, is not associated with competence for metastasis (28).

**Conditions to consider in the differential diagnosis:**
- melanoma in situ (superficial spreading type)
- pigmented spindle cell nevus
- recurrent melanocytic nevus (pseudomelanoma)
- certain Spitz nevi with pagetoid proliferation
- certain acral nevi with pagetoid proliferation

### IID3 Glandular Epithelial Proliferations

Atypical large clear cells with glandular differentiation (mucin production, lumen formation) proliferate in a normally maturing epidermis. Paget's disease (mammary or extra-mammary) is a prototypic example (48,49).

**Paget’s Disease**

**CLINICAL SUMMARY.** The cutaneous lesion in Paget’s disease of the breast begins either on the nipple or the areola of the breast and extends slowly to the surrounding skin. It is always unilateral and consists of a sharply defined, slightly infiltrated area of erythema showing scaling, oozing, and crusting. There may or may not be ulceration or retraction of the nipple. The cutaneous lesion is nearly always associated with underlying mammary carcinoma. Extramammary Paget’s disease, which usually occurs in genital skin in either sex, is similar in its clinical appearance, but is not usually associated with an underlying carcinoma.

**HISTOPATHOLOGY.** In early lesions of Paget’s disease of the breast, the epidermis usually shows only a few scattered Paget’s cells. They are large, rounded cells that are devoid of intercellular bridges and contain a large nucleus and ample cytoplasm. The cytoplasm of these cells stains much lighter than that of the adjacent squamous cells. As the number of Paget’s cells increases, they compress the squamous cells to such an extent that the latter may merely form a network, the meshes of which are filled with Paget’s cells lying singly and in groups. In particular, one often observes flattened basal cells lying between Paget’s cells and the underlying dermis. Although Paget’s cells do not, as a rule, invade the dermis from the epidermis, they may be seen extending from the epidermis into the epithelium of hair follicles.

**Conditions to consider in the differential diagnosis:**
- Paget’s disease (mammary or extra-mammary)
- superficial spreading melanoma
- pagetoid squamous cell carcinoma in situ
- Pagetoid reticulosis
**Clin. Fig. IID3.** Extramammary Paget’s disease. This elderly female presented with a one-year history of an erythematous plaque with scattered erosions on the left labium majus. Work-up for underlying malignancy was negative.

**Fig. IID3.a.** Extramammary Paget’s disease, low power. The epidermis may appear normal or irregularly thickened as here. Even at scanning magnification, large pale cells may be appreciable among otherwise mature keratinocytes.

**Fig. IID3.b.** Extramammary Paget’s disease, medium power. The large neoplastic cells have pale cytoplasm, sometimes with obvious mucin vacuoles. Their nuclei tend to be enlarged and hyperchromatic, often with prominent nucleoli.

**Fig. IID3.c.** Extramammary Paget’s disease, medium power. The stain highlights the glycoprotein constituents of the intracellular mucin contained in the lesional cells, accentuating the “pagetoid pattern” of neoplastic cells scattered among benign epithelial cells. PAS and mucicarmine stains are helpful when the mucin is less obvious than in this H&E section.
II. Localized Superficial Epidermal or Melanocytic Proliferations

IIId4 Lymphoid Proliferations

Atypical large clear lymphoid cells proliferate in a normally maturing epidermis.

Conditions to consider in the differential diagnosis:

- Pagetoid reticulosis
  - localized (Woringer-Kolopp)
  - disseminated (Ketron-Goodman)
- Paget's disease (mammary or extra-mammary)
- superficial spreading melanoma
- pagetoid squamous cell carcinoma in situ

IIIE LOCALIZED PAPILLOMATOUS EPITHELIAL LESIONS

A “papilla” may be likened to a “finger” of stroma with a few blood vessels, collagen fibers, and fibroblasts, covered by a “glove” of epithelium, which may be reactive or neoplastic, benign or malignant.

1. With Viral Cytopathic Effects
2. No Viral Cytopathic Effect

IIIE1 With Viral Cytopathic Effects

The epidermis is acanthotic with vacuolated cells (koilocytes), the granular cell layer is usually thickened with enlarged keratohyalin granules, and there is parakeratosis in tall columns overlying the thickened epidermis. Large inclusions are seen in molluscum contagiosum. Verruca vulgaris (50) and molluscum contagiosum (51) are prototypic.

Verruca Vulgaris

CLINICAL SUMMARY. Verrucae vulgares are circumscribed, firm, elevated papules with papillomatous (“verruous”) hyperkeratotic surfaces. They occur singly or in groups, most commonly on the dorsal aspects of the fingers and hands. Warts typically regress spontaneously through a combination of cell-mediated and humoral immunity; this may in many cases be accelerated by the topical application of the immune response modifier imiquimod (64).

HISTOPATHOLOGY. Verruca vulgaris is characterized by acanthosis, papillomatosis, and hyperkeratosis. The rete ridges are elongated and, at the periphery of the verruca, are often bent inward so that they appear to point radially toward the center (arborization). The characteristic features that distinguish verruca vulgaris from other papillomas are foci of vacuolated cells located in the upper stratum malpighii and in the granular layer, referred to as koilocytic cells, vertical tiers of parakeratotic cells, and foci of clumped keratohyalin granules. These three changes are quite pronounced in young verrucae vulgares. The koilocytes possess small, round, deeply basophilic nuclei surrounded by a clear halo and pale-staining cytoplasm. The vertical tiers of parakeratotic cells are often located at the crests of papillomatous elevations of the rete malpighii overlying a focus of vacuolated cells.

Verruca Plana

CLINICAL SUMMARY. Verrucae planae are slightly elevated, flat, smooth papules, which may be hyperpigmented, and affect the face and the dorsa of the hands most commonly. In rare instances, there is extensive involvement, with lesions also on the extremities and trunk.

HISTOPATHOLOGY. Verrucae planae show hyperkeratosis and acanthosis but, unlike verrucae vulgares, have no papillomatosis, only slight elongation of the rete ridges, and no areas of parakeratosis. In the upper stratum malpighii, including the granular layer, there is diffuse vacuolization

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**TABLE II.1. Junctional Dysplasia versus Pagetoid versus Lentiginous Melanoma in situ**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Junctional Dysplasia</th>
<th>Pagetoid MIS (SSM-IS)</th>
<th>Lentiginous MIS (LMM-IS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanocytes</td>
<td>Nevoid to epithelioid, small</td>
<td>Epithelioid, large</td>
<td>Nevoid to epithelioid, intermediate</td>
</tr>
<tr>
<td>Atypia</td>
<td>Mild to moderate, random</td>
<td>Moderate to severe, uniform</td>
<td>Moderate to severe, uniform</td>
</tr>
<tr>
<td>Pagetoid scatter</td>
<td>Minimal</td>
<td>Prominent</td>
<td>Often minimal</td>
</tr>
<tr>
<td>Nesting</td>
<td>Predominant</td>
<td>Prominent</td>
<td>Minimal or absent</td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>Elongated Rete</td>
<td>Irregular</td>
<td>Thinned</td>
</tr>
<tr>
<td>Dermal fibrosis*</td>
<td>Concentric</td>
<td>Diffuse</td>
<td>Minimal</td>
</tr>
<tr>
<td>Lymphocytes*</td>
<td>Patchy perivascular</td>
<td>Brisk, bandlike</td>
<td>Patchy to bandlike</td>
</tr>
</tbody>
</table>

SSM, superficial spreading melanoma; LMM, Lentigo maligna melanoma; IS, In Situ

* Fibrosis and inflammation may be minimal in some strictly in situ melanomas. “Nevoid lentigo maligna” may have features overlapping with junctional dysplasia.
**Clin. Fig. IIE1.a.** Verruca vulgaris. Multiple grouped, well-circumscribed, flesh-colored papules appeared on a child’s hand.

**Fig. IIE1.a.** Verruca vulgaris, low power. Elongated rete ridges at the periphery of the lesion often appear to point inward toward the center.

**Fig. IIE1.b.** Verruca vulgaris, medium power. Vertical tiers of parakeratotic cells are often located at the crests of papillomatous elevations of the rete malpighii.

**Fig. IIE1.c.** Verruca vulgaris, medium power. Although no granular cells are seen overlying the papillomatous crests, they are increased in number and size in the intervening valleys and contain heavy, irregular clumps of keratohyalin granules.

**Fig. IIE1.d.** Verruca vulgaris, high power. The virally altered cells, termed koilocytes, possess small, round, deeply basophilic nuclei surrounded by a clear halo and pale-staining cytoplasm.
of the cells, some of which are enlarged to about twice their normal size. The nuclei of the vacuolated cells lie at the centers of the cells, and some of them appear deeply basophilic. The granular layer is uniformly thickened, and the stratum corneum has a pronounced basket-weave appearance resulting from vacuolization of the horny cells. The dermis appears normal.

**Deep Palmoplantar Warts (Myrmecia)**

**CLINICAL SUMMARY.** Deep palmoplantar warts can be tender and occasionally swollen and red. Although they may be multiple, they do not coalesce as do mosaic warts, which are verrucae vulgares. Deep palmoplantar warts occur not only on the palms and soles but also on the lateral aspects and tips of the fingers and toes. Unlike superficial, mosaic-type palmoplantar warts, deep palmoplantar warts usually are covered with a thick callus. When the callus is removed with a scalpel, the wart becomes apparent.

**HISTOPATHOLOGY.** Whereas superficial, mosaic-type palmoplantar warts have a histologic appearance analogous to that of verruca vulgaris and represent HPV-2 or HPV-4, deep palmoplantar warts represent type HPV-1. These lesions, also known as myrmecia (“anthill”) or inclusion warts, are characterized by abundant keratohyalin, which differs from normal keratohyalin by being eosinophilic. Starting in the lower epidermis, the cytoplasm of many cells contains numerous eosinophilic granules, which enlarge in the upper stratum malpighii and coalesce to form large, irregularly shaped, homogeneous “inclusion bodies.” In addition to the large intracytoplasmic eosinophilic inclusion bodies, some of the cells in the upper stratum spinosum with vacuolated nuclei contain a small intranuclear eosinophilic “inclusion body.” It is round and of about the same size as the nucleolus, which, however, is basophilic. Both the intranuclear eosinophilic inclusion body and the basophilic nucleolus disappear as the vacuolated nucleus changes into a smaller, deeply basophilic structure.

**Condyloma Acuminatum**

**CLINICAL SUMMARY.** Condylomata acuminata, or anogenital warts, can occur on the penis, on the female genitals, and in the anal region (52). Condylomata of the skin consist of fairly soft, verrucous papules that occasionally coalesce into cauliflower-like masses. Condylomata are flatter on mucosal surfaces. Diagnostic problems in
anal pathology including the significance of dysplastic changes that may occur in condylomas, have been recently reviewed (53).

**HISTOPATHOLOGY.** The stratum corneum is only slightly thickened. Lesions located on mucosal surfaces show parakeratosis. The stratum malpighii shows papillomatosis and considerable acanthosis, with thickening and elongation of the rete ridges. The papillae tended to be rounded rather than more pointed as in verruca vulgaris. Mitotic figures may be present. Usually, invasive squamous cell carcinoma can be ruled out because the epithelial cells show an orderly arrangement and the border between the epithelial proliferations and the dermis is sharp. The most characteristic feature, important for the diagnosis, but absent or inconspicuous in many lesions, is the presence of areas in which the epithelial cells show distinct perinuclear vacuolization. These vacuolated epithelial cells are relatively large and possess hyperchromatic, round nuclei resembling the nuclei seen in the upper portion of the epidermis in verrucae vulgaris. It must be kept in mind, however, that vacuolization in condylomata acuminata can be regarded as being possibly of viral genesis only if it extends into the deeper portions of the stratum malpighii. Koilocytic (“raisin”) nuclei, double nuclei, and apoptotic keratinocytes may be present but are often less prominent than in uterine cervical lesions. In case of doubt, a descriptive diagnosis should be given. Dysplastic changes, characterized by architectural disorder and cytologic atypia, should be noted and graded, especially in anal lesions. Immunohistochemical studies of p16 and Ki-67 may be helpful in this regard (54).

**Molluscum Contagiosum**

**CLINICAL SUMMARY.** Molluscum contagiosum (55) occurs most frequently in the pediatric age group and consists of a variable number of small, discrete, waxy, skin-colored, delled, dome-shaped papules, usually 2 to 4 mm in size. In adults, molluscum contagiosum is primarily a sexually transmitted disease. In immunocompetent patients, the lesions involute spontaneously. During involution, there may be mild inflammation and tenderness. In the setting of immunosuppression, such as in HIV infection, molluscum contagiosum can attain considerable size and be widely disseminated.
HISTOPATHOLOGY. The epidermis is acanthotic, and many epidermal cells contain large, intracytoplasmic inclusion bodies—the so-called molluscum bodies, also known as Henderson–Patterson bodies. These first appear as single, minute, ovoid eosinophilic structures in the lower cells of the stratum malpighii at a level one or two layers above the basal cell layer. As infected cells move toward the surface, the molluscum bodies increase in size and in the upper layers of the epidermis; they displace and compress the nucleus so that it appears as a thin crescent at the periphery of the cell. At the level of the granular layer, the staining reaction of the molluscum bodies changes from eosinophilic to basophilic. In the horny layer, the basophilic molluscum bodies lie enmeshed in a network of eosinophilic horny fibers. In the center of the lesion, the stratum corneum ultimately disintegrates, releasing the molluscum bodies, and forming a central crater.

**Parapox Virus Infections (Milkers’ Nodules, Orf)**

CLINICAL SUMMARY. Milkers’ nodules, orf, and bovine papular stomatitis pox are clinically identical in humans and are induced by indistinguishable parapox viruses. Milkers’ nodules are acquired from udders infected with
Localized Papillomatous Epithelial Lesions

pseudocowpox or paravaccinia (parapox). This disease is called bovine papular stomatitis pox when the source of the infection is calves with oral sores. Orf (ecthyma contagiosum) is acquired from infected sheep or goats with crusted lesions on the lips and in the mouth. After an incubation period of 3 to 7 days, parapox virus infections produce one to three (rarely more) painful lesions measuring 1 to 2 cm in diameter on the fingers, or occasionally elsewhere as a result of autoinoculation. During a period of approximately 6 weeks, they pass through six clinical stages, each lasting about 1 week: (1) the maculopapular stage; (2) the target stage, during which the lesions have red centers, white rings, and red halos; (3) the acute weeping stage; (4) the nodular stage, which shows hard, nontender nodules; (5) the papillomatous stage, in which the nodules have irregular surfaces; and (6) the regressive stage, during which the lesions involute without scarring.

**HISTOPATHOLOGY.** During the maculopapular and target stages, there is vacuolization of cells in the upper third of the stratum malpighii, leading to multilocular vesicles. Eosinophilic inclusion bodies are in the cytoplasm of vacuolated epidermal cells, a distinguishing feature from herpes virus infections. Intranuclear eosinophilic inclusion bodies are also present in some cases. During the target stage, vacuolated epidermal cells with inclusion bodies are only in the surrounding white ring. The epidermis shows elongation of the rete ridges, and the dermis contains many newly formed, dilated capillaries, and a mononuclear infiltrate. In the acute weeping stage, the epidermis is necrotic throughout. A massive infiltrate of mononuclear cells extends throughout the dermis. In the later stages, the epidermis shows acanthosis with fingerlike downward projections, and the dermis shows vasodilatation and chronic inflammation, followed by resolution.

**Conditions to consider in the differential diagnosis:**
- *verruca vulgaris*
- orf
- condyloma acuminatum
- molluscum contagiosum
- Bowenoid papulosis
II. Localized Superficial Epidermal or Melanocytic Proliferations

IIE2 No Viral Cytopathic Effect

The epidermis proliferates focally. The cells may be basophilic or “basaloid” in type (seborrheic keratoses). There may be increased stratum corneum and elongation of the dermal papillae (squamous papilloma), or there may be basilar keratinocytic atypia (actinic keratosis). Seborrheic keratosis (56) is a prototypic example.

Seborrheic Keratosis

CLINICAL SUMMARY. Seborrheic keratoses are very common lesions: sometimes single but often multiple. They occur usually not before middle age, mainly on the trunk and face but also on the extremities, with the exception of the palms and soles. They are sharply demarcated, brownish in color, and slightly raised, so that they often look as if they are stuck on the surface of the skin. Most of them have a verrucous surface, which has a soft, friable consistency. Some, however, have a smooth surface but characteristically show keratotic plugs. Although most lesions measure only a few millimeters in diameter, a lesion may occasionally reach a size of several centimeters. Some may become inflamed. Seborrheic keratoses have been shown to contain mutations of keratinocyte growth factors (47).

HISTOPATHOLOGY. Seven variants may be recognized: irritated, adenoid or reticulated, plane, clonal, melanoacanthoma, inverted follicular keratosis, and benign squamous keratosis. Often more than one type is found in the same lesion. All have in common hyperkeratosis, acanthosis, and papillomatosis. The acanthosis in most instances is due entirely to upward extension of the tumor. Thus the lower border of the tumor is even and generally lies on a straight line that may be drawn from the normal epidermis at one end of the tumor to the normal epidermis at the other end. Two types of cells are usually seen in the acanthotic epidermis: basaloid cells which resemble the cells found normally in the basal layer of the epidermis tend to predominate over squamous cells.

Confluent and Reticulated Papillomatosis (Gougerot–Carteaud)

CLINICAL SUMMARY. Confluent and reticulated papillomatosis is a condition of unknown cause, originally described in 1927 by Gougerot and Carteaud. The condition presents clinically as collection of brown-gray hyperkeratotic papules and patches (57). These become confluent centrally and reticulated at the periphery. The initial site is often the mid back with spread to involve the
axillae, neck, and abdomen. This condition is more common in women of color. Speculation as to the cause varies from an endocrine etiology to that of an organism (yeast-Pitysporum sp.). The differential diagnosis includes acanthosis nigricans, tinea versicolor, seborrheic keratosis, epidermal nevus, and Naegeli–Franceschetti–Jadassohn Syndrome which is a rare autosomal dominant ectodermal dysplasia characterized by the absence of dermatoglyphics, reticulate hyperpigmentation of the skin, hypohidrosis, and heat intolerance, associated with palmoplantar keratoderma, nail dystrophy, and enamel defects (58).

**HISTOPATHOLOGY.** There is hyperkeratosis, hypogranulosis, and an increase of pigment in the basal cell layer. Epidermal pigment is due to an increased number of melanosome granules in the basilar and epidermal keratinocytes. The dermis does not demonstrate significant alteration.

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**Clin. Fig. IIE2.a.** Former Clinical Figure IIE2. *Seborrheic keratosis*. A middle-aged female developed a pigmented “stuck on” papule with a “waxy” feel. Keratin-filled ostia help to distinguish this common lesion. A slightly scaly surface can be accentuated by rubbing or light scratching of the lesion.

**Fig. IIE2.a.** *Seborrheic keratosis, low power*. The tumor extends upward above a line drawn through the normal epidermis on each side. Pseudohorn cysts (keratin tunnels (or horn cysts) containing whorls of keratin) are a prominent feature.

**Fig. IIE2.b.** *Seborrheic keratosis, medium power*. The lesion is composed predominantly of basaloid cells, with squamous differentiation beneath the stratum corneum.

**Fig. IIE2.c.** *Reticulated seborrheic keratosis, low power*. The lesion is composed of anastomosing cords of cells in a reticulated or “adenoid” pattern, with scattered “horn cysts.” (continues)
II. Localized Superficial Epidermal or Melanocytic Proliferations

**Fig. IIE2.d.** Reticulated seborrheic keratosis, medium power. The cells in the cords show basaloid and squamous differentiation. In this example, there is moderate melanin pigment in the basaloid cells.

**Fig. IIE2.e.** Pigmented seborrheic keratosis, low power. The lesion contains abundant brown melanin pigment, simulating a nodular melanoma clinically.

**Fig. IIE2.f.** Pigmented seborrheic keratosis, medium power. The pigment is located mainly in the basaloid cells. It is produced by melanocytes that populate the lesion.

**Clin. Fig. IIE2.b.** Confluent and Reticulated Papillomatosis (CARP). Dark brown, reticulated patches are often mistaken for tinea versicolor.

**Fig. IIE2.g.** Low power, showing hyperkeratosis and papillomatosis.

**Fig. IIE2.h.** Hyperkeratosis with a diminished granular layer, with little or no inflammation in the dermis.
Verrucous Melanoma

CLINICAL SUMMARY. Occasional examples of nodular melanoma may present with a “warty” or verrucous configuration, with prominent hyperkeratosis. Especially if the lesion is pigmented, the diagnosis is usually obvious, but occasional cases can simulate a wart.

HISTOPATHOLOGY. The keratinocytic epithelium demonstrates papillary hyperplasia and marked hyperkeratosis. Lesional cells in this case of very obvious because of marked hyperpigmentation.

Conditions to consider in the differential diagnosis:
- seborrheic keratosis
- acanthosis nigricans
- confluent and reticulated papillomatosis
- actinic keratosis, hypertrophic
- nonspecific squamous papilloma
- epithelial nevus/epidermal nevus
- hyperkeratosis of the nipple and areola
- verruciform xanthoma
- verrucous melanoma

Fig. IIE2.i. A quite large lesion with prominent superficial hyperkeratosis.

Fig. IIE2.j. The appearances could resemble a verrucous keratosis of some kind.

Fig. IIE2.k. Numerous neoplastic pigmented melanocytes in this case make the diagnosis obvious.
Irregular or asymmetrical proliferations of keratinocytes extending into the dermis are usually neoplastic. The differential diagnosis includes reactive pseudoepitheliomatous hyperplasia, which may be seen around chronic ulcers or in association with other inflammatory conditions (refer to VIB1).

1. Squamous Differentiation
2. Basaloid Differentiation

**Squamous Differentiation**

The epidermis is irregularly thickened, the maturation is abnormal and there may be keratinocytic atypia (squamous cell carcinoma). The proliferation is often associated with a thick parakeratotic scale. Superficial squamous cell carcinoma is prototypic (16) (see also VIB1).

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**Inverted Follicular Keratosis**

Conditions to consider in the differential diagnosis:
- lichen simplex chronicus
- squamous cell carcinoma, superficial
- keratoacanthoma
- prurigo nodularis
- actinic prurigo
- inverted follicular keratosis
- verrucous carcinoma
  - of oral mucosa
  - of genitoanal region (giant condyloma of Buschke & Lowenstein)
  - of plantar skin (epithelioma cuniculatum)
- pseudoepitheliomatous hyperplasia
- deep fungal infection
- halogenoderma
- chronic ulcers
- granular cell tumor
- Spitz nevus
- verrucous melanoma

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**Fig. IIF1.a.** *Squamous cell carcinoma, invasive, low power.* Arising from the base of the epidermis there are endophytic proliferative lobules of atypical epithelium which are associated with a patchy lymphocytic infiltrate.

**Fig. IIF1.b.** *Squamous cell carcinoma, invasive, medium power.* The haphazardly oriented lobules are of varying shapes and sizes and show an infiltrative growth pattern within the dermis.

**Fig. IIF1.c.** *Squamous cell carcinoma, invasive, high power.* At higher magnification, there is formation of ill-defined squamous pearls, whorled aggregates of parakeratin within the epithelial islands, and the atypical keratinocytes may show a spectrum of cytologic atypia from mild to severe.
Hierarchical Intraepithelial Neoplasia (HIF)

Localized Superficial Epidermal or Melanocytic Proliferations

Clinical Summary. Irregular proliferations extending into the superficial dermis are characterized by a variety of epidermal and dermal alterations. These include:

1. NODULAR/Ulcerative Basal Cell Carcinoma (BCC)
   - Begins as a small, waxy nodule often showing a few small telangiectatic vessels on its surface.
   - Nodule usually increases slowly in size and undergoes central ulceration surrounded by a pearly, rolled border.

2. Pigmented Basal Cell Carcinoma
   - Similar to nodular-ulcerative type but with brown pigmentation.

3. Morphea-like or Fibrosing Basal Cell Carcinoma
   - Presents as a solitary, flat or slightly depressed, indurated, ill-defined, smooth yellowish plaque with a high incidence of local recurrence.

4. Superficial Basal Cell Carcinoma
   - Shows buds and irregular proliferations of peripherally palisaded basaloid cells attached to the undersurface of the epidermis and penetrating only slightly into the dermis. The overlying epidermis is often atrophic.

5. Fibroepithelioma of Pinkus
   - Embedded in a fibrous stroma, often connected to the surface epidermis as buds on a branch. Usually, the tumor is quite superficial and demarcated at its lower border.

Histopathology. The histology of basal cell carcinoma varies depending on the type:

1. Nodular/Ulcerative BCC
   - Nodular masses of basaloid cells extending into the dermis in relation to a delicate, specialized, somewhat myxoid tumor stroma with characteristic separation artifact between the two. Cystic spaces may form.

2. Superficial BCC
   - Shows buds and irregular proliferations of peripherally palisaded basaloid cells extending into the superficial dermis.

3. Fibroepithelioma of Pinkus
   - Embedded in a fibrous stroma, often connected to the surface epidermis as buds on a branch. The tumor is usually superficial and demarcated at its lower border.
 Clin. Fig. IIF2.a. Nodulo-ulcerative basal cell carcinoma. The rolled, pearly borders with telangiectases and central ulceration typify basal cell carcinoma, the most common skin malignancy.

 Clin. Fig. IIF2.b. Pigmented basal cell carcinoma. An elderly man developed a forehead papule with a pigmented rolled border and central concavity.

 Fig. IIF2.a. Superficial "multicentric" basal cell carcinoma, low power. Irregular masses of basophilic cells extend from the epidermis into the dermis.

 Fig. IIF2.b. Superficial "multicentric" basal cell carcinoma, medium power. The cells at the periphery of the tumor masses are palisaded, and there is a cleft between them and the characteristic delicate collagenous stroma.

 Fig. IIF2.c. Nodular basal cell carcinoma, low power. Arising from the base of the epithelium, there are nodular aggregates of atypical basaloid cells associated with cleft formation.

 Fig. IIF2.d. Nodular basal cell carcinoma, medium power. Bluish mucinous material is seen in the cleft. The stroma of basal cell carcinomas may be fibrotic, as seen here, or may be loose with an abundance of mucinous material.
Fig. IIF2.e  *Fibroepithelioma of Pinkus, low power.* This variant of basal cell carcinoma shows numerous thin, anastomosing strands of epithelial cells which arise from the base of the epidermis.

Fig. IIF2.f  *Fibroepithelioma of Pinkus, medium power.* These epithelial strands form small basaloid buds with peripheral palisading. The stroma is hypercellular and fibrotic.

Fig. IIF2.g  *Morpheaform basal cell carcinoma, low power (inset), and medium power.* This aggressive variant of basal cell carcinoma is composed of numerous small islands of basal cell carcinoma which generally infiltrate into the reticular dermis.

Fig. IIF2.h  *Morpheaform basal cell carcinoma, high power.* At higher magnification, this lesion is composed of very small islands of atypical basaloid cells which are embedded in a fibrotic stroma. There may be perineural involvement, as here. (continues)
carcinoma. Most consider the fibroepithelioma of Pinkus to be a variant of a basal cell carcinoma.

**Molecular pathology.** Several tumor suppressor genes and proto-oncogenes have been implicated in the pathogenesis of basal cell carcinomas, including the human homologs of the Drosophila genes patched (PTCH) and smoothened (SMOH), the TP53 tumor suppressor gene, and the RAS proto-oncogene family (60). Patients with PTCH polymorphisms are at increased risk of developing the disease (61).

**Conditions to consider in the differential diagnosis:**

*basal cell carcinoma, superficial types*

### Polypoid Dermal and Compound Nevi

(See also IIA.2). A compound nevus possesses features of both a junctional and an intradermal nevus. Nevus cell nests are present in the epidermis, as well as in the dermis. Nevus cells in the upper, middle, and lower dermis may present characteristic morphologic variations called *types A, B, and C*, respectively. Usually, the Type A nevus cells in the upper dermis are cuboidal and show abundant cytoplasm containing varying amounts of melanin granules. Type B cells are distinctly smaller than type A cells, display less cytoplasm and less melanin, and generally lie in well-defined aggregates. Type C nevus cells in the lower dermis tend to resemble fibroblasts or Schwann cells, because they are usually elongated and have spindle-shaped nuclei. Lesions with prominent schwannian differentiation are termed “neurotized.” If dermal nevus cells are confined to the papillary dermis, they often retain a discrete, or “pushing” border with the stroma. However, nevus cells that enter the reticular dermis tend to disperse among collagen fiber bundles as single cells or attenuated single files of cells. This pattern of infiltration of the dermis differs from that in melanomas, where groups of cells tend to dissect and displace the collagen bundles in a more “expansive” pattern. Lesions where nevus cells extend into the lower reticular dermis and the subcutaneous fat, or are located within nerves, hair follicles, sweat ducts, and sebaceous glands, may be termed “congenital pattern nevi.” Intradermal nevi show essentially no junctional activity. The upper dermis contains nests and cords of nevus cells similar to those described above. Occasional intradermal nevi contain predominantly spindle-shaped schwannian cells embedded in abundant, loosely arranged collagenous tissue. If there are also a few nests of nevus cells, such a lesion...
Localized Superficial Epidermal or Melanocytic Proliferations

II

IIG. Superficial Polypoid Lesions

may be referred to as a neural nevus, however, if nests are completely absent the lesion is more likely to be a neurofibroma.

Conditions to consider in the differential diagnosis:

- polypoid dermal and compound nevi
- polypoid melanoma (see also VIB.3)

II G2 Spindle Cell and Stromal Lesions

The polyp contains stromal cells of types that may be seen in the dermis, including fibroblasts, fat cells, or schwannian cells. Neurofibroma is a prototypic example (63).

Neurofibroma

CLINICAL SUMMARY. Extranuclear sporadic cutaneous neurofibromas (ESCNs) (the common sporadic neurofibromas) are soft, polypoid, skin-colored or slightly tan, and small (rarely larger than a centimeter in diameter). They usually arise in adulthood. The identification of as many as four, small, cutaneous neurofibromas in a single patient, in the absence of other confirmatory findings, would not qualify as stigmata of neurofibromatosis.

HISTOPATHOLOGY. Most sporadic neurofibromas are faintly eosinophilic, and are circumscribed but not encapsulated: they are extraneural. Thin spindle cells with elongated, wavy nuclei are regularly spaced among thin, wavy collagenous strands. The strands are either closely spaced (homogeneous pattern) or loosely spaced in a clear matrix (loose pattern). The two patterns are often intermixed in a single lesion. The regular spacing of adnexa is preserved in cutaneous neurofibromas. Entrapped small nerves occasionally are enlarged and hypercellular. The differentiation from a neurotized nevus may be difficult in routinely stained sections, but distinction may be possible if a few type A or B nevus cells are present in addition to the spindle cells, or with an immunohistochemical stain for myelin basic protein, which is positive only in neurofibromas. Any given neurofibroma could be either sporadic or associated with neurofibromatosis (NF-1), however, in a comparative study, neurofibromas in NF-1 were more frequently associated with melanocytic hyperplasia, lentigo simplex-like...
changes, and diffuse and plexiform neurofibroma patterns (see VIC2) than were the sporadic neurofibromas (64).

**Fibroepithelial Polyp**

**CLINICAL SUMMARY.** Fibroepithelial polyps, also called “soft fibromas,” “acrochordons,” or “cutaneous tags,” occur as three types: (1) multiple small, furrowed papules, especially on the neck and in the axillae, generally only 1 to 2 mm long; (2) single or multiple filiform, smooth growths in varying locations, about 2 mm wide and 5 mm long; and (3) solitary baglike, pedunculated growths, usually about 1 cm in diameter but occasionally much larger, seen most commonly on the lower trunk. There may be associations with diabetes and acromegaly.

**HISTOPATHOLOGY.** The multiple small furrowed papules usually show papillomatosis, hyperkeratosis, and regular acanthosis and occasionally also horn cysts within their acanthotic epidermis. Thus there is often considerable resemblance to a pedunculated seborrheic keratosis. The common filiform, smooth growths show slight to moderate acanthosis and occasionally mild papillomatosis. The connective tissue stalk is composed of loose collagen fibers and often contains numerous dilated capillaries filled with erythrocytes. Nevus cells are found in many of the filiform growths, indicating that some of them represent involuting melanocytic nevi. The baglike, soft fibromas generally show a flattened epidermis overlying loosely arranged collagen fibers and mature fat cells in the center. In some instances, the dermis is quite thin, so that the fat cells compose a significant portion of the tumor, which may then be regarded as a lipofibroma.

**Conditions to consider in the differential diagnosis:**
- neurofibroma
- neurotized nevus
- soft fibroma (fibro-epithelial polyp, acrochordon, skin tag)
Localized Superficial Epidermal or Melanocytic Proliferations

Clin. Fig. IIG2.b. Soft fibroma. A traumatized pedunculated papule along the bra line.

Fig. IIG2.c. Fibroepithelial polyp, low power. At scanning magnification this polypoid lesion may resemble both a nevus and a neurofibroma. However, upon closer inspection, neither nevus cells nor wavy neural cells are seen within the stroma of this lesion.

Fig. IIG2.d. Fibroepithelial polyp, medium power. The core of this lesion is composed of well vascularized connective tissue and the lesion is surfaced by slightly acanthotic and papillomatous epithelium. The papillae may be prominent, as here, or may be effaced.

References


Disorders of the Superficial Cutaneous Reactive Unit

The epidermis, papillary dermis, and superficial capillary–venular plexus react together in many dermatologic conditions, and were termed the “superficial cutaneous reactive unit” by Clark. Many dermatoses are associated with infiltrates of lymphocytes with or without other cell types, around the superficial vessels. The epidermis in pathologic conditions can be thinned (atrophic), thickened (acanthotic), edematous (spongiotic) and/or infiltrated (exocytosis). The epidermis may proliferate in response to chronic irritation, infection (bacterial, yeast, deep fungal, or viral). The epidermis may proliferate in response to dermatologic conditions (psoriasis, atopic dermatitis, prurigo). The papillary dermis and superficial vascular plexus may contain a variety of inflammatory cells, can be edematous, may have increased ground substance (hyaluronic acid), and may be sclerotic or homogenized.

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SUPERFICIAL PERIVASCULAR DERMATITIS

Many dermatoses are associated with infiltrates of lymphocytes with or without other cell types, around the vessels of the superficial capillary–venular plexus, termed by Clark the “superficial cutaneous reactive unit (SCRU)”. The vessel walls may be quite unremarkable, or there may be slight to moderate endothelial swelling. Eosinophilic change (“fibrinoid necrosis”) is not seen except in cases of true vasculitis. The term “lymphocytic vasculitis” may encompass some of the conditions mentioned here, but is of debatable validity in the absence of vessel wall damage. The epidermis is variable in its thickness, amount and type of exocytotic cell, and the integrity of the basal cell zone (liquefaction degeneration). In some of the entities listed here, the perivascular infiltrate may in some examples also involve vessels of the mid and deep vessels. These conditions are also listed in Chapter V: Pathology Substantially Involving the Reticular Dermis.

1. Mostly Lymphocytes
   1a. Lymphocytes with Eosinophils
   1b. With Neutrophils
   1c. With Plasma Cells
   1d. With Extravasated Red Cells
   1e. With Prominent Melanophages

2. With Predominant Mast Cells

Superficial Perivascular Dermatitis, Mostly Lymphocytes

Lymphocytes are seen about the superficial vascular plexus. Other cell types are rare or absent. Viral exanthems are prototypic (1).

Viral Exanthem

CLINICAL SUMMARY. At least five groups of viruses are well known to affect the skin or the adjoining mucous surfaces: (1) the herpesvirus group, including herpes simplex types 1 and 2 and the varicella-zoster virus, which are DNA-containing organisms that multiply within the nucleus of the host cell; (2) the poxvirus group, including smallpox, milkers' nodules, orf, and molluscum contagiosum, which are DNA-containing agents that multiply within the cytoplasm; (3) the papovavirus group, including the various types of verrucae, which contain DNA and replicate in the nucleus; (4) the picornavirus group, including coxsackievirus group A, causing hand-foot-and-mouth disease, which contain RNA rather than DNA in their nucleoids; and (5) retroviruses, including human immunodeficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS). Primary HIV infection may be associated with both an exanthem and an exanthem, which are histologically nondescript lymphocytic infiltrates. The array of skin lesions associated with HIV is generally a consequence of eventual immunosuppression. Seborrheic dermatitis, psoriasis, xerosis, and pruritic papular eruptions may be seen in the early stages. As the infection advances and the CD4/CD8 ratio decreases, oral hairy leukoplakia, chronic herpes simplex, recurrent herpes zoster, Kaposi's sarcoma, and other opportunistic infections, are also common (2). These associations have been recently reviewed (3). There is no unique histology of HIV infection in the skin. Primary exanthems of HIV show nonspecific lymphocytoid infiltrates with mild epidermal changes, primarily spongiosis (4). Seborrheic dermatitis in patients with AIDS may show nonspecific changes, including spotty keratinocytic necrosis, leukoexocytosis, and plasma cells in a superficial perivascular infiltrate (5). A “papular eruption” may exhibit nonspecific perivascular eosinophils with mild folliculitis, although epitheloid cell granulomas have also been reported (6). An “interface dermatitis” shows, as the name implies, vacuolar alteration of the basal cell layer, scattered necrotic keratinocytes, and a superficial perivascular lymphohistiocytic infiltrate. The vacuolar alteration and number of necrotic keratinocytes tend to be more pronounced than in drug eruptions. Biopsies of AIDS-related eruptions are often nonspecific.

The prototypic viral rash is the morbilliform rash of measles. Measles virus is a single stranded RNA virus that belongs to the family Paramyxoviridae. Measles is an epidemic disease with a worldwide distribution. Measles virus is transmitted via respiratory secretions, predominantly as aerosols but also by direct contact. The symptoms usually last for 10 days and resolve without consequence. However, there is an increased risk of more severe diseases, such as severe pneumonitis or encephalitis, in immunocompromised individuals.

HISTOPATHOLOGY. A biopsy of the rash shows nonspecific perivascular lymphocytic inflammation with epidermal spongiosis and mild vesiculation with scattered degenerated keratinocytes. Biopsies from AIDS patients with measles show necrosis of clusters of keratinocytes in the upper spinous layer and granular layer of the epidermis. Unlike in erythema multiforme the necrosis occurs in the basal layer keratinocytes. Multinucleated keratinocytes may or may not be prominent in the measles biopsy. Cytoplasmic swelling of the keratinocytes in the granular layer may be present even when multinucleated cells are sparse.

Tinea Versicolor

See Clin. Fig. IIIA.1.b and Fig. IIIA.1.d.e.

Lupus Erythematosus, Acute

See Clin. Fig. IIIA.1.c and Fig. IIIA.1.f–h.

Guttate Parapsoriasis

See Clin. Fig. IIIA.1.d and Fig. IIIA.1.i–k.
**Clin. Fig. IIIA1.a.** *Viral exanthem.* Red macules and papules that blanch are characteristic of this unique exanthem called unilateral laterothoracic viral exanthem.

**Fig. IIIA1.a.** *Morbilliform viral exanthem, low power.* There is an inflammatory infiltrate about dermal vessels in the reticular dermis.

**Fig. IIIA1.b.** *Morbilliform viral exanthem, medium power.* A thin keratin scale overlies a slightly acanthotic epidermis. There is vascular ectasia in the upper reticular dermis.

**Fig. IIIA1.c.** *Morbilliform viral exanthem, high power.* A lymphocytic inflammatory infiltrate is seen about the dermal vessels. There are no eosinophils and no plasma cells.
Clin. Fig. IIIA1.b  
Fungal forms in stratum corneum (“spaghetti & meatballs”)

Clin. Fig. IIIA1.c  
Former Clin. Fig. IIIA1.b. Lupus erythematosus, acute. A photosensitive female presented with edematous malar erythema—a “butterfly rash”. Lack of papules and pustules helps to distinguish lupus from rosacea.

Fig. IIIA1.d  
Tinea versicolor, medium power. In the hyperkeratotic stratum corneum there are basophilic staining hyphae and spores. The epidermis is acanthotic with basal layer pigmentation and a sparse lymphocytic infiltrate.

Fig. IIIA1.e  
Tinea versicolor, medium power. A Grocott stain demonstrates the fungal forms in the stratum corneum.

Clin. Fig. IIIA1.f  
Lupus erythematosus, acute, low power. There is hyperkeratosis with a thinned and focally thickened epidermis and vacuolar change at the interface. There is an infiltrate about dermal vessels seen in the reticular dermis. (continues)
III. Disorders of the Superficial Cutaneous Reactive Unit

Fig. IIIA1.g. *Lupus erythematosus, acute, medium power.* Vacuolar change is seen at the dermal-epidermal interface with an overlying hyperkeratotic scale. The inflammatory infiltrate in the dermis is lymphocytic.

Fig. IIIA1.h. *Lupus erythematosus, acute, medium power.* There is prominent vacuolar change at the dermal-epidermal interface. The inflammatory cells are exocytotic to the alternatingly acanthotic and atrophic epidermis.

Clin. Fig. IIIA1.d. Former Clin. Fig. IIIA1.c. *Parapsoriasis.* Brown finely scaled macular fingerlike morphology with atrophy characterizes the benign digitate variant.

Fig. IIIA1.i. *Guttate parapsoriasis, low power.* There is a focal parakeratotic scale overlying an acanthotic epidermis. In the dermis there is a dense infiltrate about superficial dermal vessels in a localized area.
Conditions to consider in the differential diagnosis:

- morbilliform viral exanthem
- papular acrodermatitis (Gianotti–Crosti – more often spongiotic)
- stasis dermatitis
- pityriasis lichenoides et varioliformis acuta (PLEVA), early
- Jessner’s lymphocytic infiltrate
- tinea versicolor
- candidiasis
- superficial gyrate erythemas
- lupus erythematosus, acute
- mixed connective tissue disease
- dermatomyositis
- early herpes simplex, zoster
- morbilliform drug eruption
- cytomegalovirus inclusion disease
- polymorphous drug eruption
- progressive pigmented purpura
- parapsoriasis, small plaque type (digitate dermatosis)
- guttate parapsoriasis
- Langerhans cell histiocytosis (early lesions)
- mucocutaneous lymph node syndrome (Kawasaki disease)
- secondary syphilis

**Morbilliform Drug Eruption**

**CLINICAL SUMMARY.** Virtually any drug may be associated with a morbilliform eruption; the nonspecific clinical and histologic changes make definitive implication of a specific agent difficult (8, 9). The most common class of medications causing morbilliform eruptions is antibacterial antibiotics. The morbilliform rash consists of fine blanching papules, which appear suddenly, are symmetric, and often are brightly erythematous in Caucasian patients.

**HISTOPATHOLOGY.** The typical morbilliform drug eruption displays a variable, often sparse, mainly perivascular infiltrate of lymphocytes and eosinophils. Eosinophils may be absent. In a recent study, 82% of 108 cases of drug eruptions (which had been identified in a single institution by pathologic diagnosis supported by chart review) exhibited an inflammatory infiltrate confined to the superficial dermis. Eighty percent exhibited a perivascular and interstitial pattern of dermal infiltrate. The infiltrate was composed of lymphocytes and eosinophils in approximately 29% of cases, lymphocytes and neutrophils in approximately 10% of cases, and lymphocytes, eosinophils, and neutrophils in approximately 21% of cases. Therefore, eosinophils were present in only 50% of cases. Approximately half (53%) of the cases exhibited epidermal–dermal interface (e.g., vacuolar) changes (10). There is a variable degree of urticarial edema (allergic urticarial eruption, see the following text). Distinction of morbilliform drug eruption from viral exanthem in the absence of eosinophils is generally not possible. More than occasional dyskeratotic epidermal cells should prompt consideration...
III. Disorders of the Superficial Cutaneous Reactive Unit

of erythema multiforme and related conditions, for example, toxic epidermal necrolysis, Stevens–Johnson syndrome, or fixed drug eruption.

Allergic Urticarial Reaction (Morphilliform Drug Eruption)

See Clin. Fig. IIIA1.a.a and Fig IIIA1a.a–c.

Urticaria

CLINICAL SUMMARY. Urticaria is characterized by the presence of transient, recurrent wheals, which are raised, and erythematous areas of edema usually accompanied by itching. When large wheals occur, in which the edema extends to the subcutaneous tissue, the process is referred to as angioedema (11). Acute episodes of urticaria generally last only several hours. When episodes of urticaria last up to 24 hours and recur over a period of at least 6 weeks, the condition is considered chronic urticaria. Urticaria and angioedema may occur simultaneously, in which case the affliction tends to have a chronic course. In approximately 15% to 25% of patients with urticaria, an eliciting stimulus or underlying predisposing condition can be identified, including soluble antigens in foods,
III. Superficial Perivascular Dermatitis

Disorders of the Superficial Cutaneous Reactive Unit

Drugs, insect venom, and contact allergens; physical stimuli such as pressure, vibration, solar radiation, cold temperature; occult infections and malignancies; and some hereditary syndromes. The reaction pattern of urticaria can also be seen in other conditions, notably bullous pemphigoid (7).

HISTOPATHOLOGY. In acute urticaria one observes interstitial dermal edema, dilated venules with endothelial swelling, and a paucity of inflammatory cells. In chronic urticaria interstitial dermal edema and a perivascular and interstitial mixed-cell infiltrate with variable numbers of lymphocytes, eosinophils, and neutrophils are present. In angioedema the edema and infiltrate extend into the subcutaneous tissue. In hereditary angioedema there is subcutaneous and submucosal edema without infiltrating inflammatory cells.

Clin. Fig. IIIA1a.b. Urticaria. Large edematous plaques with central clearing and geographic configuration are typical of urticaria.

Fig. IIIA1a.d. Urticaria, low power. Sparse superficial perivascular and interstitial inflammatory infiltrate, and separation of collagen bundles by edema fluid.

Fig. IIIA1a.e. Urticaria, high power. Interstitial infiltrate of eosinophils, neutrophils and lymphocytes.

Urticarial Bullous Pemphigoid

See Clin. Fig. IIIA1a.c and Fig. IIIA1a.f–h.

Conditions to consider in the differential diagnosis:

- arthropod bite reaction
- allergic urticarial reaction (drug)
- bullous pemphigoid, urticarial phase
- urticaria
- erythema toxicum neonatorum
- Well's syndrome
- mastocytosis/telangiectasia eruptiva macularis perstans
- angiolymphoid hyperplasia with eosinophilia
- Kimura's disease
- Langerhans cell histiocytosis (early lesions)
In addition to lymphocytes, neutrophils are present in varying numbers, with both a perivascular and interstitial distribution. Cellulitis and erysipelas are prototypic (see also Section VC.2).

**Erysipelas**

**CLINICAL SUMMARY.** Erysipelas is an acute superficial cellulitis of the skin caused by group A streptococci (12). It is characterized by the presence of a well-demarcated, slightly indurated, dusky red area with an advancing, palpable border. In some patients, erysipelas has a tendency...
to recur periodically in the same areas. In the early antibiotic era, the incidence of erysipelas appeared to be on the decline and most cases occurred on the face. More recently, however, there appears to have been an increase in the incidence, and facial sites are now less common whereas erysipelas of the legs is predominant. Potential complications in patients with poor resistance or after inadequate therapy may include abscess formation, spreading necrosis of the soft tissue, infrequently necrotizing fasciitis, and septicemia. Erysipelas is usually produced by non-nephritogenic and non-rheumatogenic strains of streptococci.

**HISTOPATHOLOGY.** The dermis shows marked edema and dilatation of the lymphatics and capillaries. There is a diffuse infiltrate, composed chiefly of neutrophils, that extends throughout the dermis and occasionally into the subcutaneous fat. It shows a loose arrangement around dilated blood and lymph vessels. This pattern may be descriptively termed “cellulitis” and is not diagnostic of erysipelas specifically. In erysipelas, streptococci may be found in the tissue and within lymphatics, in sections stained with the Giemsa or Gram stain.

**Erysipelas/Cellulitis**

See Clin. Fig. IIIA1b and Fig. IIIA1b.a–c.

**Conditions to consider in the differential diagnosis:**
- cellulitis
- erysipelas

**Clin. Fig. IIIA1b.** *Erysipelas.* A 51-year-old man had fever, chills and an expanding sharply marginated erythematous edematous plaque on the cheek.

**Fig. IIIA1b.a.** *Cellulitis, low power.* The dermis shows marked edema with separation of collagen bundles and there is a diffuse cellular infiltrate involving the dermis and subcutis.

**Fig. IIIA1b.b.** *Cellulitis, medium power.* There is marked dermal edema and a diffuse infiltrate of lymphocytes and neutrophils as well as fragmented neutrophils.

**Fig. IIIA1b.c.** *Cellulitis, medium power.* In the dermis and subcutis there is a prominent inflammatory infiltrate, with neutrophils predominating and with histiocytes, lymphocytes and perhaps plasma cells. Bacteria may be demonstrable, however their apparent absence does not rule out sepsis.
**III A1c  Superficial Perivascular Dermatitis With Plasma Cells**

Plasma cells are seen about the dermal vessels as well as in the interstitium. They are most often admixed with lymphocytes. Secondary syphilis is the prototype.

---

**Secondary Syphilis**

**CLINICAL SUMMARY.** Secondary syphilis (13), (14) is typically characterized by a generalized eruption, comprising brown–red macules and papules, papulosquamous lesions resembling guttate psoriasis, and, rarely, pustules.

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**Clin. Fig. IIIA1c.a**. Secondary syphilis. Note characteristic scaly brown macules on the soles of the feet.

**Fig. IIIA1c.a.** Secondary syphilis, low power. There is a thin keratin scale overlying an acanthotic epidermis. There is a dense infiltrate at the dermal-epidermal interface and about the superficial dermal vessels.

**Fig. IIIA1c.b.** Secondary syphilis, medium power. There is exocytosis of mononuclear cells into an acanthotic epidermis. The dermis is edematous and there is a dense collection of cells about dermal vessels and in the interstitium.

**Fig. IIIA1c.c.** Secondary syphilis, high power. The inflammatory infiltrate in the dermis is composed of plasma cells, lymphocytes and histiocytes, the latter forming ill-defined granulomas.
Lesions may be follicular-based, annular, or serpiginous, particularly in recurrent attacks. Other skin signs include alopecia and condylomata lata, the latter comprising broad, raised, gray, confluent papular lesions arising in anogenital areas, pitted hyperkeratotic palmoplantar papules termed “syphilis cornee,” and, in rare severe cases, ulcerating lesions that define “lues maligna.” Some patients develop mucous patches composed of multiple shallow, painless ulcers.

**HISTOPATHOLOGY.** The two fundamental pathologic changes in syphilis are: (1) swelling and proliferation of endothelial cells, and (2) a predominantly perivascular infiltrate composed of lymphoid cells and often plasma cells. In late secondary and tertiary syphilis, there are also granulomatous infiltrates of epithelioid histiocytes and giant cells. Biopsies generally reveal varying degrees of lichenoid inflammation and psoriasiform hyperplasia of the epidermis with variable spongiosis and basilar vacuolar alteration. Exocytosis of lymphocytes, spongiform pustulation, and parakeratosis also may be observed, with or without intracorneal neutrophilic abscesses. Scattered necrotic keratinocytes may be observed. The dermal changes include variable papillary dermal edema and a perivascular and/or periadnexal infiltrate that usually includes plasma cells and may be lymphocyte predominant, lymphohistiocytic, histiocytic predominant, or frankly granulomatous and that is of greatest intensity in the papillary dermis and extends as loose perivascular aggregates into the reticular dermis. Vascular changes such as endothelial swelling and mural edema accompany the angiocentric infiltrates in about half of the cases. A silver stain shows the presence of spirochetes in about a third of the cases, mainly within the epidermis and less commonly around the blood vessels of the superficial plexus. Immunohistochemistry, especially when combined with specialized microscopy, results in superior detection rates (15). Lesions of condylomata lata show all of the aforementioned changes observed in macular, papular, and papulosquamous lesions, but more florid epithelial hyperplasia and intraepithelial microabscess formation are observed. Silver or IHC stains show numerous treponemes. In addition to small, sarcoidal granulomata in papular lesions of early secondary syphilis, late secondary syphilis may show extensive lymphoplasmacellular and histiocytic infiltrates resembling nodular tertiary syphilis.

**Kaposi’s Sarcoma, Patch Stage**

The histologic spectrum of Kaposi’s disease can be divided into stages roughly corresponding to the clinical type of lesion: early and late macules, plaques, nodules, and aggressive late lesions. In early macules there is usually a patchy, sparse, upper dermal perivascular infiltrate consisting of lymphocytes and plasma cells. Narrow cords of cells, with evidence of luminal differentiation, are insinuated between collagen bundles. Usually a few dilated irregular or angulated lymphatic-like spaces lined by delicate endothelial cells are also present. Vessels with
Fig. IIIA1c.e. Kaposi's sarcoma, patch stage, low power. There is a perivascular and diffuse cellular infiltrate and an increased number of thin walled blood vessels.

Fig. IIIA1c.f. Kaposi's sarcoma, patch stage, high power. There are ill-defined jagged thin-walled vessels with hemorrhage and a mononuclear cell infiltrate. The infiltrate about the dermal vessels includes lymphocytes and plasma cells.

Fig. IIIA1c.g. Kaposi's sarcoma, patch stage, high power. In addition to the jagged vessels, there are spindle cells placed among dermal collagen bundles, with a tendency to form slit-like spaces.

Fig. IIIA1c.h. Kaposi's sarcoma, patch stage, low power. HHV8 immunostaining in a patch stage lesion shows positive intranuclear positivity in scattered cells in the reticular dermis.
“jagged” outlines tending to separate collagen bundles are especially characteristic. Normal adnexal structures and preexisting blood vessels often protrude into newly formed blood vessels, a finding known as the “promontory sign”. In late macular lesions there is a more extensive infiltrate of vessels in the dermis, with “jagged” vessels and with cords of thicker-walled vessels similar to those in granulation tissue. At this stage, red blood cell extravasation and siderophages may be encountered. The presence of slit-like vascular spaces is a characteristic histologic finding. This condition is now known to be associated with HHV-8 infection in a susceptible host (see Section VIC5).

Conditions to consider in the differential diagnosis:
- secondary syphilis
- arthropod bite reaction
- Kaposi’s sarcoma, non-specific patch stage
- actinic keratoses and Bowen’s disease
- Zoon’s plasma cell balanitis circumspecta
- erythroplasia of Queyrat

**Pityriasis Rosea**

**CLINICAL SUMMARY.** Pityriasis rosea is a self-limited dermatitis lasting from 4 to 7 weeks. It frequently starts with a larger herald patch followed by a disseminated eruption. The lesions, found chiefly on the trunk, neck, and proximal extremities, consist of round to oval salmon-colored patches following the lines of cleavage and showing peripherally attached, thin, cigarette-paper-like scales. Several typical and atypical clinical variants have been described including papular, vesicular, urticarial, purpuric, and recurrent forms. The cause of pityriasis rosea is still unknown, although a viral etiology such as human herpesvirus 7 (HHV-7) is suspected (18). Cell-mediated immunity may be involved in the pathogenesis due to the presence of activated helper-inducer T lymphocytes in the epidermal and dermal infiltrate in association with an increased number of Langerhans’ cells, and the expression of HLA-DR + antigen on the surface of keratinocytes located around the area of lymphocytic exocytosis (19).

**HISTOPATHOLOGY.** The patches of the disseminated eruption show a superficial perivascular infiltrate in the dermis that consists predominantly of lymphocytes, with occasional eosinophils and histiocytes. Lymphocytes extend into the epidermis (exocytosis), where there is

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**III A1c.1** Kaposi’s sarcoma, patch stage, low power. The HHV8 positive cells are seen to be lining vascular channels.

**III A1c.1.** Kaposi’s sarcoma, patch stage, low power. HHV8 positive cells infiltrating among reticular dermis collagen bundles as single cells and as cells lining vascular channels.

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**III A1d** **Superficial Perivascular Dermatitis, With Extravasated Red Cells**

A perivascular lymphocytic infiltrate is associated with extravasation of lymphocytes, without fibrinoid necrosis of vessels. Pityriasis rosea (16,17) and PLEVA are prototypic.
III. Disorders of the Superficial Cutaneous Reactive Unit

spongiosis, with intracellular edema, mild to moderate acanthosis, areas of decreased or absent granular layer, and focal parakeratosis with or without plasma cells. Intraepidermal spongiotic vesicles and a few necrotic keratinocytes are found in some cases. A common feature is the presence of extravasated erythrocytes in the papillary dermis, which sometimes extends into the overlying epidermis. Occasionally, multinucleated keratinocytes in the affected epidermis can be seen. Late lesions from the disseminated eruption are more likely to have a psoriasiform or lichen planus-like appearance and a relatively increased number of eosinophils in the inflammatory infiltrate.

Clin. Fig. IIIA1d.a. *Pityriasis rosea.* Oval brown patches following the lines of cleavage which may show peripheral, thin scales.

Fig. IIIA1d.a. *Pityriasis rosea, low power.* There is an ortho and parakeratotic scale overlying an epidermis that is acanthotic and spongiotic. The papillary dermis is edematous and contains an infiltrate of lymphocytes and red blood cells. This inflammatory infiltrate is seen about dermal vessels.

Fig. IIIA1d.b. *Pityriasis rosea, medium power.* The dermal papillae are widened, edematous and contain an infiltrate of lymphocytes and red blood cells.

Fig. IIIA1d.c. *Pityriasis rosea, high power.* The edematous papillary dermis is hemorrhagic. There may be exocytosis of mononuclear cells as well as red blood cells into the acanthotic, spongiotic epidermis. The ortho and parakeratotic scale forms characteristic small mounds of parakeratosis.
Pityriasis Lichenoides

**CLINICAL SUMMARY.** Pityriasis lichenoides is an uncommon cutaneous eruption usually classified in two forms that differ in severity. The milder form, called *pityriasis lichenoides chronica*, is characterized by recurrent crops of brown–red papules 4 to 10 mm in size, mainly on the trunk and extremities, which are covered with a scale and generally involute within 3–6 weeks with postinflammatory pigmentary changes. The more severe form, called PLEVA or Mucha–Habermann disease, consists of a fairly extensive eruption, present mainly on the trunk and proximal extremities. It is characterized by erythematous papules that develop into papulonecrotic, occasionally hemorrhagic or vesiculopustular lesions that resolve within a few weeks, and can result in scarring (see also Section VB2). Febrile ulceronecrotic Mucha–Habermann disease (FUMHD) is a rare very severe variant that can be life-threatening (20).

**HISTOPATHOLOGY.** In pityriasis lichenoides chronica, there is a superficial perivascular infiltrate composed of lymphocytes that extend into the epidermis, where there is vacuolar alteration of the basal layer, mild spongiosis, a few necrotic keratinocytes, and confluent parakeratosis. Melanophages and small numbers of extravasated erythrocytes are commonly seen in the papillary dermis. In PLEVA, the more severe form, the perivascular (predominantly lymphocytic) infiltrate is dense in the papillary dermis and extends into the reticular dermis in a wedge-shaped pattern. The infiltrate obscures the dermal–
III. Disorders of the Superficial Cutaneous Reactive Unit

Clin. Fig. IIIA1d.c. Pityriasis lichenoides chronica. A 29-year-old man gave an eight month history of asymptomatic dully erythematous macules and papules with light scale on the trunk and extremities.

Fig. IIIA1d.f. Pityriasis lichenoides chronica. A focal lesion characterized by hyperkeratosis and a lichenoid inflammatory infiltrate.

Fig. IIIA1d.g. Pityriasis lichenoides chronica. There is hyperkeratosis without the scale-crust or frank necrosis that may be seen in lesions of PLEVA.

Fig. IIIA1d.h. Pityriasis lichenoides chronica. There is vacuolar alteration of the basal layer, with mild spongiosis. In addition to lymphocytes, extravasated erythrocytes are present in the papillary dermis and in the epidermis.

epidermal junction with pronounced vacuolar alteration of the basal layer, marked exocytosis of lymphocytes and erythrocytes, and intercellular and intracellular edema leading to variable degree of epidermal necrosis. Ultimately, erosion or even ulceration may occur. The overlying cornified layer shows parakeratosis and a scaly crust with neutrophils in the more severe cases. Variable degrees of papillary dermal edema, endothelial swelling, and extravasated erythrocytes are seen in the majority of cases. Most of the cells in the inflammatory infiltrate are activated T lymphocytes. There is a predominance of CD8+ (cytotoxic-suppressor) over CD4+ (helper-inducer) T lymphocytes in the infiltrate, and there is expression of HLA-DR on the surrounding keratinocytes, suggesting a direct cytotoxic immune reaction in the pathogenesis of epidermal necrosis. Recent studies have suggested that PLEVA is a clonal T-cell disorder (21), although reports of patients with pityriasis lichenoides who have developed cutaneous lymphoma are rare. It is suggested that monoclonal expansion of T cells results most likely from a host immune response to an as yet unidentified antigen, perhaps a viral one (19).
**Pigmented Purpuric Dermatosis**

**CLINICAL SUMMARY.** Although several variants of pigmented purpuric dermatosis (PPD) have been described, they are all closely related and often cannot be reliably distinguished on clinical or histologic grounds (22). Clinically, the primary lesion consists of discrete puncta often limited to the lower extremities. Gradually, telangiectatic puncta appear as a result of capillary dilatation, and pigmentation as a result of hemosiderin deposits. In some cases, the findings may mimic those of stasis. Not infrequently, clinical signs of inflammation are present, such as erythema, papules, scaling, and lichenification. There are no systemic symptoms related to this disease process. The categorization of PPD as a form of cutaneous lymphoid dyscrasia has been suggested (23).

**HISTOPATHOLOGY.** The basic process is a lymphocytic perivascular infiltrate limited to the papillary dermis. In some instances, the infiltrate may assume a band-like or lichenoid pattern, and may involve the reticular dermis in a perivascular distribution. Evidence of vascular damage may be present. The extent of vascular injury is usually mild and insufficient to justify the term “vasculitis”,

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Clin. Fig. IIIA1d.d. *Pigmented purpuric dermatosis (Gougerot Blum).* 15-year-old boy developed asymptomatic nonblanching orange-brown and erythematous lichenoid papules on the lower extremities.

Fig. IIIA1d.i. *Pigmented purpuric dermatosis, low power.* An ortho and parakeratotic scale are present overlying an acanthotic epidermis. There is an inflammatory infiltrate in the papillary dermis.

Fig. IIIA1d.j. *Pigmented purpuric dermatosis, medium power.* The papillary dermis shows hemorrhage and a mononuclear cell infiltrate. There is superficial telangiectasia. Hemorrhage may be seen within the papillary dermis.

Fig. IIIA1d.k. *Pigmented purpuric dermatosis, high power.* The epidermis is acanthotic and shows exocytosis of lymphocytes as well as red blood cells. There is inflammation and hemorrhage in the papillary dermis. (continues)
commonly consisting only of endothelial cell swelling and dermal hemorrhage. Extravasated red blood cells are usually found in the vicinity of the capillaries. In old lesions, the capillaries often show dilatation of their lumen and proliferation of their endothelium. Extravasated red blood cells may no longer be present, but one frequently finds hemosiderin, in varying amounts. The inflammatory infiltrate is less pronounced than in the early stage.

Conditions to consider in the differential diagnosis:

- pityriasis rosea
- lupus erythematosus, subacute
- lupus erythematosus, acute
- postinflammatory hyperpigmentation
- stasis dermatitis
- Kaposi’s sarcoma, patch stage
- PLEVA
- pityriasis lichenoides chronica
- pigmented purpuric dermatoses (Gougerot-Bloom)

**Superficial Perivascular Dermatitis, Melanophages Prominent**

There is a perivascular infiltrate of lymphocytes, with an admixture of pigment-laden melanophages, indicative of prior damage to the basal layer, and “pigmentary incontinence”. Some degree of residual interface damage may also be evident. Postinflammatory hyperpigmentation is a prototype (24).

**Postinflammatory Hyperpigmentation**

**CLINICAL SUMMARY.** Postinflammatory hyperpigmentation may follow any dermatitis that affects the dermal–epidermal junction and results in release of melanin pigment from basal keratinocytes into the dermis. Lichenoid dermatoses such as lichen planus, vacuolar dermatoses such as discoid lupus, or apoptotic/cytotoxic dermatoses such as erythema multiforme or fixed drug
eruptions may all result in this reaction pattern. Lesions are sometimes biopsied to rule out melanoma. If features diagnostic of a specific underlying dermatosis are lacking in the biopsy, the descriptive diagnosis of post-inflammatory hyperpigmentation may be all that can be made.

**HISTOPATHOLOGY.** Sections show the phenomena of pigmentary incontinence. Melanin pigment deposited in the dermis is taken up by melanophages. These are large cells with abundant cytoplasm stuffed with pigment and with plump nuclei having open chromatin and sometimes a small nucleolus.
III. Disorders of the Superficial Cutaneous Reactive Unit

Conditions to consider in the differential diagnosis:
postinflammatory hyperpigmentation
post-chemotherapy hyperpigmentation
chlorpromazine pigmentation
amyloidosis

III A2 Superficial Perivascular Dermatitis, Mast Cells Predominant

Mast cells are the main infiltrating cells seen in the dermis. Lymphocytes are also present, and there may be a few eosinophils. Urticaria pigmentosa is the example.

Urticaria Pigmentosa

CLINICAL SUMMARY. Urticaria pigmentosa (25) can be divided into four forms: (1) urticaria pigmentosa arising in infancy or early childhood without significant systemic lesions, (2) urticaria pigmentosa arising in adolescence or adult life without significant systemic lesions, (3) systemic mast cell disease, and (4) mast cell leukemia. Five types of cutaneous lesions are seen. The maculopapular type, the most common, consists usually of dozens or even hundreds of small brown lesions that urticate on stroking; a second type exhibits multiple brown nodules or plaques,

Clin. Fig. IIIA2.a

Clin. Fig. IIIA2.b

Fig. IIIA2.a

Fig. IIIA2.b

Clin. Fig. IIIA2.a. Urticaria pigmentosa, nodular type. A 2–year-old had a recurrently erythematous and “swollen” solitary 2 cm yellow brown nodule on volar forearm.

Clin. Fig. IIIA2.b. Telangiectasia macularis eruptive perstans. A 78–year-old woman with 2-year history of telangiectatic erythematous blanching macules on the trunk, neck and thighs. Darier’s sign (urtication after stroking) was positive.

Fig. IIIA2.a. Adult mast cell disease (TMEP), low power. The epidermis is slightly acanthotic. There is a perivascular infiltrate of mononuclear cells about dermal vessels.

Fig. IIIA2.b. Adult mast cell disease, medium power. There is, in the dermis, a diffuse as well as perivascular infiltrate of lymphocytes and mast cells.
and, on stroking, shows urtication and occasionally blister formation. A third type, seen almost exclusively in infants, is characterized by a usually solitary, large cutaneous nodule, which on stroking often shows not only urtication but also large bullae. The fourth type, the diffuse erythrodermic type, always starts in early infancy and shows generalized brownish red, soft infiltration of the skin, with urtication on stroking. The fifth type of lesion, telangiectasia macularis eruptiva perstans (TMEP), which usually occurs in adults, consists of an extensive eruption of brownish red macules showing fine telangiectasias, with little or no urtication on stroking. Although mastocytosis is most typically a benign, self-limited disorder of childhood, up to 30% of adolescent and adult-onset disease represents cutaneous involvement by underlying systemic mastocytosis. CD25 immunoreactivity in a skin infiltrate may be a useful, though not specific, marker for systemic involvement (26).

**HISTOPATHOLOGY.** In all five types of lesions, the histologic picture shows an infiltrate composed chiefly of mast cells, which are characterized by the presence of metachromatic granules in their cytoplasm. These granules can be visualized with a Giemsa or toluidine blue stain, or with the naphthol AS-D chloroacetate esterase reaction (Leder stain). The lesional cells are also positive with immunostains for KIT and mast cell tryptase (26). In the maculopapular type and in telangiectasia macularis eruptiva perstans, the mast cells are limited to the upper third of the dermis and are generally located around capillaries. In some mast cells, the nuclei may be round or oval, but in most, they are spindle shaped. The diagnosis may be missed unless special staining is employed. In cases with multiple nodules or plaques or with a solitary large nodule, the mast cells lie closely packed in tumor-like aggregates and the infiltrate may extend into the subcutaneous fat. In the diffuse, erythrodermic type, there is a dense, band-like infiltrate of mast cells in the upper dermis. Eosinophils may be present in small numbers in all types of urticaria pigmentosa with the exception of TMEP, in which eosinophils are generally absent because of the small numbers of mast cells within the lesions.

**Conditions to consider in the differential diagnosis:**

- urticaria pigmentosa, nodular type
- TMEP, adult mast cell disease

**SUPERFICIAL DERMATITIS WITH SPONGIOSIS (SPONGIOTIC DERMATITIS)**

Spongiotic dermatitis is characterized by intercellular edema in the epidermis (27). In mild or early lesions, the intercellular space is increased with stretching of desmosomes but the integrity of the epithelium is intact. In more severe spongiotic conditions, there is separation of keratinocytes to form spaces (vesicles). For this reason, the spongiotic dermatoses are also listed below in Section IV, Acantholytic, Vesicular and Pustular Disorders.

1. Spongiotic Dermatitis, Lymphocytes Predominant
1a. Spongiotic Dermatitis, With Eosinophils
1b. Spongiotic Dermatitis, With Plasma Cells
1c. Spongiotic Dermatitis, With Neutrophils
Acute Spongiotic Dermatitis

In acute spongiotic dermatitis (28), the stratum corneum is normal in a very early lesion, but there is slight hyperkeratosis in a somewhat later lesion. If the lesion persists, parakeratosis will develop as it evolves further. The epidermal keratinocytes are partially separated by intercellular edema, which stretches the intercellular bridges or desmosomes and renders them more prominent than normal. If the lesion is more severe, the desmosomal attachments rupture, and intercellular spaces appear, usually in the spinous layer, forming spongiotic vesicles. Lymphocytes and occasionally larger Langerhans histiocytes are present in the spaces and in the edematous epidermis. In addition, there is a loose perivascular infiltrate around the vessels of the superficial capillary-venular plexus.

Subacute Spongiotic Dermatitis

In subacute spongiotic dermatitis, after a spongiotic lesion persists, there is epithelial hyperplasia, which tends to elongate the rete ridges in a pattern that is termed “psoriasiform”. Unlike in psoriasis, the suprapapillary plates of keratinocytes are not thinned, indeed they tend to be somewhat thickened. The etiology of the process is made apparent by the presence of spongiotic changes in the epidermis similar to those described above, though vesicle formation is often minimal. A similar perivascular infiltrate is present in the superficial dermis. Because the pattern of subacute spongiotic dermatitis is predominantly psoriasiform, these conditions are also discussed in section IIID, “psoriasiform dermatitis”.

Chronic Spongiotic Dermatitis

In chronic spongiotic dermatitis, there is prominent hyperkeratosis and parakeratosis. Spongiosis is usually present but may be quite inconspicuous in a given biopsy. Psoriasiform hyperplasia is prominent and when florid and complex may border on pseudoepitheliomatous hyperplasia. A perivascular lymphocytic infiltrate is present and may include an admixture of histiocytes and even plasma cells, depending on the etiology of the condition. There is often a distinctive pattern of increased collagen fibers arranged vertically between the elongated rete ridges. This papillary dermis sclerosis may be attributable to chronic rubbing or scratching of the lesions, resulting in the condition termed lichen simplex chronicus, which may have as its underlying basis any of the chronic pruritic dermatoses.

The disorders listed below all tend to follow the course listed above, from an acute to a subacute to a chronic spongiotic dermatitis, if the condition persists, and depending on associated factors such as the severity of the condition, the effects of treatment, and the effects of added irritants including the presence of excoriations of chronic rubbing and scratching. The differential diagnosis suggested by a given biopsy specimen may vary to some extent as discussed below, depending for example on the admixture of cell types such as eosinophils or plasma cells, and on the patterns of hyperkeratosis and parakeratosis, of psoriasiform epidermal hyperplasia, and of papillary dermis sclerosis. However, in a given biopsy it is often difficult or impossible to distinguish among the various etiologic categories of spongiotic dermatitis. While a biopsy may be of value to rule out other competing possibilities, such as lymphoma, and may tend to favor one or another of the possibilities listed in the differential diagnosis tables, the exact classification of these disorders usually depends on clinicopathologic correlation.

IIIB Spongiotic Dermatitis, Lymphocytes Predominant

There is marked intercellular edema (spongiosis) within the epidermis. In the dermis, perivascular lymphocytes are predominant. Nummular dermatitis is prototypic.

Nummular Dermatitis (Eczema)

CLINICAL SUMMARY. The eruption is characterized by pruritic, coin-shaped (nummular), erythematous, scaly, crusted plaques. The lesions tend to develop on the extensor surfaces of the extremities. Hypersensitivity to haptens such as metals may be involved in the pathogenesis of nummular dermatitis in some patients (29).

HISTOPATHOLOGY. Nummular dermatitis is the prototype of acute and subacute spongiotic dermatitis. There is mild to moderate spongiosis, usually without vesiculation, and a superficial perivascular infiltrate composed of lymphocytes, histiocytes, and occasional eosinophils. The epidermis is moderately acanthotic and parakeratotic. The stratum corneum contains aggregates of coagulated plasma and scattered neutrophils, forming a crust. Mild papillary dermal edema and vascular dilatation may be present.

Eczematous dermatitis.

Meyerson’s Nevus (See Clin. Fig. IIIB1.a and Figs. IIIB1.a–c)

CLINICAL SUMMARY. Meyerson’s nevus is a melanocytic nevus that is associated with an erythematous, eczematous halo that may symmetrically or eccentrically encircle the nevus (30). The lesion may be pruritic and scaly. Spontaneous resolution of the eczema over the course of weeks, without disappearance of the nevus, usually occurs. Meyerson’s nevi usually occur on the trunk and are more common in males. The simultaneous appearance of a Sutton’s (halo) nevus and Meyerson’s nevus has been reported after sunburn, as has the subsequent development of a Sutton’s nevus and vitiligo 6 months after removal of a Meyerson’s nevus, but this is not typical. Interferon-alpha therapy has been shown to induce Meyerson’s nevus (31).

HISTOPATHOLOGY. The melanocytic nevus may be banal, congenital (32), or dysplastic (33), with superimposed
changes of an eczematous dermatitis characterized by epidermal acanthosis and spongiosis which encompass the nevus and the adjacent epidermis (the eczematous halo). Spongiotic intraepidermal vesicles and eosinophilic spongiosis may be present. The stratum corneum may show focal parakeratosis with collections of serum. The superficial dermal infiltrate is composed of lymphocytes, histiocytes, and eosinophils. The lymphocytes have been shown to be predominantly CD4+ (helper) T cells, in contrast to the CD8+ (suppressor) T cells that are found in halo nevi.

Conditions to consider in the differential diagnosis:
- eczematous dermatitis
- atopic dermatitis
- allergic contact dermatitis
- photoallergic drug eruption
- irritant contact dermatitis
- nummular eczema
- dyshidrotic dermatitis
- Meyerson’s nevus
- parapsoriasis, small plaque type (digitate dermatosis)
**Clin. Fig. IIIB1.b.** Meyerson's nevus. Note the “eczematous” reaction surrounding the atypical nevus.

**Fig. IIIB1.d.** *Meyerson's nevus, low power.* The epidermis is acanthotic, spongiotic, and surmounted by parakeratotic scale with collections of serum.

**Fig. IIIB1.e.** *Meyerson's nevus, low power.* A mononuclear cell inflammatory infiltrate is present in the upper dermis, predominantly around vessels. Nevus cells are inconspicuous.

**Fig. IIIB1.f.** *Meyerson's nevus, medium power.* Pigmented nevomelanocytes and melanophages are seen in the dermis on closer inspection. The overlying epidermis shows separation of keratinocytes by intercellular edema.

**Fig. IIIB1.g.** *Meyerson's nevus, high power.* There is intense spongiosis in the epidermis. Nested nevus cells are seen in the dermis.
polymorphous light eruption
lichen striatus
chronic actinic dermatitis (actinic reticuloid)
actinic prurigo, early lesions
“id” reaction
seborrheic dermatitis
stasis dermatitis
erythroderma
miliaria
pityriasis rosea

Sezary syndrome
papular acrodermatitis (Gianotti-Crosti)

**IIIBa Spongiotic Dermatitis, With Eosinophils**

There is marked intercellular edema (spongiosis) within the epidermis. In the dermis, lymphocytes are predominant. Eosinophils can be found in most examples of atopy, and allergic contact dermatitis, and are numerous in incontinentia pigmenti. Allergic contact dermatitis is the prototype (27).

Clin. Fig. IIIB1a.a. *Allergic contact dermatitis*. Vesicles and bullae developed on volar forearm after application of perfume.

**Fig. IIIB1a.a. Acute allergic contact dermatitis, low power.** The stratum corneum consists of normal basket-weave keratin, indicative of an acute disorder that has not had time to elicit alterations in the pattern of keratinization. The epidermis is thickened by spongiosis and exocytosis, with prominent vesicle formation. A dense infiltrate of mononuclear cells is seen about dermal vessels.

**Fig. IIIB1a.b. Acute allergic contact dermatitis, high power.** Tense spongiotic vesicles are formed by the confluence of spongiotic intercellular edema.

**Fig. IIIB1a.c. Acute allergic contact dermatitis, high power.** The epidermis is spongiotic with a diffuse infiltrate of eosinophils (eosinophilic spongiosis).
Allergic Contact Dermatitis

**CLINICAL SUMMARY.** The prototype of acute spongiotic dermatitis is allergic contact dermatitis, for example as a reaction to poison ivy exposure. Usually between 24 and 72 hours after exposure to the antigen, the patient develops pruritic, edematous, erythematous papules and plaques and, in some cases, vesicles. Linear papules and vesicles are common in allergic contact dermatitis to poison ivy, reflecting the points of contact between the plant and the skin. Markers of genetic susceptibility to contact allergy are beginning to be identified (34).

**HISTOPATHOLOGY.** Early lesions are an acute spongiotic dermatitis. If vesicles develop, they may contain clusters of Langerhans cells. Eosinophils may be present in the dermal infiltrate as well as within areas of spongiosis. In patients with continued exposure to the antigen, the biopsy may show a subacute or later a chronic spongiotic dermatitis, often lichen simplex chronicus due to rubbing. In a recent study, eosinophilic spongiosis and multinucleate dermal dendritic fibrohistiocytic cells, in the presence of acanthosis, lymphocytic infiltrate, dermal eosinophils, and hyperkeratosis, were considered to be particularly suggestive of allergic contact dermatitis compared to other spongiotic dermatoses (27).

**Allergic Contact Dermatitis**

See Clin. Fig. IIIB1a.a, Fig. IIIB1a.a–c, Clin. Fig. IIIB1a.b and Fig. IIIB1a.d–g.

**Conditions to consider in the differential diagnosis:**
- spongiotic (eczematous) dermatitis
- atopic dermatitis
- allergic contact dermatitis
- photoallergic drug eruption
- incontinentia pigmenti, vesicular stage
- eczematous nevus (Meyerson’s nevus)
- erythema gyratum repens
- scabies
- erythema toxicum neonatorum

**Clin. Fig. IIIB1a.b**

Subacute contact dermatitis. Elderly woman had several month history of pruritic scaly facial erythema and positive fragrance mix patch test.

**Fig. IIIB1a.d**

Psoriasiform epidermal hyperplasia

**Clin. Fig. IIIB1a.d.** Subacute allergic contact dermatitis, low power. The stratum corneum is altered by compact orthokeratosis. The epidermis is thickened by mild spongiotic edema, and by moderately prominent psoriasiform hyperplasia (i.e., characterized by elongation of the rete ridges as in psoriasis).

**Fig. IIIB1a.e.** Subacute allergic contact dermatitis, medium power. The epidermis is spongiotic. There is an inflammatory infiltrate in the edematous papillary dermis.
IIIB. Superficial Dermatitis With Spongiosis (Spongiotic Dermatitis)

**IIIB1a.** Subacute allergic contact dermatitis, medium power. There is a focal scale-crust in the superficial epidermis, the site of a several day old vesicle. The papillary dermis is edematous and has an infiltrate of lymphocytes and eosinophils diffusely as well as about dermal vessels.

**IIIB1a.g.** Subacute allergic contact dermatitis, high power. There is a parakeratotic scale overlying a spongiotic epidermis that shows exocytosis of eosinophils. There are numerous eosinophils in the dermal infiltrate.

**IIIB1b** Spongiotic Dermatitis, With Plasma Cells

There is marked intercellular edema (spongiosis) within the epidermis. In the dermis, perivascular lymphocytes are predominant, and plasma cells are present. Syphilis is the prototype (see Section IIIA1c.a–c).

**Conditions to consider in the differential diagnosis:**
- syphilis, primary or secondary lesions
- pinta, primary or secondary lesions
- seborrheic dermatitis in HIV

**IIIB1c** Spongiotic Dermatitis, With Neutrophils

There is marked intercellular edema (spongiosis) within the epidermis. Lymphocytes are present in the dermis. There is focal and shoulder parakeratosis, with a few neutrophils in the stratum corneum. Seborrheic dermatitis is a prototype (35).

**Seborrheic Dermatitis**

**CLINICAL SUMMARY.** Clinically, patients develop erythema and greasy scale on the scalp, paranasal areas, eyebrows, nasolabial folds, and central chest. Rarely, patients with seborrheic dermatitis develop generalized lesions. Patients with HIV infection often have severe, recalcitrant disease (2). In infants, the scalp (“cradle cap”), face, and diaper areas are often involved.

**HISTOPATHOLOGY.** The histopathologic features are a combination of those observed in psoriasis and spongiotic dermatitis. Mild cases may exhibit only a slight subacute spongiotic dermatitis. The stratum corneum contains focal areas of parakeratosis, with a predilection for the follicular ostia, a finding known as “shoulder parakeratosis.” Occasional pyknotic neutrophils are present within parakeratotic foci. There is moderate acanthosis with regular elongation of the rete ridges, mild spongiosis, and focal exocytosis of lymphocytes. The dermis contains a sparse mononuclear cell infiltrate. In HIV-infected patients, the epidermis may contain dyskeratotic keratinocytes, and the dermal infiltrate may contain plasma cells.

**Conditions to consider in the differential diagnosis:**
- dermatophytosis
- *seborrheic dermatitis*
- toxic shock syndrome
III. Disorders of the Superficial Cutaneous Reactive Unit

Clin. Fig. IIIB1c. Seborrheic dermatitis. Greasy erythema involving the nasolabial folds, glabella, medial eyebrows and chin characterize this condition.

Fig. IIIB1c.a. Seborrheic dermatitis, medium power. An ortho and parakeratotic scale overlie an acanthotic epidermis that also has spongiosis and exocytosis.

Fig. IIIB1c.b. Seborrheic dermatitis, high power. Fragments of polymorphonuclear leukocytes are seen within the keratotic scale overlying an acanthotic epidermis.

IIC

SUPERFICIAL DERMATITIS WITH EPIDERMAL ATROPHY
(ATROPHIC DERMATITIS)

Most inflammatory dermatoses are associated with epithelial hyperplasia. Only a few chronic conditions exhibit epidermal atrophy.

1. Atrophic Dermatitis, Scant Inflammatory Infiltrates.
2. Atrophic Dermatitis, Lymphocytes Predominant
2a. Atrophic Dermatitis With Papillary Dermal Sclerosis

IIC1 Atrophic Dermatitis, Scant Inflammatory Infiltrates

The epidermis is thinned, only a few cell layers thick. There is a scanty lymphocytic infiltrate about the superficial capillary-venular plexus. Aged skin is the prototype (36).

Conditions to consider in the differential diagnosis:
- aged skin
- chronic actinic damage
- radiation dermatitis
- porokeratosis
- acrodermatitis chronica atrophicans
- malignant atrophic papulosis
- poikiloderma atrophicans vasculare

Aged Skin

Although not an inevitable consequence of aging in the skin, actinic elastosis is a prominent feature in the sun-exposed skin of susceptible individuals. A validated grading scheme for actinic elastosis has been described (37).

Radiation Dermatitis (See also Section VF1)

See Fig. IIIC1.c and Fig. IIIC1.d.
Clin. Fig. IIC1. Aged skin. Dorsal hand has transparent, wrinkled skin with prominent vessel and solar purpura.

Fig. IIC1.a. Aged skin, low power. There is an effaced atrophic epidermis. The dermis shows marked solar elastosis with dilated thin walled vessels. The inflammatory infiltrate is sparse.

Fig. IIC1.b. Aged skin, medium power. The epidermis is evenly effaced. It overlies a dermis that has marked solar elastosis and a sparse inflammatory infiltrate. Grades of elastosis can be identified from bottom up: Grade I: Single fibers of gray elastotic material in the deep dermis where penetration of UV is less; Grade II: Bunches or “bushels” of fibers in the mid layer; Grade III: Confluent homogeneous material in the upper dermis.

Clin. Fig. IIC1. Radiation dermatitis, low power. The low power shows epidermal atrophy with discrete areas of acanthosis and basal layer pigmentation. The dermis is homogeneous and there is telangiectasia.

Fig. IIC1.c. Radiation dermatitis, medium power. There is dermal homogenization with vascular ectasia and a sparse infiltrate about dermal vessels. The epidermis shows atrophy with basal layer pigmentation.
**Atrophic Dermatitis, Lymphocytes Predominant**

The epidermis is thinned, but not as marked as in aged or irradiated skin. In the dermis there are few to many lymphocytes about the superficial capillary-venular plexus.

**Conditions to consider in the differential diagnosis:**
- parapsoriasis/early mycosis fungoides
- lupus erythematosus
- mixed connective tissue disease
- pinta, tertiary lesions
- dermatomyositis
- poikiloderma atrophicans vasculare

**Poikiloderma Atrophicans Vasculare**

**CLINICAL SUMMARY.** Clinically, the term poikiloderma atrophicans vasculare is applied to lesions that, in the early stage, show erythema with slight, superficial scaling, a mottled pigmentation, and telangiectases. In the late stage the skin appears atrophic and the mottled pigmentation and the telangiectases are more pronounced. The condition may be seen in three different settings: (1) in association with certain genodermatoses; (2) as an early stage of mycosis fungoides (38); and (3) in association with dermatomyositis and, less commonly, lupus erythematosus.

Genodermatoses in which the cutaneous lesions are poikilodermatous include: (1) poikiloderma congenitale of Rothmund–Thomson, with the lesions present largely on the face, hands, and feet, and occasionally also on the arms, legs, and buttocks (39); (2) Bloom’s syndrome, with poikiloderma-like lesions on the face, hands, and forearms (40); (3) dyskeratosis congenita, in which there may be extensive net-like pigmentation (41), and (4) Kindler syndrome which is categorized as a subtype of epidermolysis bullosa and is characterized by poikiloderma, trauma-induced skin blistering, mucosal inflammation, and photosensitivity (42).

Poikiloderma-like lesions as features of early mycosis fungoides may be seen in one of two clinical forms: either as the large plaque (>10 cm) type of parapsoriasis en plaques, also known as poikilodermatous parapsoriasis, or as parapsoriasis variegata, which shows papules arranged in a net-like pattern. Although these two types of parapsoriasis are thought to represent an early stage of mycosis fungoides, not all cases progress clinically into fully developed mycosis fungoides.

The third group of diseases in which lesions of poikiloderma atrophicans vasculare occur is represented by dermatomyositis and SLE. Dermatomyositis is much more commonly seen as the primary disease than lupus erythematosus, and the association with dermatomyositis often is referred to as poikilodermatomyositis. In contrast to mycosis fungoides, in which poikilodermatous lesions are seen in the early stage, the lesions found in dermatomyositis and SLE generally represent a late stage.

**HISTOPATHOLOGY.** In early lesions of any cause, there is moderate thinning of the epidermis, with effacement of the rete ridges, and hydropic degeneration of the basal cells. In the upper dermis there is a band-like infiltrate, which in places invades the epidermis. The infiltrate consists mainly of lymphoid cells but also contains a few histiocytes. Melanophages filled with melanin as a result of pigmentary incontinence are found in varying numbers within the infiltrate. In addition, there is edema in the upper dermis and the superficial capillaries are often dilated. In the late stage the epidermis is apt to be markedly thinned and flattened, but the basal cells still show hydropic degeneration. Melanophages and edema of the upper dermis are still present, and telangiectasia may be pronounced.

The amount and type of dermal infiltrate vary with the underlying cause. In the genodermatoses and in dermatomyositis or SLE there is only slight dermal inflammation. In contrast, the inflammatory infiltrate seen in poikiloderma associated with early mycosis fungoides increases with time. Cells with large, hyperchromatic nuclei, so-called mycosis cells, are likely to be present and there is often marked epidermotropism of the infiltrate, which may result in Pautrier microabscesses (43). Even in developing lesions, the papillary dermis is expanded by fibrosis and collagen bundle thickening which increases in rough proportion to lesional age. Thus, in the earliest patches, fibrosis is noticeable but subtle, whereas the papillary dermis is coarsely fibrotic late in the patch stage or in fully developed plaques. Thickened collagen bundles often lie roughly parallel to the epidermal surface, in contrast to the vertically oriented collagen bundles that develop secondary to lichenification. The overlying epidermis is nearly normal in the earliest patch lesions, but typically shows slight, regular psoriasiform hyperplasia and hyperkeratosis, although atrophy can be seen in poikilodermatous patches. Because the specific histologic features of MF are attenuated in poikilodermatous disease, multiple biopsies may be necessary for unequivocal diagnosis.

**Dermatomyositis**

See Clin. Fig. IIIC2.b and Fig. IIIC2.d–f.
Clin. Fig. IIC2.a. *Poikiloderma vasculare atrophicans.* Chronic skin changes in dermatomyositis reveal skin thinning, capillary dilatation, and mild pigmentary change.

Fig. IIC2.a. *Poikiloderma atrophicans vasculare, low power.* There is a thin, keratotic scale overlying an atrophic epidermis. The papillary dermis is edematous and has a subtle diffuse infiltrate of mononuclear cells.

Fig. IIC2.b. *Poikiloderma atrophicans vasculare, medium power.* The thinned atrophic epidermis shows basal layer vacuolar degeneration. In the papillary dermis there is an infiltrate of lymphocytes seen diffusely as well as about thin walled dermal vessels.

Fig. IIC2.c. *Poikiloderma atrophicans vasculare, high power.* The epidermis shows focal basal layer liquefaction degeneration and a diffuse infiltrate of lymphocytes in an edematous papillary dermis, with a few lymphocytes extending among basal keratinocytes.

**IIC3 Atrophic Dermatitis With Papillary Dermal Sclerosis**

The epidermis is thinned, there can be hyperkeratosis. The dermis is homogenized and edematous, inflammation is minimal. Lichen sclerosus et atrophicus is prototypic (44,45).

**Lichen Sclerosus Et Atrophicus**

**CLINICAL SUMMARY.** Lichen sclerosus (LS) encompasses the disorders known as *lichen sclerosus et atrophicus, balanitis xerotica obliterans* (LS of the male glans and prepuce), and *kraurosis vulvae* (LS of the female labia majora, labia minora, perineum, and perianal region). Lichen
sclerosus is an inflammatory disorder of unknown etiology that affects patients 6 months of age to late adulthood. In both males and females genital involvement is the most frequent, and often the only, site of involvement. Extragenital lesions may occur with or without coexisting genital lesions. Lesions of LS are characterized by white polygonal papules that coalesce to form plaques. Comedo-like plugs on the surface of the plaque correspond to dilated appendageal ostia. The plugs may disappear as the lesion ages, leaving a smooth, porcelain-white plaque. Solitary or generalized lesions may become bullous and hemorrhagic.

**HISTOPATHOLOGY.** The salient histologic findings in cutaneous lesions of lichen sclerosus et atrophicus are: (1) hyperkeratosis with follicular plugging, (2) atrophy of the stratum malpighii with hydropic degeneration of basal

**Clin. Fig. IIIC2.b.** *Dermatomyositis.* Heliotrope lavender pruritic edematous periorbital changes in middle aged woman indicates a search for malignancy.

**Fig. IIIC2.d.** *Dermatomyositis, low power.* The epidermis is little altered in this example. In the dermis there is an infiltrate of mononuclear cells. The papillary dermis is expanded and edematous.

**Fig. IIIC2.e.** *Dermatomyositis, medium power.* There is a sparse lichenoid infiltrate at the dermal-epidermal junction that causes basal layer liquefaction degeneration. The papillary dermis is expanded. The infiltrate is diffuse as well as being perivascular and is lymphocytic in type.

**Fig. IIIC2.f.** *Dermatomyositis, high power.* The basal layer shows distinct basal layer degeneration. The papillary dermis has telangiectatic vessels, and a perivascular as well as diffuse infiltrate of lymphocytes.
cells, (3) pronounced edema and homogenization of the collagen in the upper dermis, and (4) an inflammatory infiltrate in the mid-dermis. Beneath the hyperkeratotic and atrophic epidermis is a broad zone of pronounced lymphedema. Within this zone, the collagen fibers are swollen and homogeneous and contain only a few nuclei. The blood and lymph vessels are dilated, and there may be areas of hemorrhage. In areas of severe lymphedema,

**Clin. Fig. IIC3.** Lichen sclerosus et atrophicus. A “keyhole” ivory colored, sclerotic plaque with hemorrhage, which evolved in a child who had genital pruritus.

**Fig. IIC3.a.** Lichen sclerosus et atrophicus, low power. There is hyperkeratosis overlying an atrophic epidermis. The papillary dermis appears pale and there is an underlying perivascular infiltrate of mononuclear cells.

**Fig. IIC3.b.** Lichen sclerosus et atrophicus, medium power. Hyperkeratosis overlies an atrophic epidermis. The papillary dermis shows homogenization and there is an underlying infiltrate of lymphocytes about dermal vessels.

**Fig. IIC3.c.** Lichen sclerosus et atrophicus, high power. There is hyperkeratosis overlying an atrophic effaced epidermis. Underlying the area of homogenization of the papillary dermis is a perivascular as well as a diffuse (often band-like) infiltrate of lymphocytes in the reticular dermis. (*continues*)
clinically visible subepidermal bullae may form. Except in lesions of long duration, an inflammatory infiltrate is present in the dermis. In very early lesions the infiltrate may be found in the uppermost dermis, in direct apposition to the basal layer. The histologic features in early LS may be subtle and may be more prominent in adnexa, with various combinations of acanthosis, hyperkeratosis and hypergranulosis, dystrophic hairs, and basement membrane thickening. The epithelium begins to develop irregular acanthosis, occasionally psoriasiform, and focal basement membrane thickening. Early dermal changes of homogenized collagen and wide ectatic capillaries in superficial
dermal papillae are followed by the development of a lymphocytic infiltrate which can be sparse or dense, lichenoid, perivascular or interstitial, with epidermal lymphocyte exocytosis. Dermal melanophages indicate preceding destruction of pigmented keratinocytes and/or melanocytes. Biopsy specimens of early lesions rarely display all features (44). With time, a narrow zone of edema and homogenization of the collagen displaces the inflammatory infiltrate farther down, so that, in well-developed lesions, the infiltrate is found in the mid-dermis. The infiltrate can be patchy, but it is often band-like and composed of lymphoid cells admixed with plasma cells and histiocytes.

**Conditions to consider in the differential diagnosis:**
- lichen sclerosus et atrophicus
- thermal burns
- parapsoriasis/early mycosis fungoides
- poikilodema atrophicans vasculare

### IIID SUPERFICIAL DERMATITIS WITH PSORIASIFORM PROLIFERATION (PSORIASIFORM DERMATITIS)

Psoriasiform proliferation, so called because it is a characteristic feature of psoriasis, is a form of epithelial hyperplasia characterized by uniform elongation of rete ridges. Although the surface may be slightly raised to form a plaque, the epidermal proliferation tends to extend downwards into the dermis, in contrast to a papillomatous pattern in which the rete ridges are elongated upwards above the plane of the epidermal surface and a papilloma (such as a wart) is formed. The prototype is psoriasis, in which the supra-papillary plates are thinned. In most other psoriasiform conditions, the supra-papillary plates are thickened, but not as much as the elongated rete. Because of the increased epithelial turnover, there is often associated hypogranulosis and parakeratosis.

1. Psoriasiform Dermatitis, Mostly Lymphocytes
   1a. Psoriasiform Dermatitis, With Plasma Cells
   1b. Psoriasiform Dermatitis, With Eosinophils
2. Psoriasiform Dermatitis, Neutrophils Prominent (Neutrophilic/Pustular Psoriasiform Dermatitis)

### IIID1 Psoriasiform Dermatitis, Mostly Lymphocytes

The epidermis is evenly and regularly thickened in a psoriasiform pattern, spongiosis is variable (rare to absent in psoriasis; common in seborrheic and inflammatory dermatoses). There is an infiltrate of lymphocytes about dermal vessels. Pityriasis rubra pilaris is a prototypic example (46,47).

### Pityriasis Rubra Pilaris

**CLINICAL SUMMARY.** Pityriasis rubra pilaris is an erythematous squamous disorder characterized by follicular plugging and perifollicular erythema that coalesces to form orange–red scaly plaques that frequently contain islands of normal–appearing skin. As the erythema extends, the follicular component is often lost, but it persists longest on the dorsa of the proximal phalanges. The lesions spread caudally and may progress to a generalized erythroderma. Other clinical findings are palmoplantar keratoderma and scaling of the face and scalp. Most patients clear within 3 years, but some cases are more persistent, especially the circumscribed juvenile type, which is characterized by sharply demarcated lesions on the knees and elbows. Some cases usually in adults progress to generalized exfoliative erythroderma. There is a proposed new category that is associated with HIV infection and has different clinical features and a poorer prognosis (48).

**HISTOPATHOLOGY.** The histologic picture of a fully developed erythematous lesion shows acanthosis with broad and short rete ridges, slight spongiosis, thick suprapapillary plates, focal or confluent hypergranulosis, and alternating orthokeratosis and parakeratosis oriented in both vertical and horizontal directions. In the dermis there is a mild superficial perivascular lymphocytic infiltrate and moderately dilated blood vessels.

Areas corresponding to follicular papules show dilated infundibula filled with an orthokeratotic plug and often display perifollicular shoulders of parakeratosis and a mild perifollicular lymphocytic inflammation. Erythrodermic lesions have a thinned or absent cornified layer, plasma exudates, and a diminished granular zone.

### Mycosis Fungoides, Patch-Plaque Stage

**CLINICAL SUMMARY.** Mycosis fungoides (49,50) (MF) is a form of T-cell lymphoma that initially involves the epidermis and papillary dermis, comprising the patch stage of the disease. With time, the neoplastic lymphocytes often acquire the capacity to proliferate within the reticulardermis, and plaques, nodules, and tumors (plaque and tumor stages) are manifest clinically. In some patients, generally after extended periods of time, the neoplasm disseminates to extracutaneous sites such as lymph nodes and viscera. The term MF was coined by Alibert after
observing mushroom-like nodules in the tumor stage of the disease. Patches of MF are usually pinkish red and slightly scaly, typically distributed on the trunk and proximal extremities. The buttocks and breasts are often involved. At least some of the patches exceed 10 cm in diameter in most patients, corresponding to the morphologic pattern of “large plaque parapsoriasis.” The proportion of patients with patch stage MF that will progress to develop plaques is not precisely known but is thought to be low. Plaques of MF are sharply margined and are usually red to reddish brown. The centers of plaques can involute, yielding annular or serpiginous morphology. Tumors

**Clin. Fig. IIID1.a.** *Pityriasis rubra pilaris.* A 22-year-old woman developed confluent well-demarcated orange red scaling patches with prominent keratotic follicular papules on the trunk, with “skip areas” of normal skin.

**Clin. Fig. IIID1.b.** *Pityriasis rubra pilaris.* “Keratodermic sandals” present with thick yellow waxy fissured sometimes painful palms and soles.

**Fig. IIID1.a.** *Pityriasis rubra pilaris, low power.* There is follicular hyperkeratosis with an alternating scale of ortho and parakeratin overlying an acanthotic epidermis. A perivascular infiltrate of mononuclear cells is seen in the dermis.

**Fig. IIID1.b.** *Pityriasis rubra pilaris, medium power.* The parakeratotic scale shows alternating vertical as well as linear parakeratosis. The epidermis is acanthotic with slight spongiosis. (continues)
of MF are morphologically indistinguishable from tumors of other cutaneous lymphomas, except that residual patch and plaques are virtually always evident.

**HISTOPATHOLOGY.** The microscopic findings in the earliest patches of MF are subtle, consisting of a sparse intraepidermal and papillary dermal infiltrate of lymphocytes, arrayed within a fibrotic papillary dermis below an epidermis that shows slight psoriasiform hyperplasia. Because of the sparse infiltrate, multiple biopsies and close clinicopathologic correlation are often needed for diagnosis. Small numbers of lymphocytes, with relatively small but irregular nuclei, are arrayed within the epidermis with minimal associated spongiosis. The lymphocytes are often distributed in a linear array on the epidermal side of the basement membrane zone, an arrangement that has been likened to a string of pearls. Although clusters of intraepidermal lymphocytes, so-called Pautrier’s microabscesses, are often sought as the key to a diagnosis of MF, a pattern in which lymphocytes are dispersed among keratinocytes is more common in biopsies of macular lesions. Architectural alterations involve both the papillary dermis and the epidermis. The papillary dermis is expanded by fibrosis, whose degree increases in rough proportion to lesional age. Thickened collagen bundles often lie roughly parallel to the epidermal surface, in contrast to the vertically oriented collagen bundles that develop secondary to lichenification. The overlying epidermis typically shows slight, regular psoriasiform hyperplasia and hyperkeratosis in the more advanced lesions. Readily discernible nuclear atypia of lymphocytes is the exception rather than the rule in conventional histologic sections of patch stage disease, but at high magnification, some degree of nuclear convolution is usually appreciable, especially among the intraepithelial lymphocytes. A working group has recently defined an algorithm for diagnosis of early MF in which clinical, histologic, immunopathologic and molecular criteria are all considered in a point system (Table III-1) (50). This system will likely add specificity to the process, and emphasizes that none of these attributes, taken in isolation, is uniformly diagnostic.

In plaque stage MF, the papillary dermis is similarly expanded by coarse fibrosis and contains denser, band-like infiltrates of lymphocytes, with as a rule more prominent epidermotropism. In combination with slight, regular epidermal thickening, these features account for the “lichenoid-psoriasiform” pattern that is characteristic of the late patch stage and the plaque stage. In addition to a papillary dermal infiltrate, the reticular dermis holds superficial and deep perivascular or nearly diffuse infiltrates of lymphocytes. Cytologic atypism, particularly of intraepidermal lymphocytes, is often conspicuous in biopsies from plaques, in contrast to the subtle cytologic changes evident in macular lesions.

**Fig. IID1.c.** Pityriasis rubra pilaris, medium power. The papillary dermis has a sparse to moderate, perivascular infiltrate of lymphocytes.

**Fig. IID1.d.** Pityriasis rubra pilaris, high power. There is parakeratosis dipping into the follicular orifice.
IMMUNOPATHOLOGY. Early stages of mycosis fungoides display a predominant CD4+ T-helper 1 (Th1) cytokine profile. It is believed that a shift in cytokine profile from Th1 to Th2 accompanies disease progression. Malignant CD4+ T cells, after stimulation with immature dendritic cells, can adopt a CD4+CD25+ Treg cell phenotype, then appearing to function as immune suppressors by secreting interleukin-10 and transforming growth factor-beta (51).

CLINICOPATHOLOGIC DIAGNOSIS. In many cases, the diagnosis of MF can be made with confidence on a skin biopsy accompanied by clinical information. However, a definitive histopathologic diagnosis by light microscopy alone may be difficult to make in early MF or in erythroderma, in which inflammatory cells often predominate in the dermal infiltrate (if any is present). The International Society for Cutaneous Lymphoma has proposed a diagnostic algorithm for early mycosis fungoides (Table III.1) (52).

**Parapsoriasis**

**GENERAL.** Parapsoriasis is a chronic dermatosis which has been divided into two categories: large plaque parapsoriasis and small plaque parapsoriasis. The relationship between parapsoriasis and early mycosis fungoides is not clearly defined and has been controversial. Large plaque parapsoriasis is generally agreed to be either pre-lymphomatous or early established lymphoma. Small plaque parapsoriasis, which has been known as “chronic superficial dermatitis” or “superficial persistent dermatitis,” describing its salient clinical characteristics, is generally considered to be a reactive chronic dermatosis with an almost invariably benign clinical course. Ackerman stated that even small plaque parapsoriasis should be considered to represent early mycosis fungoides (53). Although some cases of evolution have probably been described, this is rare and patients with small plaque parapsoriasis should not be lumped together with those who have a true lymphoma with potential for life-threatening progression. Simple light microscopy even with immunohistochemical analysis for CD4/CD8 ratio, aberrant expression of T-cell antigens, and expression of proliferation markers, is often unable to establish a more definitive diagnosis (54). Clinical and molecular criteria are then required. Criteria presented in Table III.1 may be used to help distinguish these difficult cases from early mycosis fungoides.

### Conditions to consider in the differential diagnosis:
- chronic spongiotic dermatitis
  - atopic dermatitis
  - seborrheic dermatitis
  - nummular eczema
- lichen simplex chronicus
- prurigo nodularis
- psoriasis
- psoriasiform drug eruptions
- pityriasis rosea
- exfoliative dermatitis
- pityriasis rubra pilaris
- parapsoriasis/early mycosis fungoides
- verrucous hyperkeratotic mycosis fungoides
- inflammatory linear verrucous epidermal nevus (ILVEN)
- pellagra
- necrolytic migratory erythema (chronic lesions)
- acrodermatitis enteropathica
- kwashiorkor
- reticulated hyperpigmentations (e.g., Dowling-Degos disease)

### Table III.1. Algorithm for the Diagnosis of Early MF

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Major</th>
<th>Minor</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent and/or progressive patches and plaques plus</td>
<td>Any 2</td>
<td>Any 1</td>
</tr>
<tr>
<td>(1) Non–sun-exposed location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Size/shape variation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Poikiloderma</td>
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<td></td>
</tr>
<tr>
<td><strong>Histopathologic</strong></td>
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<tr>
<td>Superficial lymphoid infiltrate plus</td>
<td>Both</td>
<td>Either</td>
</tr>
<tr>
<td>(1) Epidermotropism without spongiosis</td>
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<td></td>
</tr>
<tr>
<td>(2) Lymphoid atypia*</td>
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<td></td>
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<tr>
<td><strong>Molecular/biologic:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonal TCR gene rearrangement</td>
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<td>Present</td>
</tr>
<tr>
<td><strong>Immunopathologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) CD2,3,5 less than 50% of T cells</td>
<td>NA†</td>
<td>Any 1</td>
</tr>
<tr>
<td>(2) CD7 less than 10% of T cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Epidermal discordance from expression of CD2,3,5 or CD7 on dermal T cells</td>
<td></td>
<td></td>
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</tbody>
</table>

NA indicates not applicable.

* Lymphoid atypia is defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours.
† Not applicable since it cannot fulfill any major criteria.
Adapted from (50).
Clin. Fig. IID1.c. *Parapsoriasis/early mycosis fungoides*. Chronic pruritic maculopapular changes became increasingly indurated with erosions.

Clin. Fig. IID1.d. *Mycosis fungoides*. A 66-year-old woman presented with a 30 year history of erythematous scaly patches and plaques with telangiectases, atrophy and pigmentation.

Fig. IID1.e. *Mycosis fungoides, patch stage, low power*. A thin keratin layer overlies an acanthotic epidermis. The papillary dermis is edematous. A mononuclear cell infiltrate about dermal vessels is in the upper reticular dermis.

Fig. IID1.f. *Mycosis fungoides, patch stage, medium power*. Exocytosis of hyperchromatic lymphocytes into an acanthotic non-spongiotic epidermis is seen. The papillary dermis shows edema and a similar infiltrate that is diffuse within the papillary dermis.

Fig. IID1.g. *Mycosis fungoides, patch stage, high power*. Exocytosis is characterized by the presence of hyperchromatic mononuclear cells within the acanthotic epidermis; in addition the cells align along the DEJ. Clinicopathologic correlation would be important to help establish the diagnosis in this case (see Table III.1).
Psoriasiform Dermatitis, With Plasma Cells

The epidermis is evenly thickened and may be spongiotic. There may be exocytosis of lymphocytes. The stratum corneum is variable, often parakeratotic. Plasma cells are found about the superficial vessels in varying numbers, admixed with lymphocytes. Lichen simplex chronicus is a prototype.

Lichen Simplex Chronicus (See also Section IIIE)

CLINICAL SUMMARY. Any patient with pruritus who chronically rubs the skin may develop lichen simplex chronicus. It often develops in the setting of atopic dermatitis or allergic contact dermatitis. The lesions are pruritic, thickened plaques often with excoriation, in which the normal skin markings are accentuated, the latter finding known as lichenification. The process is commonly seen in chronic vulvar lesions (55).

HISTOPATHOLOGY. Lichen simplex chronicus is the prototype for chronic dermatitis. There is hyperkeratosis interspersed with areas of parakeratosis, acanthosis with irregular elongation of the rete ridges, hypergranulosis, and broadening of the dermal papillae. Slight spongiosis may be observed, but vesiculation is absent. There may be a sparse superficial perivascular infiltrate without exocytosis. In the papillary dermis, there is an increased number of fibroblasts and vertically oriented collagen bundles. As rubbing increases in intensity and chronicity, epidermal hyperplasia becomes more florid, and the fibrosis more marked.

Conditions to consider in the differential diagnosis:
- arthropod bite reactions
- secondary syphilis
- cutaneous T-cell lymphoma (mycosis fungoides)
- prurigo nodularis
Clin. Fig. IID1a.a. *Lichen simplex chronicus*. Chronic “rubbing” of posterior neck led to accentuation and thickening of skin markings.

**Fig. IID1a.a.** *Lichen simplex chronicus, low power*. There is a patchy parakeratotic scale overlying an irregularly acanthotic epidermis in which there is fusion of the rete ridges. The dermis is papillomatous, with a perivascular infiltrate of mononuclear cells.

**Fig. IID1a.b.** *Lichen simplex chronicus, medium power*. The epidermis shows marked acanthosis without significant exocytosis. There is papillomatosis and a diffuse as well as perivascular infiltrate in the fibrocellular dermis.

**Fig. IID1a.c.** *Lichen simplex chronicus, medium power*. There are vertically oriented collagen fibers in the elongated dermal papillae.

**Fig. IID1a.d.** *Lichen simplex chronicus, high power*. The dermal infiltrate consists of lymphocytes and (in this case) plasma cells.
III. Disorders of the Superficial Cutaneous Reactive Unit

**III D1b** Psoriasiform Dermatitis, With Eosinophils

The epidermis is evenly thickened and may be spongiotic, and there may be exocytosis of inflammatory cells, including eosinophils. Eosinophils are easily identified in the dermis and may be numerous in some conditions (e.g., incontinentia pigmenti). Chronic spongiotic dermatitis is prototypic (see also Sections IIIB1a and IIIE).

**Chronic Spongiotic Dermatitis**

In chronic spongiotic dermatitis (e.g., chronic contact dermatitis), there is hyperkeratosis with areas of parakeratosis, often hypergranulosis, and moderate to marked psoriasiform acanthosis. Although spongiosis may be present focally, it is minimal. The inflammatory infiltrate is sparse, often with scattered eosinophils, and papillary dermal fibrosis may be a prominent feature. With chronic rubbing and scratching, the pathology becomes that of lichen simplex chronicus (see also Section IIIE).

**Conditions to consider in the differential diagnosis:**

- chronic spongiotic dermatitis
- chronic atopic dermatitis
- exfoliative dermatitis
- cutaneous T-cell lymphoma
- incontinentia pigmenti, verrucous stage

**III D2** Psoriasiform Dermatitis, Neutrophils Prominent (Neutrophilic/Pustular Psoriasiform Dermatitis)

The epidermis is evenly thickened, and there is exocytosis (migration of inflammatory cells through the epidermis) of neutrophils. These may collect into abscesses in the epidermis at the level of the stratum corneum (Munromicroabscess). The stratum corneum is thickened, parakeratotic, and contains neutrophils. Psoriasis vulgaris is the prototype (56–58).

**Psoriasis Vulgaris**

**CLINICAL SUMMARY.** Psoriasis is a common chronic skin disease which affects approximately 2% of the population. The disease is probably best placed within the spectrum of autoimmune-related diseases, characterized by chronic inflammation and the absence of non-infectious agents or antigens (59). Psoriasis vulgaris accounts for the majority of patients with the disease, and is characterized by pink to red papules and plaques which are of variable size, sharply demarcated, dry, and usually covered with layers of fine, silvery scales. As the scales are removed by gentle scraping, fine bleeding points usually are seen, the so-called Auspitz sign. The scalp, sacral region, and extensor surfaces of the extremities are commonly involved, although in some patients the flexural and intertriginous areas (inverse psoriasis) are mainly affected. An acute
Clin. Fig. IIID2.a. *Pustular psoriasis.* Rapid development of sterile pustules complicated a case of erythroderma.

Clin. Fig. IIID2.b. *Psoriasis, plaque lesion.* Well demarcated erythematous plaque with a thick, white silvery scale on extensor surfaces.

**Fig. IIID2.a.** *Psoriasis vulgaris, low power.* The hyperkeratotic scale is composed of ortho and parakeratin. The epidermis is evenly acanthotic. There is papillomatosis and an infiltrate about dermal vessels and in the dermal papillae.

**Fig. IIID2.b.** *Psoriasis vulgaris, medium power.* The parakeratotic scale contains fragments of neutrophils. The epidermis shows even acanthosis with some rete ridge fusion. The papillary dermis is edematous and well vascularized.

**Fig. IIID2.c.** *Psoriasis vulgaris, high power.* The scale contains a collection of polymorphonuclear leukocytes and parakeratin. The epidermis is acanthotic. The papillary dermis is well vascularized with discrete areas of hemorrhage.
variant, guttate or eruptive psoriasis, is often seen in younger patients and is characterized by an abrupt eruption of small lesions associated with acute group A beta-hemolytic streptococcal infections. Involvement of the nails is common, and can present with splinter hemorrhages, oil spots, pitting, onycholysis, and subungual hyperkeratosis. In severe cases the disease may affect the entire skin and present as generalized erythrodermic psoriasis. Pustules generally are absent in psoriasis vulgaris, although pustules on palms and soles occasionally occur, and rarely, severe psoriasis vulgaris develops into generalized pustular psoriasis. Oral lesions such as stomatitis areata migrans (geographic stomatitis) and benign migratory glossitis may be seen in psoriasis. Psoriatic arthritis characteristically involves the terminal interphalangeal joints, but frequently the large joints are also affected so that a clinical differentiation from rheumatoid arthritis often is impossible, although rheumatoid factor generally is absent.

Clin. Fig. IID2.c  Guttate psoriasis. Eruptive “drop-like” and small plaques which cleared following therapy for Beta-hemolytic streptococcal infection.

Fig. IID2.d  Guttate psoriasis, low power. Psoriasiform hyperplasia and a parakeratotic scale.

Fig. IID2.e  Guttate psoriasis, medium power. Parakeratotic scale and slight epidermal spongiosis.

Fig. IID2.f  Guttate psoriasis, high power. There is a focal collection of neutrophils in the parakeratotic stratum corneum.
HISTOPATHOLOGY. The histology varies considerably with the stage of the lesion and usually is diagnostic only in early, scaling papules and near the margin of advancing plaques. At first, there is capillary dilatation and edema in the papillary dermis, with a lymphocytic infiltrate surrounding the capillaries. Keratinocytes in psoriasis appear to be sensitive to the effects of T-cell activation and cytokine production, interferon (IFN)-gamma, by responding with psoriasiform hyperplasia (60). The lymphocytes extend into the lower epidermis, where slight spongiosis develops. Then focal changes occur in the upper epidermis, where granular cells become vacuolated and disappear, and mounds of parakeratosis are formed. Neutrophils are often seen in the summits of some of the mounds of parakeratosis and scattered through an otherwise orthokeratotic cornified layer, representing the earliest manifestation of Munro microabscesses. When there is marked exocytosis of neutrophils, they may aggregate in the uppermost portion of the spinous layer to form small spongiform pustules of Kogoj. A spongiform pustule shows aggregates of neutrophils within the interstices of a sponge-like network formed by degenerated and thinned epidermal cells. Munro microabscesses are located within parakeratotic areas of the cornified layer, and consist of accumulations of neutrophils and pyknotic nuclei of neutrophils that have migrated there from capillaries in the papillae through the suprapapillary epidermis. Lymphocytes remain confined to the lower epidermis, which, as more and more mitoses occur, becomes increasingly hyperplastic. The epidermal changes at first are focal but later on become confluent, leading clinically to plaques.

In the fully developed lesions of psoriasis, as best seen at the margin of enlarging plaques, the histologic picture is characterized by (1) acanthosis with regular elongation of the rete ridges with thickening in their lower portion, (2) thinning of the suprapapillary epidermis with the occasional presence of small spongiform pustules, (3) pallor of the upper layers of the epidermis, (4) diminished to absent granular layer, (5) confluent parakeratosis, (6) the presence of Munro microabscesses; (7) elongation and edema of the dermal papillae, and, (8) dilated and tortuous capillaries. Of all these, only the spongiform pustules of Kogoj and Munro microabscesses are most consistent with psoriasis, and, in their absence, the diagnosis rarely can be made with certainty on a histologic basis. Spongiform pustules are not pathognomonic of psoriasis, being seen also on occasion in candidiasis, reactive arthritis or Reiter syndrome, geographic tongue, and rarely in secondary syphilis.

Guttate Psoriasis

An acute variant of psoriasis, guttate or eruptive psoriasis, is often seen in younger patients and is characterized by an abrupt eruption of small lesions associated with acute group A beta-hemolytic streptococcal infections. It is generally accepted that guttate psoriasis has a better prognosis than other types of psoriasis because it involutes rapidly and usually has a longer remission period; however, some cases persist and progress to plaque type psoriasis (61).

Conditions to consider in the differential diagnosis:
- psoriasis vulgaris
- Pustular psoriasis
- Keratoderma blennorrhagicum
- Reactive arthritis—Reiter syndrome
- pustular drug eruption
- geographic tongue (lingua geographica)
- candidiasis
- pustular secondary syphilis (rare)
- dermatophytosis

Psoriasiform Dermatitis, With Epidermal Pallor and Necrosis (“Nutritional Pattern” Dermatoses)

In this group of conditions, often associated with nutritional deficiency, the epidermis is thickened with elongated rete ridges, especially in chronic lesions, and in many cases there is characteristic pallor and individual or confluent necrosis of superficial keratinocytes, attributable to deficiency of essential nutrients, or idiopathic in some cases. Necrolytic migratory erythema is prototypic (62).

Necrolytic Migratory Erythema (Glucagonoma Syndrome)

CLINICAL SUMMARY. Necrolytic migratory erythema is the name given to the cutaneous manifestations of a glucagon–secreting pancreatic carcinoma originating from alpha islet cells (63), (64), (65). Due to elevated serum glucagon, patients have sustained gluconeogenesis, which results in negative nitrogen balance with amino acid degradation. This gives a clinical picture similar to nutritional deficiencies such as acrodermatitis enteropathica and pelagra. The skin lesions are characteristically distributed periorificially on the face, the perineum and genitals, and shins, feet, and ankles. There are erythematous patches and plaques that may appear circinate due to peripheral spreading. Flaccid blisters may develop that rupture easily, leaving erosions. Lesions heal rapidly while new ones continually develop, resulting in daily fluctuations in the appearance of the eruption. Mucosal lesions may be manifested by cheilitis and glossitis. Nails may be involved and become brittle. The eruption can precede other findings of pancreatic carcinoma by years, and in approximately 50% of patients metastases are present at the time of diagnosis.

Non-skin manifestations of the glucagonoma syndrome include weight loss, anemia, glucose intolerance, and adult-onset diabetes. Surgical resection of the tumor or infusion of amino acids can produce resolution of skin lesions. Conditions other than glucagonoma including various...
carcinomas, cirrhosis, and glucagon cell adenomatosis, a benign condition that may nevertheless have devastating endocrine effects, have been reported to give a similar rash (66).

**HISTOPATHOLOGY.** A fresh, acute lesion yields the most diagnostic information, as it characteristically shows necrosis of the upper layers of the epidermis, which can then detach from the viable layers beneath. Keratinocytes undergoing necrosis may show hydropic swelling, pallor, or eosinophilia with nuclear pyknosis. Neutrophils enter the epidermis and may produce a subcorneal pustule, while in the superficial dermis there is a perivascular lymphocytic infiltrate and often papillary dermal edema. In chronic lesions there is psoriasiform epidermal hyperplasia. All phases can show architectural disarray with vacuolar change and a diminished granular cell layer. The stratum corneum often shows broad areas of parakeratosis.

**Necrolytic Acral Erythema**

**CLINICAL SUMMARY.** Necrolytic acral erythema (NAE) is a recently described papulosquamous eruption that occurs in association with hepatitis C virus infection (67,68). Many of the described cases have occurred in Egypt, however it has also been reported in the United States. In many cases, the condition appears before the discovery of the hepatitis C infection (69). Early lesions may present with erosions and flaccid blisters. Fully evolved lesions are erythematous, dusky, hyperpigmented plaques with a darker peripheral rim. Hyperkeratosis may be prominent. The characteristic distribution is involvement...
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of the distal extremities, however, proximal extremities and truncal lesions have also been described.

**HISTOPATHOLOGY.** Histopathologic findings of NAE include psoriasiform epidermal hyperplasia, hyperkeratosis with parakeratosis, and a diminished granular cell layer. Characteristic findings also include individual keratinocyte necrosis and pallor of the superficial epidermal layer. Vacuolar alteration may be present. The dermis reveals a superficial perivascular mononuclear cell infiltrate. There are overlap histologic features with psoriasis; however, the presence of spongiform pustules would favor a diagnosis of psoriasis; individual keratinocyte necrosis favors NAE. The histologic findings of NAE may be indistinguishable from necrolytic migratory erythema, fatty acid deficiency, zinc deficiency (acrodermatitis enteropathica), pellagra, and biotin deficiency. These diagnoses must be excluded clinically.

**Fig. IIID3.g.** Necrolytic acral erythema, medium power. There is psoriasiform epidermal hyperplasia with a thickened ortho and parakeratotic stratum corneum. There is a mild perivascular mixed inflammatory infiltrate in the superficial dermis.

**Fig. IIID3.h.** Necrolytic acral erythema, high power. There are areas of hypogranulosis and/or pallor of the upper epidermal layers. There may be edema of the papillary dermis, as here.

**Fig. IIID3.i.** Necrolytic acral erythema, medium power. The epidermis may also show scattered dyskeratotic keratinocytes.

**Pellagra**

See Figs. IIID3.j, k.

**Conditions to consider in the differential diagnosis:**
- necrolytic migratory erythema
- fatty acid deficiency
- acrodermatitis enteropathica
- pellagra
- biotin deficiency
- psoriasis
- GVHD
- subacute cutaneous lupus erythematosus
- dermatomyositis
- pityriasis rubra pilaris
- toxic drug eruptions
- cystic fibrosis associated dermatitis
Irregular thickening and thinning of the epidermis is seen in some reactive conditions, but the possibility of squamous cell carcinoma should also be considered. As in other conditions associated with increased epithelial turnover, there may be hypogranulosis and parakeratosis.

1. Hypertrophic Dermatitis, Lymphocytes Predominant
   1a. Irregular Epidermal Proliferation, Plasma Cells Present
   2. Irregular Epidermal Proliferation, Neutrophils Prominent
   3. Irregular Epidermal Proliferation, Neoplastic

**Hypertrophic Dermatitis, Lymphocytes Predominant**

The epidermis is irregularly thickened, with areas of normal thickness, of acanthosis and of thinning. Lymphocytes are the predominant inflammatory cell about the dermal vessels. Prurigo nodularis is a prototype.

**Prurigo Nodularis**

**CLINICAL SUMMARY.** Prurigo nodularis (70) is a chronic skin dermatitis characterized by discrete, raised, firm hyperkeratotic papulonodules, usually from 5 to 12 mm in diameter but occasionally larger. They occur chiefly on the extensor surfaces of the extremities and are intensely pruritic. The disease usually begins in middle age and women are more frequently affected than men. Prurigo nodularis may coexist with lesions of lichen simplex chronicus and there may be transitional lesions. The cause remains unknown but local trauma, insect bites, atopic background, metabolic or systemic diseases, have been implicated as predisposing factors in some cases. Recently, an association with H pylori infection of the stomach has been described (71).

**HISTOPATHOLOGY.** Sections show pronounced hyperkeratosis and irregular acanthosis. There may be papillomatosis and irregular downward proliferation of the epidermis and adnexal epithelium approaching pseudo-carcinomatous hyperplasia. In the papillary dermis, there is a predominantly lymphocytic inflammatory infiltrate and vertically oriented collagen bundles. Occasionally, prominent neural hyperplasia may be observed; however, this is an uncommon finding and is not considered by some authors to be an essential feature for the diagnosis of prurigo nodularis. Eosinophils and marked eosinophil degranulation may be seen more frequently in patients with an atopic background. Plasma cells may be present in many examples. In a systematic analysis of 136 cases, findings highly characteristic for PN included the presence of thick compact orthohyperkeratosis; the “hairy palm sign” (folliculosebaceous units in nonvolar skin in conjunction with other features)
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with a thick and compact cornified layer, like that of volar skin); irregular epidermal hyperplasia or pseudoepitheliomatous hyperplasia; focal parakeratosis; hypergranulosis; fibrosis of the papillary dermis with vertically arranged collagen fibers; increased number of fibroblasts and capillaries; a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils (72).

**Conditions to consider in the differential diagnosis:**

- lichen simplex chronicus
- inflammatory linear verrucous nevus (ILVEN, psoriasiform category)
- prurigo nodularis
- lichen simplex chronicus
- incontinentia pigmenti, verrucous stage
- pellagra (niacin deficiency)
- Hartnup disease

![Clin. Fig. IIIE1](image1.png)

**Clin. Fig. IIIE1.** Prurigo nodularis. Hyperpigmented ill-defined papules and nodules in accessible body sites result from repeated picking and scratching.

**Fig. IIIE1.a.** Prurigo nodularis/lichen simplex chronicus, low power. There is marked irregular hyperplasia of the epidermis as well as hyperkeratosis. At the periphery of prurigo nodularis, the changes are those of lichen simplex chronicus.

**Fig. IIIE1.b.** Prurigo nodularis/lichen simplex chronicus, medium power. At higher magnification there may be hypergranulosis and the hyperplastic epithelium is composed of bland appearing keratinocytes without cytologic atypia. In a fully-evolved case, there is irregular downward proliferation of the epidermis and adnexal epithelium approaching pseudocarcinomatous hyperplasia.

**III1Ea Irregular Epidermal Proliferation, Plasma Cells Present**

The epidermis is irregularly acanthotic. Plasma cells are found about the dermal vessels admixed with lymphocytes.

**Actinic Keratosis (See also Section IIA1)**

See Figs. IIIE1.a,b.

**Conditions to consider in the differential diagnosis:**

- squamous cell carcinoma in situ (Bowen’s disease)
- erythroplasia of Queyrat
- syphilitic secondary syphilis, condyloma lata
- yaws, primary or secondary
- pinta, primary or secondary lesions
- actinic keratosis
- pseudoepitheliomatous hyperplasia
- pemphigus vegetans
IIIE. Superficial Dermatitis With Irregular Epidermal Proliferation ("Hypertrophic Dermatitis")

The epidermis has focal areas of acanthosis, neutrophils can be seen as exocytotic cells, and are found in the dermis in abscesses and about dermal vessels without there being a primary vasculitis. Most examples of these epithelial reactions are associated with inflammation that involves the reticular dermis as well as the papillary dermis. Keratoacanthoma is a neoplastic example.

Keratoacanthoma (See also Section VIB1)

See Fig. IIIE2.a.

Conditions to consider in the differential diagnosis:
- deep fungal infections (superficial biopsy, see following text)
- halogenodermas
- botryomycosis
- keratoacanthoma
- impetigo contagiosa
- granuloma inguinale

IIIE2 Irregular Epidermal Proliferation, Neutrophils Prominent

The epidermis is irregularly acanthotic. There is an associated neoplastic infiltrate, in the epidermis or dermis, or in both. Most of these neoplasms involve the reticular dermis as well as the papillary dermis (see also Section VI).

Verrucous Melanoma (See also Section VIB3)

In a series of lesions classified as "verrucous nevoid and keratotic malignant melanomas", a clinical diagnosis of
benign lesions (warty nevi, papillomas, seborrheic keratoses and cysts) had been made in over 50% of the cases. Microscopically, these lesions exhibited a spectrum of nevoid and/or keratotic features such as symmetry, exophytic and papilliferous growth pattern, hyperkeratosis and pseudo-epitheliomatous hyperplasia. Most also had lateral intra-epidermal spread and were composed of large epithelioid cells exhibiting various degrees of cellular pleomorphism. Initially, 10% of the cases were histologically diagnosed as benign, however, 7 of 20 patients with these lesions ultimately died of their disease (73).

Conditions to consider in the differential diagnosis:
- malignant melanoma (“ verrucous” pattern)
- granular cell tumor

**SUPERFICIAL DERMATITIS WITH LICHENOID INFILTRATES
( LICHENOID DERMATITIS)**

Lichenoid inflammation is a dense “ band-like” infiltrate of small lymphocytes clustered about the dermal–epidermal junction and obscuring the interface. The epidermis is variable in its thickness, amount of exocytotic lymphocytes, and the integrity of the basal cell zone (liquefaction degeneration). Hypergranulosis due to delayed epidermal maturation is a commonly associated feature. For the same reason, there may be orthokeratotic hyperkeratosis. Apoptotic or necrotic keratinocytes are often present. In lichen planus, these are called Civatte bodies. Pigmentary incontinence (melanin-laden macrophages in the papillary dermis) is common, as in any condition in which there is destruction of basal keratinocytes.

1. Lichenoid Dermatitis, Lymphocytes Exclusively
2. Lichenoid Dermatitis, Lymphocytes Predominant
2a. Lichenoid Dermatitis, Eosinophils Present
2b. Lichenoid Dermatitis, Plasma Cells Present
2c. Lichenoid Dermatitis, With Melanophages
3. Lichenoid Dermatitis, Histiocytes Predominant
4. Lichenoid Dermatitis, Mast Cells Predominant

**IIF1 Lichenoid Dermatitis, Lymphocytes Exclusively**

The band-like infiltrate is composed almost exclusively of lymphocytes. Eosinophils and plasma cells are essentially absent. Lichen planus is the prototype (74).

**Lichen Planus**

**CLINICAL FEATURES.** Lichen planus is a subacute or a chronic dermatosis that may involve skin, mucous membranes, hair follicles, and nails. In glabrous skin, the eruption is characterized by small, flat-topped, shiny, polygonal, violaceous papules that may coalesce into plaques. The papules often show a network of white lines known as Wickham’s striae. Itching is usually pronounced. The disease has a predilection for the flexor surfaces of the forearms, legs, and the glans penis. The eruption may be localized or extensive and Koebner’s phenomenon (exacerbation or elicitation of lesions by trauma) is commonly seen. A common variant is hypertrophic lichen planus, which is usually found on the shins and consists of thickened, often verrucous plaques. Possible associations of LP with hepatitis B and C infections have been observed (75).

A longitudinal follow-up study of patients with oral lichen planus demonstrated a significant increase in the risk for oral squamous cell carcinoma (76), suggesting that this may be a premalignant lesion; however, distinction of oral lichen planus from lichenoid inflammation in an already established squamous dysplasia of the oral mucosa can be difficult. Cutaneous lichen planus is not considered a premalignant condition.

**HISTOPATHOLOGY.** Typical papules of lichen planus show (1) compact orthokeratosis with very few, if any, parakeratotic cells, a fact that is important for the diagnosis, (2) wedge-shaped hypergranulosis with coarse and abundant keratohyalin granules, (3) irregular acanthosis giving rise to dome-shaped dermal papillae and to pointed or “ saw-toothed” rete ridges, (4) damage to the basal cell layer with vacuolar degeneration and apoptosis of the
basal cells giving rise to the characteristic round eosinophilic apoptotic bodies (as colloid, hyaline, cytoid, or Civatte bodies), and (5) a band-like dermal lymphocytic infiltrate which is composed almost entirely of lymphocytes intermingled with macrophages. A few eosinophils and/or plasma cells may be seen in close approximation to the epidermis, but these are rare except in some examples of hypertrophic lichen planus. Wickham’s striae are believed to be caused by a focal increase in the thickness of the granular layer and of the total epidermis.

**Clin. Fig. IIF1.a.** Lichen planus. 1 to 5 mm violaceous polygonal papules on coronal sulcus with Wickham’s striae followed longstanding lacy changes on buccal mucosa.

**Clin. Fig. IIF1.b.** Lichen planus. Multiple flat-topped violaceous polygonal papules.

**Fig. IIF1.a.** Lichen planus, low power. There is a band-like infiltrate that occupies the papillary dermis and obscures the dermo-epidermal interface. A thin keratin scale covers the epidermis.

**Fig. IIF1.b.** Lichen planus, medium power. The infiltrate of lymphocytes at the dermal–epidermal interface obscures and obliterates basal cells. There are also areas of separation. The epidermis is thickened and there is hypergranulosis.

**Fig. IIF1.c.** Lichen planus, high power. There is focal hypergranulosis with overlying hyperkeratosis. The infiltrate consists of lymphocytes with the presence of eosinophilic bodies (Civatte bodies) within the inflammatory infiltrate.
Occasionally, small areas of artifactual separation between the epidermis and the dermis, known as Max-Josef spaces, are seen. In some instances, the separation occurs in vivo and subepidermal blisters form (bullous lichen planus). These vesicles form as a result of extensive damage to the basal cells. In old lesions the cellular infiltrate decreases in density, but the number of macrophages increases. In areas in which a basal cell layer has reformed, the dermal infiltrate no longer lies in close approximation to the epidermis. Chronic lesions may show considerable acanthosis, papillomatosis, and hyperkeratosis (hypertrophic lichen planus). Recent work has suggested that a number of different lichenoid skin disorders share a common inflammatory signaling pathway involving the actions of plasmacytoid dendritic cell-derived IFN-alpha. This signaling pathway appears to amplify cytotoxic T cell injury to the epidermal basal cell compartment (77).

**Graft-Versus-Host Disease**

Graft versus host disease (78) presents with both lichenoid and vacuolar dermatitis (see also Section IIIH1):

**CLINICAL FEATURES.** GVHD occurs in situations in which donor immunocompetent T cells are transferred into allogeneic hosts incapable of rejecting them. The sources of the T cells include primarily peripheral blood stem cell and bone marrow transplant and, infrequently, unirradiated blood products, solid organ transplants, and maternofetal lymphocyte engraftment. A graft versus tumor response also occurs and is an important component of the therapeutic regimen.

The condition can be divided into an acute and a chronic phase. Acute GVHD typically occurs between 7 and 21 days after transplantation but may be seen as late as 3 months; chronic GVHD arises after a mean of 4 months, but may occur as soon as 40 days posttransplantation. Many patients have both phases, either merging with one another or separated by an asymptomatic period. In the acute phase, the classic triad includes skin lesions, hepatic dysfunction, and diarrhea. The eruption is characterized by extensive macular erythema, a morbilliform eruption, purpuric lesions, violaceous scaly papules and plaques, bullae, or in rare cases a toxic epidermal necrolysis-like epidermal detachment. There is a predilection for the cheeks, ears, neck, upper chest, and palms and soles. Occasionally, follicular papules are seen simulating a folliculitis. In the chronic phase, an early lichenoid stage and a late sclerodermoid stage can be distinguished. Each stage can occur without the other. Although usually generalized, the involvement is in rare instances localized to a few areas. In the lichenoid stage, both the cutaneous and oral lesions may be clinically similar to those in lichen planus. In addition, the skin may show extensive erythema and irregular hyperpigmentation. A poikiloderma phase may precede the eventual sclerodermoid stage. Other late manifestations include a lupus erythematosus-like eruption, cicatricular alopecia, chronic ulcerations, pyogenic granuloma and angiomatous lesions.

**HISTOPATHOLOGY.** In 2006, the National Institutes of Health Consensus Development Project Pathology Working Group proposed histologic criteria for GVHD. Their minimal histologic criteria for active cutaneous GVHD required apoptosis within the basilar or lower spinosum layers of the epidermis, outer root sheath of the hair follicle or acrosyringium. Marked apoptotic activity was defined as more than five epidermal apoptotic bodies per section from a 4 mm punch biopsy. It was noted that no single histologic feature is pathognomonic of cutaneous GVHD. Both acute and chronic GVHD feature an interface dermatitis that can be characterized by either a lichenoid pattern of lymphocytic inflammation (with or without lymphocyte satellitosis) or primarily vacuolar changes of the basilar layer. In traditional grading of acute GVHD, grade I is characterized by vacuolar change, grade II by keratinocyte necrosis, grade III by focal separation at the DEJ, and grade IV by bullae. Epidermal compact orthokeratosis, hypergranulosis, and acanthosis are consistent with a diagnosis of lichenoid GVHD. In the late sclerodermoid phase, the epidermis is atrophic, with the keratinocytes being small, flattened, and hyperpigmented. Basal layer vacuolization, inflammation, and colloid body formation are rare or absent. The dermis is thickened, with sclerosis extending into the subcutaneous tissue resulting in septal hyalination. The adnexal structures are destroyed. Lichen sclerosus and eosinophilic fasciitis-like lesions complete the spectrum of chronic cutaneous GVH (78).

**PATHOGENESIS.** Acute and chronic forms of the disease have a different pathogenesis. In acute GVHD, it is believed that preparative regimen before the infusion of the graft cause extensive tissue damage, which releases inflammatory cytokines and exposes recipient major histocompatibility complex (MHC) antigens. Recognition of the host antigen by donor T cells, and activation and proliferation of them is crucial in the initial phase. In skin, young rete ridge keratinocytes, follicular stem cells, and Langerhans cells are preferred targets. Less is understood about the pathophysiology of chronic GVHD. The role of donor T cells against the recipient’s tissue has been demonstrated.

**DIFFERENTIAL DIAGNOSIS.** The acute phase of GVHD is similar to erythema multiforme, with scattered necrotic keratinocytes and the formation of subepidermal clefts through hydropic degeneration of basal cells. In severe cases, the fulminant lesions resemble toxic epidermal necrolysis. These patients are also at increased risk for drug eruptions, chemotherapy-induced eruptions and radiation dermatitis, all of which may be indistinguishable from acute GVHD. If there is follicular dyskeratosis, the diagnosis is much more likely to be acute GVHD. The presence of
eosinophils is not necessarily in favor of drug reaction, as eosinophils are occasionally observed in GVHD.

The eruption of lymphocyte recovery occurs predominantly in patients after receiving cytoreductive therapy (without bone marrow transplant) for acute myelogenous leukemia. The eruption is typically morbilliform and develops between 6 and 21 days of chemotherapy, correlating with the earliest recovery of lymphocytes to the circulation. In contrast to patients with GVHD, these patients do not develop diarrhea or liver abnormalities. Resolution occurs over several days. Histopathologically, a superficial perivascular mononuclear cell infiltrate, basal vacuolization, spongiosis, and rare dyskeratotic keratinocytes are present. The changes may be indistinguishable from those of early allogeneic or autologous GVHD, and clinical information is essential. The systemic administration of recombinant cytokines prior to marrow recovery leads to a relatively heavy lymphocytic infiltrate with nuclear pleomorphism and hyperchromasia. Distinguishing between the lichenoid lesions of GVHD and lichen planus is often impossible. However, late sclerotic lesions can be differentiated from scleroderma by the marked atrophy of the epidermis.

Clin. Fig. IIIF1.c. Graft versus Host Disease. Note lichenoid papules that are symmetrically distributed.

Fig. IIIF1.d. Graft versus host disease, lichenoid, low power. There is an inflammatory infiltrate in the superficial dermis.

Fig. IIIF1.e. Graft versus host disease, lichenoid, medium power. The stratum corneum is normal, indicative of a recent onset. Lymphocytes are seen “tagging” at the dermal-epidermal junction in a lichenoid pattern. Lymphocytes and a few melanophages are present in the papillary dermis.

Fig. IIIF1.f. Graft versus host disease, lichenoid, high power. There is vacuolar alteration at the dermal-epidermal junction, and there are many necrotic (apoptotic) keratinocytes near the interface. Lymphocytes are adherent to some of the eosinophilic apoptotic keratinocytes, constituting so-called “satellite-cell necrosis.”
Active synthesis of collagen takes place largely in the upper third of the dermis; in scleroderma, collagen is synthesized mainly in the lower dermis and in the subcutaneous tissue.

**Mycosis Fungoides, Patch/Plaque Stage**

Clinical features and histopathology of patch and plaque stage mycosis fungoides, which may present as a lichenoid infiltrate, are discussed elsewhere (see Section IIID1). A lichenoid infiltrate which may be dense or sparse, as here, is a common presentation and typically involves lymphocytes “tagging” along the interface.

**Conditions to consider in the differential diagnosis:**
- lichen planus-like keratosis (BLK)
- lupus erythematosus, lichenoid forms
- mixed connective tissue disease
- acrodermatitis chronica atrophicans
- poikiloderma atrophicans vasculare
- pigmented purpurtic dermatitis (PPD), lichenoid type (Gougerot-Blum)
- GVHD, lichenoid stage
- erythema multiforme
- PLEVA, early lesions
- parapsoriasis/mycosis fungoides, patch/plaque stage
- Sezary syndrome

**Lichenoid Dermatitis, Lymphocytes Predominant**

The band-like lichenoid infiltrate is composed almost exclusively of lymphocytes. A few plasma cells and eosinophils may also be present. Lichen planus-like keratosis is a prototype (79, 80).

**Lichen Planus-Like Keratosis (BLK)**

**CLINICAL SUMMARY.** Lichen planus-like keratosis (LPLK), also known as “BLK,” or lichenoid keratosis (LK), is a common lesion that occurs predominantly on the trunk and upper extremities of adults between the fifth and seventh decades, and consists of a nearly always solitary nonpruritic papule or slightly indurated plaque. It usually measures 5 to 20 mm in diameter and its color varies from bright red to violaceous to brown. Its surface may be smooth or slightly verrucous. LPLK probably represents the inflammatory stage of involuting solar lentigines. Clinically it can mimic a basal cell carcinoma and is often biopsied to evaluate for this possibility.

**HISTOPATHOLOGY.** Histologic examination shows, at least in a part of the lesion, a lichenoid pattern that may be indistinguishable from lichen planus (81). As in lichen planus, there is vacuolar alteration of the basal cell layer and a
Superficial Dermatitis With Lichenoid Infiltrates (Lichenoid Dermatitis)

A band-like lymphocytic infiltrate that obscures the dermal–epidermal junction. Necrotic keratinocytes are commonly seen and may be numerous. As in lichen planus, the epidermis often shows increased eosinophilia, hypergranulosis, and hyperkeratosis. In contrast to lichen planus, however, parakeratosis is fairly common, and eosinophils and plasma cells may be present in the infiltrate. In a recent study of 1040 cases five different pathologic subtypes were identified: a classic type; a bullous type; an atypical type with cytologically atypical lymphocytes; an early or interface type; and a late regressed or atrophic type. A residual solar lentigo at the edge of the lesion supports the diagnosis of LPLK. If marked keratinocytic atypia is found in association with a lichenoid inflammatory pattern, a lichenoid actinic keratosis should be considered in the differential diagnosis.

Conditions to consider in the differential diagnosis:
- lichen planus-like keratosis (BLK)
- parapsoriasis/mycosis fungoides, patch/plaque stage
- Sezary syndrome
- paraneoplastic pemphigus
- secondary syphilis
- halo nevus
- lichenoid tattoo reaction
- lichen striatus

**IIIF. Superficial Dermatitis With Lichenoid Infiltrates (Lichenoid Dermatitis)**

**Conditions to consider in the differential diagnosis:**

**IIIF2a Lichenoid Dermatitis, Eosinophils Present**

Eosinophils are found in the lichenoid dermal infiltrate, about the dermal vessels and in some instances around the adnexal structures. Lichenoid drug eruptions are prototypic. Langerhans cell histiocytosis is an important differential diagnosis.

**Lichenoid Drug Eruptions**

**Clinical Summary.** Lichenoid drug eruption is clinically similar to lichen planus. Erythematous to violaceous papules and plaques develop on the trunk and extremities in association with drug ingestion. Implicated agents include gold, antihypertensive medications (especially captopril), penicillamine, and chloroquine.

**Histopathology.** Lichenoid drug eruption is also similar to lichen planus histologically. In comparison with erythema multiforme and toxic epidermal necrolysis, lichenoid drug eruptions are more heavily inflamed with a more prominent interstitial pattern. Differentiation from lichen planus may not be possible. Numerous eosinophils, parakeratosis, and perivascular inflammation around the mid and deep dermal plexuses are generally absent in...
Fig. IIIF2a.a. *Lichenoid drug eruption, low power.* There is a orthokeratosis and a relatively undisturbed epidermis, indicative of a lesion of very recent onset. The papillary dermis is filled with an infiltrate of mononuclear cells that obscures the dermal epidermal interface. The inflammatory infiltrate extends to the mid-reticular dermis about dermal vessels.

Fig. IIIF2a.b. *Lichenoid drug eruption, medium power.* The papillary dermis is edematous and filled with an infiltrate of mononuclear cells.

Fig. IIIF2a.c. *Lichenoid drug eruption, medium power.* The inflammatory infiltrate in the dermis consists of lymphocytes, histiocytes, and eosinophils. These cells are seen as exocytotic cells into the irregularly acanthotic epidermis.

Fig. IIIF2a.d. *Lichenoid drug eruption, high power.* Eosinophils are seen in the infiltrate. The epidermis shows some disorganization and exocytosis, with apoptotic “Civatte” bodies. The presence of a few apoptotic cells in a superficial inflammatory infiltrate is a clue to a drug eruption.
lichen planus and should prompt consideration of a lichenoid drug eruption.

**Conditions to consider in the differential diagnosis:**
- lichenoid drug eruptions
- lichenoid actinic keratoses
- lichen planus, hypertrophic arthropod bite reactions
- CTCL, mycosis fungoides, patch/plaque stage
- Langerhans cell histiocytosis (Letterer-Siwe)
- mastocytosis/telangiectasia eruptiva macularis perstans

**IIIF2b Lichenoid Dermatitis, Plasma Cells Present**

Plasma cells are found in the lichenoid infiltrate; their number is variable, but they do not as a rule comprise the major portion of the dermal infiltrate. Lichenoid actinic keratosis is a prototype (80).

**Lichenoid Actinic Keratosis**

(See Section also IIA.1). A variant of the hypertrophic type of actinic keratosis, which demonstrates nuclear atypia, irregular acanthosis and hyperkeratosis, the presence of basal cell liquefaction, degeneration of the basal cell layer, and a band-like “lichenoid” infiltrate in close apposition to the epidermis. Fairly numerous eosinophilic, homogeneous apoptotic Civatte-like bodies may be seen in the upper dermis. The presence of nuclear atypia distinguishes these lesions from lichen planus and BLK. Care should also be taken to distinguish these lesions from melanoma in situ in sun damaged skin. Melan A staining can be positive in non-melanocytic cells including “pseudomelanocytic nests” of antigen positive cells that may be keratinocytes or histiocytes located at the dermal–epidermal junction (85). This reaction pattern should not be over interpreted. Concurrent use of an MITF stain will demonstrate no increase of melanocytes in these nests.

**Secondary Syphilis (See also Section IIIA1c)**

See Figs. IIIF2b.d–f.

**Conditions to consider in the differential diagnosis:**
- lichenoid actinic keratosis
- Bowen's Disease
- erythroplasia of Queyrat
- keratosis lichenoides chronica
- secondary syphilis
- pinta, primary or secondary lesions
- arthropod bite reaction
- CTCL, mycosis fungoides, patch/plaque stage
- Zoon's plasma cell balanitis

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**Fig. IIIF2b.a**

*Fig. IIIF2b.a. Lichenoid actinic keratosis, low power.* There is an ortho and parakeratotic scale overlying an evenly acanthotic epidermis. In the papillary dermis there is a nodular as well as diffuse lichenoid inflammatory infiltrate that obscures the dermal–epidermal interface.

**Fig. IIIF2b.b**

*Fig. IIIF2b.b. Lichenoid actinic keratosis, medium power.* The basal cell zone is obliterated by the inflammatory infiltrate. The cells are lymphocytes and are exocytotic to the irregularly thickened epidermis. Necrotic keratinocytes are seen within this epidermis.

**Fig. IIIF2b.c**

*Fig. IIIF2b.c. Lichenoid actinic keratosis, medium power.* The epidermis shows subtle keratinocyte atypia (best seen away from the more intense part of the lichenoid inflammation) with an overlying ortho and parakeratotic scale. Within the dermal infiltrate, there are lymphocytes and often plasma cells.
III. Disorders of the Superficial Cutaneous Reactive Unit

Superficial and deep mixed inflammatory infiltrate

Fig. IIIF2b.d. Secondary syphilis, low power. There is a prominent band-like lichenoid and a dense superficial and deep perivascular and interstitial infiltrate of mononuclear cells.

Fig. IIIF2b.e. Secondary syphilis, medium power. There is a mixed infiltrate of lymphocytes and plasma cells, with lichenoid inflammation and Civatte-like bodies.

Fig. IIIF2b.f. Secondary syphilis, high power. The infiltrate includes plasma cells, and nodular clusters of lymphocytes. Germinal centers may be present.

Lichen planus, low power. There is a thick orthokeratotic scale overlying an epidermis that is thinned and effaced. The papillary dermis is expanded and occupied by an infiltrate of mononuclear cells.

Lichen planus, medium power. Hyperkeratosis overlies an effaced epidermis, with hypergranulosis. In the dermis there is an inflammatory infiltrate of lymphocytes as well as brown pigmented melanophages.
Most of the conditions listed as lichenoid dermatoses may be associated with release of pigment from damaged basal keratinocytes into the papillary dermis “pigmentary incontinence.” If a specific dermatosis cannot be identified, the appearances may be classified as postinflammatory hyperpigmentation (see Section IIA.1e).

Conditions to consider in this category:
- postinflammatory hyperpigmentation

Lichenoid Dermatitis, With Melanophages

Histiocytes are the predominant cell type in the dermal infiltrate. Lichen nitidus is the prototype (86).

Lichen Nitidus

CLINICAL SUMMARY. This chronic, usually asymptomatic, dermatitis begins commonly in childhood or early adulthood and is characterized by round, flat-topped, flesh-colored papules 2 to 3 mm in diameter that may occur in groups but do not coalesce. The lesions appear frequently as a localized eruption affecting predominantly the arms, trunk, or penis with a few cases reported to occur on palms, soles, nails, and mucous membranes. The clinical course is unpredictable; in some patients the eruption may become generalized and in others spontaneous resolution may be seen.

HISTOPATHOLOGY. Histologically, the papules show a parakeratotic “cap,” epidermal atrophy, liquefaction degeneration of the basal layer, and a dermal infiltrate of lymphocytes, epithelioid cells, and sometimes giant cells (86). Each papule consists of a well-circumscribed mixed-cell granulomatous infiltrate that is closely attached to the lower surface of the epidermis and confined to a widened dermal papilla. The dermal infiltrate is composed of lymphocytes, numerous foamy or epithelioid histiocytes, and a few multinucleated giant cells. The infiltrate often extends slightly into the overlying epidermis, which is flattened and shows vacuolar alteration of the basal cell layer, focal subepidermal clefting, a diminished granular layer, and focal parakeratosis. Transepidermal perforation of the infiltrate through the thinned epidermis may occur. At each lateral margin of the infiltrate, rete ridges tend to extend downward and seem to clutch the infiltrate in the manner of a “claw clutching a ball.” Follicular involvement has been described. The differential diagnosis includes giant cell lichenoid dermatitis which is thought to be an unusual lichenoid drug eruption, characterized by areas of epidermal hyperplasia and atrophy with focal vacuolar alteration of the basal layer, exocytosis and cytoid body formation. The dermis contains a band-like, mononuclear cell
Clin. Fig. IIIF3. *Lichen nitidus.* Myriads of minute flesh colored papules on the shaft of the penis.

**Fig. IIIF3.a.** *Lichen nitidus, low power.* There is a localized nodular infiltrate in a focally expanded papillary dermis. The epidermis surrounding the infiltrate is focally acanthotic.

**Fig. IIIF3.b.** *Lichen nitidus, medium power.* In an expanded dermal papilla there is a mixed inflammatory infiltrate of lymphocytes and histiocytes.

**Fig. IIIF3.c.** *Lichen nitidus, high power.* The nodular infiltrate within the expanded papillary dermis consists of histiocytes surrounded by a mantle of lymphocytes.

Infiltrate at the dermoepidermal junction with admixed eosinophils, plasma cells and large multinucleate cells (87).

**Conditions to consider in the differential diagnosis:**

- *lichen nitidus*
- giant cell lichenoid dermatitis
- sarcoidosis
- actinic reticuloid/chronic actinic dermatitis
- Langerhans cell histiocytosis (Letterer-Siwe, Hand-Schuller-Christian)
- granulomatous slack skin

**IIIF4 Lichenoid Dermatitis, Mast Cells Predominant**

Mast cells are the predominant cell type in the dermis. They are frequently accompanied by eosinophils.
Urticaria pigmentosa is a prototypic form of mastocytosis (25, 88).

**Urticaria Pigmentosa, Lichenoid Examples (See also Section IIIA2)**

In the diffuse, erythrodermic type of urticaria pigmentosa, and in some papulo-nodular lesions, there is a dense, band-like infiltrate of mast cells in the upper dermis that may obscure the dermal–epidermal junction in a lichenoid pattern. Eosinophils may be present in small numbers.

**III F  Lichenoid Dermatitis With Dermal Fibroplasia**

Lymphocytes are the predominant cell type often with an admixture of eosinophils, plasma cells, and histiocytes. In...
pigmented skin types and in regressed pigmented lesions, melanophages may be prominent. Mycosis fungoides is prototypic (see Section IIID).

**Mycosis Fungoides, Patch Stage**

See Figs. IIIF5a–d.

**Conditions to consider in the differential diagnosis:**

- *mucosis fungoides, patch-plaque stage*
- LK
- actinic keratosis
- regressed pigmented lesions including regressed melanomas

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**SUPERFICIAL VASCULITIS AND VASCULOPATHIES**

Endothelial swelling, eosinophilic degeneration of the vessel wall (“fibrinoid necrosis”), and infiltration of the vessel wall by neutrophils, with nuclear fragmentation or leukocytoclasis resulting in “nuclear dust,” define true vasculitis. There are extravasated red cells in the vessel walls and adjacent dermis. If the vasculitis is severe, ulceration or sub-epidermal separation (“bullous vasculitis”) can occur. “Lymphocytic vasculitis” in which there is no vessel wall damage is a controversial term and is discussed under lymphocytic infiltrates. A “vasculopathy” includes any abnormality of the vessel wall that does not meet the criteria above for vasculitis, such as fibrosis or hyalinization of the vessel wall without inflammation or necrosis.

1. Neutrophilic Vasculitis
2. Mixed Cell and Granulomatous Vasculitis
3. Vasculopathies with Scant Inflammation
4. Vasculopathies with lymphocytic inflammation
5. Thrombotic, Embolic and Other Microangiopathies

### IIIG Neutrophilic Vasculitis

In the dermis, vessels are necrotic, fibrinoid is present and there are perivascular and intravascular neutrophils with leukocytoclasis and nuclear dust. Cutaneous necrotizing (leukocytoclastic) vasculitis is the prototype (89–91).

**Cutaneous Necrotizing (Leukocytoclastic) Vasculitis**

**CLINICAL SUMMARY.** A large number of different disease processes can be accompanied by small-vessel vasculitis with predominantly neutrophilic infiltrates. The clinical hallmark is palpable purpura which may be the clinical appearance of dermal leukocytoclastic small-vessel vasculitis secondary to infection (e.g., gonococcal meningococcal or rickettsial sepsis), immune-complex-mediated
Clin. Fig. IIIG1.a. Leukocytoclastic vasculitis. Palpable purpuric tender papules on the legs of a 25-year-old woman resolved after therapy for streptococcal pharyngitis.

Fig. IIIG1.a. Leukocytoclastic vasculitis, low power. In the papillary dermis there is hemorrhage and an infiltrate about dermal vessels.

Fig. IIIG1.b. Leukocytoclastic vasculitis, medium power. The dermis is edematous and shows a distinct perivascular inflammatory infiltrate of lymphocytes, polymorphonuclear leukocytes and hemorrhage.

Fig. IIIG1.c. Leukocytoclastic vasculitis, medium power. There is vascular destruction with an infiltrate of fragmented neutrophils and eosinophils, scattered hemorrhage, and lymphocytes.

Fig. IIIG1.d. Leukocytoclastic vasculitis, high power. Eosinophilic homogenous fibrinoid material is seen within the walls of vascular structures. The inflammatory infiltrate consists of lymphocytes, polymorphonuclear leukocytes and fragmented polymorphonuclear leukocytes (leukocytoclasia).
vasculitis (e.g., serum sickness, cryoglobulinemia or Henoch-Schönlein purpura), ANCA-associated vasculitis (e.g., Wegener’s granulomatosis), allergic vasculitis (e.g., reaction to a drug), vasculitis associated with connective tissue diseases, or a paraneoplastic phenomenon. It is important, therefore, to interpret the histologic findings in the context of clinical information to reach an appropriate diagnosis. Often, additional laboratory data, such as from microbiologic cultures, special stains for organisms, or immunofluorescence or serologic studies, are needed. Because the treatment for infectious vasculitides is so radically different from the treatment for immune-mediated diseases, the most important diagnostic step in the evaluation of a vasculitis is to rule out an infectious process. If noninfectious vasculitis is suspected, evidence for systemic vasculitis must be sought. Clinical findings—such as hematuria, arthritis, myalgia, enzymatic assays for muscle or liver enzymes, and serologic analysis for ANCAs, antinuclear antibodies, cryoglobulins, hepatitis B and C antibodies, IgA-fibronectin aggregates, and complement levels—are important to further delineate the disease process. Exposure to a potential allergen, such as a drug, that might have elicited a hypersensitivity reaction should be sought. It is also important to address the possibility that the histologic findings of vasculitis may be a secondary phenomenon, as, for example, in ulceration from localized trauma.

Clin. Fig. IIIG1.b

Gonococcemia. A 25-year-old woman developed hemorrhagic pustules of palms, knees and elbows, associated with joint tenderness and swelling. Blood and vaginal cultures were positive.

Fig. IIIG1.e

Gonococcemia, low power. A mixed perivascular and diffuse infiltrate of mixed cells with prominent hemorrhage in the upper and mid dermis.

Fig. IIIG1.f

Gonococcemia, medium power. Mixed inflammatory cells with prominent hemorrhage in the dermis and extending into the epidermis, with vacuolar change and eosinophilic degeneration of the epidermis, probably due to ischemia. In a slightly more advanced lesion, a necrotic hemorrhagic bulla is often produced.

Fig. IIIG1.g

Gonococcemia, high power. An inflammatory and thrombotic microangiopathy, with fibrin in the lumen of a small vessel, and neutrophils in its wall.
HISTOPATHOLOGY OF NEUTROPHILIC SMALL-VEssel VASCULITIS. Neutrophilic small-vessel vasculitis is a reaction pattern of small dermal vessels, almost exclusively postcapillary venules, characterized by a combination of vascular damage and an infiltrate composed largely of neutrophils. Because there is often fragmentation of nuclei (karyorrhexis or leukocytoclasia), the term leukocytoclastic vasculitis (LCV) is frequently used. Depending on its severity, this process may be subtle and limited to the superficial dermis or be pandermal and florid and associated with necrosis and ulceration. If edema is prominent, a subepidermal blister may form. If the neutrophilic infiltrate is dense and there is pustule formation, the term pustular vasculitis may be applied. In a typical case of LCV, the dermal vessels show swelling of the endothelial cells and deposits of strongly eosinophilic strands of fibrin within and around their walls, giving the vessel walls a "smudgy" appearance referred to as fibrinoid degeneration. Actual necrosis of the perivascular collagen, however, is seen only rarely in conjunction with ulcerative lesions. If the vascular changes are severe, the vessel lumen may be occluded. The cellular infiltrate consists mainly of neutrophils and of varying numbers of eosinophils and mononuclear cells. The infiltrate also is scattered throughout the upper dermis in association with fibrin deposits between and within collagen bundles. Extravasation of erythrocytes (purpura) is commonly present.

Gonococcemia

See Clin. Fig. IIIG1.b and Fig. IIIG1.e–g.

Conditions to consider in the differential diagnosis:
- cutaneous necrotizing (leukocytoclastic) vasculitis
- Henoch–Schoenlein purpura
- cryoglobulinemia

Mixed Cell and Granulomatous Vasculitis

There is vessel wall damage, and a mixed infiltrate in the dermis that includes eosinophils, plasma cells, histiocytes, and giant cells. Granuloma faciale is prototypic.

Granuloma Faciale

CLINICAL SUMMARY. Granuloma faciale (92,93) presents clinically as one or several asymptomatic, soft, brown-red, slowly enlarging papules or plaques, almost always on the face.

HISTOPATHOLOGY. There is a dense polymorphous infiltrate, mainly in the upper half of the dermis, but occasionally extending even into the subcutaneous tissue. The infiltrate is typically separated from the epidermis or the pilosebaceous appendages by a narrow "grenz" zone of normal collagen, and the pilosebaceous structures tend to remain intact. The infiltrate consists in large part of neutrophils and eosinophils, but mononuclear cells, plasma cells, and mast cells are also present. Frequently, there is leukocytoclasia with formation of nuclear dust, especially in the vicinity of the capillaries, and often there is some evidence of vasculitis with deposition of fibrinoid material within and around vessel walls. Occasionally, some hemorrhage is noted. Foam cells are sometimes observed as connective tissue associated (RA, LE)
- septicemia esp. meningococcemia/gonococcemia
- urticarial vasculitis
- erythema elevatum diutinum
- miscellaneous
- microscopic polyarteritis nodosa
- vasculitis in exanthemic pustulosis (drug-induced)

Fig. IIIG2.a

Clin. Fig. IIIG2. Granuloma faciale. A boggy erythematous plaque on the scalp in a middle-aged man.

Fig. IIIG2.a. Granuloma faciale, low power. There is a dense diffuse dermal infiltrate spanning the reticular dermis. (continues)
well as areas of fibrosis in older lesions. Direct immuno-
fluorescence data suggest an immune-complex-mediated
event with deposition of mainly IgG in and around vessels.
The distinction between granuloma faciale and erythema
elevatum diutinum may be difficult; in a recent study only
4 of 26 criteria distinguished between the two condi-
tions—the density of the infiltrate, and the number of
plasma cells and eosinophils were higher in granuloma
faciale, while granulomas were never found in granuloma
faciale but were present in some cases of erythema eleva-
tum diutinum. A grenz zone was observed in about three
quarters of the cases in both groups (94).

Conditions to consider in the differential diagnosis:
- Churg-Strauss vasculitis
- Wegener's granulomatosis
- giant-cell arteritis
- granuloma faciale
- Buerger's disease

A histologic diagnosis of a “lymphocytic vasculitis” may be
made if there is sufficient evidence of vascular damage and
the inflammatory infiltrate is predominantly lymphocytic.
Often, the vascular damage is subtle and in many cases
there may be disagreement as to whether or not the term
“vasculitis” is warranted. Clear-cut evidence of vasculitis
requires the presence of an inflammatory infiltrate
together with fibrinoid necrosis of the vascular wall. These
changes are not often seen in combination with a strictly
lymphocytic infiltrate. The purpuric dermatoses are exem-
plary of a pattern of vasculopathy that usually falls short
of frank vasculitis, in association with a lymphocytic infil-
strate that may involve the vessel walls (95,96).

Pigmented Purpuric Dermatoses

CLINICAL SUMMARY. Historically, four variants of pur-
pura pigmentosa chronica have been described: purpura
annularis telangiectoides of Majocchi, progressive pig-
mentary dermatosis of Schamberg, PPD of Gougerot and
Blum, and eczematoïd-like purpura of Doucas and Kapa-
nakis. They are all closely related and often cannot be reli-
ably distinguished on clinical and histologic grounds.
Therefore, their classification as distinct entities is not nec-
essary. It is likely that lichen aureus is a closely related vari-
ant as well, because the clinical lesion suggests a purpuric
component and the histologic findings are similar to those
of the other four variants of PPD. The general terms “PPD,”
“chronic purpuric dermatitis,” and “purpura pigmentosa
chronica” appear suitable for this disease spectrum. These
lesions have been found in some cases to be associated
with hepatitis B and C infection (97).
Clinically, the primary lesion consists of discrete telangiectatic puncta as a result of capillary dilatation, and pigmentation as a result of hemosiderin deposits. In some cases, telangiectasia (Majocchi’s disease) predominates; in others, pigmentation (Schamberg’s disease) predominates. In Majocchi’s disease, the lesions are usually irregular in shape and occur predominantly on the lower legs. In some cases, the findings may mimic those of stasis. Not infrequently, clinical signs of inflammation are present, such as erythema, papules, and scaling (Gougerot-Blum disease) or papules, scaling, and lichenification (eczematoid-like purpura). The disorder is often limited to the lower extremities, but it may be extensive. Mild pruritus may be present. A localized variant of PPD is lichen aureus, in which one or a few closely set, flat papules or macules of a rust, copper, or orange color are present, most commonly on the legs.

**HISTOPATHOLOGY.** The basic process is a lymphocytic perivascular infiltrate limited to the papillary dermis. Epidermal alterations may include slight acanthosis and basal layer vacuolopathy. There is variability in the pattern of the dermal infiltrate. In some instances, the infiltrate may assume a band-like or lichenoid pattern, particularly in the lichenoid variant of Gougerot-Blum disease, and may involve the reticular dermis in a perivascular distribution. Evidence of vascular damage may be present. However, the extent of vascular injury is usually mild and often insufficient to justify the term “vasculitis.” Vascular damage commonly consists only of endothelial cell swelling and dermal hemorrhage. Extravasated red blood cells are usually found in the vicinity of the capillaries. Less commonly one may observe deposition of fibrinoid material in vessel walls. In some instances, the infiltrate involves the epidermis and may be associated with mild spongiosis and patchy parakeratosis. This is observed particularly in some cases of pigmented purpuric lichenoid dermatitis of Gougerot and Blum and eczematoid-like purpura of Doucas and Kapetanakis. The pattern of the infiltrate often is not strictly confined to the perivascular area and may infiltrate the adjacent papillary dermis (between vessels).

In old lesions, the capillaries often show dilatation of their lumen and proliferation of their endothelium. Extravasated red blood cells may no longer be present, but one frequently finds varying amounts of hemosiderin. The inflammatory infiltrate is less pronounced than in the early stage.
In lichen aureus, a dense lymphohistiocytic infiltrate is present in the superficial dermis, typically distributed in a band-like fashion and often associated with an increase in dermal capillaries. Exocytosis of mononuclear cells into the epidermis may be seen. Scattered within the infiltrate are hemosiderin-laden macrophages.

Conditions to consider in the differential diagnosis:
- arthropod bites
- hypersensitivity reactions to drugs
- urticarial vasculitis
- pigmented purpuric dermatoses
- autoimmune and connective tissue diseases
- pernio (chilblains)
- polymorphous light eruption
- atrophie blanche
- viral processes
- cutaneous T-cell infiltrates
- pityriasis lichenoides chronica (PLC)
- lymphomatoid papulosis (LyP).

**Stasis Dermatitis**

**CLINICAL SUMMARY.** Patients with long-standing venous insufficiency and lower extremity edema may develop pruritic, erythematous, and scaly papules and plaques on the lower legs, often in association with brown pigmentation and hair loss.

**HISTOPATHOLOGY.** The epidermis is hyperkeratotic with areas of parakeratosis, acanthosis, and focal spongiosis. The superficial dermal vessels may be arranged in lobular aggregates. The proliferation may be florid, mimicking Kaposi’s sarcoma (acroangiodermatitis). Inflammation may be minimal or there may be a superficial, perivascular lymphohistiocytic infiltrate that around plump, thickened capillaries, and venules. The reticular dermis is often fibrotic. Hemosiderin is usually present superficially but may be identified about the deep vascular plexus as well.

**Stasis Dermatitis**

See Clin. Fig. IIIG4.a and Fig. IIIG4.a–c.

**Conditions to consider in the differential diagnosis:**
- stasis dermatitis
- atrophie blanche (segmental hyalinizing vasculitis)
- malignant atrophic papulosis (Degos)
- cryoglobulinemia (type I)

**Vasculopathies With Scant Inflammation**

There is fibrosis or hyalinization of the vessel walls, with few inflammatory cells. Stasis dermatitis is a prototype.

**Clin. Fig. IIIG4.a**

*Stasis dermatitis. Lower leg brawny, violaceous pigmentation, edema, and “bottle neck” deformity resulted from chronic venous insufficiency in an elderly woman.*

*Fig. IIIG4.a. Stasis dermatitis, low power. There is hyperkeratosis overlying an acanthotic epidermis. The papillary dermis is expanded with a scant infiltrate about the prominent dermal vessels.*
There are thrombi or emboli within the lumens of small vessels (98). In other microangiopathies, the vessel walls may be thickened with compromise of the lumen (amyloidosis, calciphylaxis). The antiphospholipid syndromes are prototypic (99,100).

**Lupus Anticoagulant and Anti-cardiolipin Syndromes**

**CLINICAL SUMMARY.** The antiphospholipid syndrome occurs in patients with SLE and other autoimmune diseases who develop immunoglobulins that can prolong phospholipid-dependent coagulation tests. Antiphospholipid antibodies are directed against phospholipid–protein complexes and include lupus anticoagulant, anticardiolipin antibodies, and anti-beta-2 glycoprotein I antibodies. Antiphospholipid antibody syndrome is a common cause of acquired thrombophilia and is characterized by venous or arterial thromboembolism (101). These immunoglobulins occur in association with SLE and other autoimmune diseases, but are found unassociated with them as well. The lupus anticoagulant occurs in about 10% of SLE patients. Affected patients are at greater risk for thromboembolic disease including deep venous thrombosis, pulmonary emboli, and other large vessel thrombosis. Other associated findings are recurrent fetal wastage, renal vascular thrombosis, thrombosis of dermal vessels, and thrombocytopenia. Anticardiolipin antibody occurs five times more often than lupus anticoagulant antibody. It is associated with recurrent arterial and venous thrombosis, valvular abnormalities, cerebrovascular thromboses, and essential hypertension (Sneddon’s syndrome). Other cutaneous findings include livedo reticularis, necrotizing purpura, disseminated intravascular coagulation, and stasis ulcers of the ankles. In severe forms of coagulopathies, large areas of ecchymosis may be present, typically located on the extremities. Large hemorrhagic bullae may overlie the ecchymoses, and some of the ecchymotic areas may undergo necrosis.

**HISTOPATHOLOGY.** The histologic features are nonspecific. In mild forms, the only histologic manifestation may be dermal hemorrhage—that is, extravasation of red blood cells into perivascular connective tissue. With increasing severity of the disease process, intravascular fibrin thrombi may be found. In severe cases, thrombotic vascular occlusion may lead to hemorrhagic infarcts, epidermal and dermal necrosis, or subpidermal bulla formation.

**Cryoglobulinemia**

**CLINICAL SUMMARY.** There are three major types of cryoglobulinemia (102): in type I cryoglobulinemia, monoclonal IgG or IgM cryoglobulins are found, often associated with lymphoma, leukemia, Waldenstrom’s macroglobulinemia, or multiple myeloma, or without known underlying disease. In type II cryoglobulinemia, the cryoprecipitate consists of both monoclonal and polyclonal immunoglobulins, with one member of the complex acting as an antibody against the other. These cryoglobulins are circulating immune complexes. The most common combination is IgG–IgM. In type III cryoglobulinemia, the
III. Disorders of the Superficial Cutaneous Reactive Unit

Immunoglobulins are polyclonal. Type II and III or mixed cryoglobulinemias are frequently associated with connective tissue disorders, such as lupus erythematosus, rheumatoid arthritis, and Sjögren’s syndrome, or may be related to infection—in particular, hepatitis C infection. Idiopathic forms of type II and III cryoglobulinemias are also termed essential mixed cryoglobulinemia.

Clinically, cutaneous lesions in patients with cryoglobulinemia may manifest as chronic palpable purpura, urticaria-like lesions, livedo reticularis, acrocyanosis, digital gangrene, and leg ulcers. Raynaud’s phenomenon is common. Systemic manifestations may include arthralgia, hepatosplenomegaly, lymphadenopathy, and glomerulonephritis.

**Histopathology.** In type I cryoglobulinemia, amorphous material (precipitated cryoglobulins) is deposited subjacent to endothelium and throughout the vessel wall as well as within the vessel lumen, resulting in a thrombus-like appearance. These precipitates stain pink with hematoxylin and eosin and bright red with PAS stain, as opposed to less intense staining of fibrinoid material. Some capillaries are filled with red blood cells, and extensive extravasation of erythrocytes may be present. An inflammatory infiltrate is usually lacking in contrast to mixed cryoglobulinemia, which typically shows a leukocytoclasic vasculitis. PAS-positive intramural and intravascular cryoprecipitates may be found also in mixed cryoglobulinemia, although less frequently than in type I cryoglobulinemia.

Other small-vessel vasculitides with the histologic pattern of a leukocytoclasic vasculitis may be found in association with Waldenström’s hyperglobulinemia (hyperglobulinemic purpura) and in Schnitzler’s syndrome, which manifests as chronic urticaria with macroglobulinemia (usually monoclonal IgM) and other paraproteinemias.

**Conditions to consider in the differential diagnosis:**
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Cryoglobulinemia/macroglobulinemia
- Antiphospholipid syndrome
- Lupus anticoagulant & anti-cardiolipin syndromes
- Connective tissue disease (rheumatoid, mixed)
- Calciphylaxis
- Amyloidosis
- Porphyria cutanea tarda and other porphyrias
- Cholesterol emboli

![Fig. IIIG5.a](superficial_hemorrhage.png)

**Fig. IIIG5.a.** *Non-inflammatory thrombi, low power.* There is an effaced epidermis with an overlying keratotic scale. The dermis shows hemorrhage with its greatest concentration in the papillary dermis but also within the reticular dermis.

![Fig. IIIG5.b](delicate_fibrin_platelet_red_cell_microthrombi.png)

**Fig. IIIG5.b.** *Non-inflammatory thrombi, medium power.* The papillary dermis is edematous with hemorrhage. Vessels are engorged with red cell—fibrin thrombi.

![Fig. IIIG5.c](non_inflammatory_thrombi.png)

**Fig. IIIG5.c.** *Non-inflammatory thrombi, high power.* Dermal vessels show red cell—fibrin thrombi without an inflammatory response.
Lymphocytes approximate the dermal–epidermal junction. Cellular degeneration and edema in the basal cell zone produces interface vacuoles. The dermis usually has perivascular lymphocytes and there may be pigment incontinence.

1. Vacuolar Dermatitis, Apoptotic/Necrotic Cells Prominent
2. Vacuolar Dermatitis, Apoptotic Cells usually Absent
3. Vacuolar Dermatitis, Variable Apoptosis
4. Vacuolar Dermatitis, Basement Membranes Thickened

**Erythema Multiforme**

**CLINICAL SUMMARY.** Erythema multiforme is an acute, self-limited dermatosis characterized by multiform lesions, including macules, papules, vesicles, and bullae, typically with target or iris lesions that have the form of a bull’s-eye surrounded by a ring of erythema. The disease may be divided into a minor and major form, the latter also known as Stevens–Johnson syndrome. The most frequent etiology in erythema multiforme is infection, *Herpes simplex virus* and drugs being the most common agents. In viral and idiopathic but not in drug-induced cases, HSV DNA has been detected in lesions of erythema multiforme by PCR (104). In Stevens–Johnson syndrome, medications, in particular sulfonamides, are the offending agents in most patients. Patients with herpes simplex virus-associated erythema multiforme have recurrent lesions, affecting primarily the oral mucosa or the extremities, with typical target or iris lesions. Those with drug-induced Stevens–Johnson syndrome have truncal involvement, a more purpuric macular eruption, and atypical target lesions. Patients often present with fever. Involvement of the oral, conjunctival, nasal, and genital mucosa is common. In toxic epidermal necrolysis (Lyell’s syndrome), which frequently overlaps with Stevens–Johnson disease and is usually regarded as a form of erythema multiforme, a widespread blotchy erythema develops. This is soon followed by the development of large, flaccid bullae and detachment of the epidermis in large sheets, leaving the dermis exposed and giving a moist, eroded appearance. The disease has a high mortality rate because of fluid loss and sepsis. In nearly 90% of cases it is caused by medications, most commonly sulfonamides. The “cytotoxic” or “erythema multiforme-like” drug eruptions overlap with authentic erythema multiforme and with toxic epidermal necrolysis, both of which may be drug-induced. Medications associated with increased risk for these entities include sulfonamides, trimethoprim-sulfamethoxazole,
Clin. Fig. IIIH1.a. *Erythema multiforme*. Steroid responsive “target” papules characterized by central bullae with surrounding erythema appeared after antibiotic therapy.

Fig. IIIH1.a. *Erythema multiforme, low power*. The epidermis is effaced and there is a dense perivascular infiltrate of mononuclear cells.

Fig. IIIH1.b. *Erythema multiforme, medium power*. The epidermis shows spongiosis and exocytosis. The reticular and papillary dermis has a dense infiltrate of lymphocytes with scattered areas of hemorrhage.

Fig. IIIH1.c. *Erythema multiforme, medium power*. The epidermis shows necrotic/apoptotic keratinocytes, vacuolar degeneration at the basal cell zone and a lichenoid inflammatory infiltrate of lymphocytic cells.

Fig. IIIH1.d. *Erythema multiforme, high power*. There is basketweave orthokeratin overlying an epidermis that shows exocytosis, basal layer liquefaction degeneration and necrotic keratinocytes. The dermal vessels are thickened and there is an infiltrate of lymphocytes without eosinophils or plasma cells.
phenobarbital, carbamazipine, phenytoin, oxicam nonsteroidal anti-inflammatory agents, allopurinol, chlorimezone, and corticosteroids.

**HISTOPATHOLOGY.** Erythema multiforme is considered the prototype of the vacuolar form of interface dermatitis. Because of its acute nature, there is an orthokeratotic stratum corneum. The earliest changes include vacuolization of the basal cell layer, tagging of lymphocytes along the dermoepidermal junction, and a sparse, superficial, perivascular lymphoid infiltrate. Mild spongiosis and exocytosis are seen. Necrosis of individual keratinocytes ("apoptosis") occurs in the stratum malpighii, and is the hallmark of erythema multiforme. Satellite cell necrosis, characterized by intraepidermal lymphocytes in close association with apoptotic keratinocytes, is frequently present. In more papular, edematous lesions, there is papillary dermal edema and more significant spongiosis and inflammation. Intraepidermal vesicles associated with exocytosis may be noted on occasion. Although some authors have noted a significant number of eosinophils in drug-induced erythema multiforme, this has not been noted by others. In addition to the clinical differences, some histologic differences have been noted between drug-induced and herpes simplex-associated erythema multiforme. In the former, there is more widespread keratinocyte necrosis, microscopic blister formation, and more pigmented incontinence. In cases associated with herpes simplex virus infection, there is more spongiosis, exocytosis, liquefaction degeneration of the basal layer, and papillary dermal edema. Nuclear dust may be identified in the papillary dermis in the latter.

In toxic epidermal necrolysis, in bullous lesions, and in the central portion of target lesions, there are numerous necrotic keratinocytes, even full-thickness epidermal necrosis, and a subepidermal bulla. The dermal inflammatory infiltrate is more sparse in toxic epidermal necrolysis than in erythema multiforme. Extravasated erythrocytes are commonly found within the blister cavity. Melanophages within the papillary dermis occur in late lesions.

**Fixed Drug Eruption**

See Clin. Fig. IIIH1.b and Fig. IIIH1.e–h.
III. Disorders of the Superficial Cutaneous Reactive Unit

Pigmentary incontinence

Suprabasal apoptosis

Fig. IIIH1.g, h. Fixed drug eruption. Vacuolar alteration is present at the dermal-epidermal junction. Mostly in the suprabasal epidermis, there are scattered apoptotic keratinocytes.

Fig. IIIH1.i

Fig. IIIH1.j

“Satellite cell necrosis”

Graft versus host disease, acute. In this Grade 3 graft versus host reaction, subepithelial separation has resulted from confluent vacuolar change.

Fig. IIIH1.j, k. Graft versus host disease, acute. Lymphocytes tagging at the dermal-epidermal junction and eliciting “satellite-cell necrosis” of predominantly basal keratinocytes.
Graft Versus Host Disease, Acute

The two major patterns of GVHD are a lichenoid pattern, discussed in IIIG1, and a vacuolar-interface pattern, illustrated here.

Conditions to consider in the differential diagnosis:

- erythema multiforme
- toxic epidermal necrolysis (Lyell's syndrome)
- Stevens-Johnson Syndrome
- fixed drug eruption
- phototoxic drug eruption
- radiation dermatitis
- sunburn reaction
- thermal burn
- PLEVA
- GVHD, acute
- eruption of lymphocyte recovery
- bullous vulgaris

Vacuolar Dermatitis, Apoptotic/Necrotic Cells Usually Absent

There is basilar keratinocyte vacuolar destruction, apoptotic cells are rare or absent. The dermis has perivascular lymphocytes and may show pigment incontinence. Dermatomyositis is a prototype (105,106).

Dermatomyositis

CLINICAL SUMMARY. Dermatomyositis manifests as an inflammatory myopathy with characteristic cutaneous findings, which has peaks of incidence in children and adults aged 45 to 65. In the absence of cutaneous findings, the diagnosis of polymyositis is applied. The cutaneous disease alone, without muscular involvement, has been termed amyopathic dermatomyositis or dermatomyositis sine myositis. In some instances the cutaneous eruption precedes the development of muscular weakness by many months or even by several years. Diagnostic criteria for dermatomyositis include proximal symmetric muscle weakness, elevated muscle enzymes, lack of neuropathy on electromyelography, consistent muscle biopsy changes, and cutaneous findings.

Two distinctive cutaneous lesions are found in dermatomyositis. One is violaceous, slightly edematous periorbital patches that primarily involve the eyelids, known as the heliotrope rash. The other is discrete red-purple papules over the bony prominences, particularly the knuckles, knees, and elbows, known as Gottron's papules. These may evolve into atrophic plaques with pigmented alterations and telangiectasia and are then known as Gottron's sign. Other cutaneous findings include periangual telangiectasia, hypertrophy of cuticular tissues of the nail unit associated with splinter hemorrhages, as well as photosensitivity, and poikiloderma. There may be subcutaneous and periaricular calcification, usually centered in the proximal muscles of the shoulders and pelvic girdle.

Controversy exists over the association of dermatomyositis with malignancy. The pathogenesis of the disease is uncertain. Associated antibodies include PM1, Jo1 (correlates with pulmonary fibrosis), Ku (associated with sclerodermatomyositis), and M2.

HISTOPATHOLOGY. The erythematous-edematous lesions of the skin in dermatomyositis may show only nonspecific inflammation. However, quite frequently the histologic changes are indistinguishable from those seen in SLE. There may be epidermal atrophy, basement membrane degeneration, vacuolar alteration of basilar keratinocytes, a sparse lymphocytic inflammatory infiltrate around blood vessels, and interstitial mucin deposition. With severe inflammation, there may be subepidermal fibrin deposition. Immune complexes are not detected at the dermal–epidermal junction as in lupus erythematosus. Old cutaneous lesions with the clinical appearance of poikiloderma atrophicans vasculare usually show a band-like infiltrate under an atrophic epidermis with hydropic degeneration of the basal cell layer. The Gottron's papules overlying the knuckles also show vacuolization of the basal cell layer, but acanthosis rather than epidermal atrophy. Subcutaneous tissue may show focal areas of panniculitis associated with mucoid degeneration of fat cells in early lesions. Extensive areas of calcification may be present in the subcutis at a later stage.

Three types of muscle biopsy changes may be observed in active disease: (1) interstitial lympho-histiocytic inflammatory infiltrates; (2) segmental muscle fiber necrosis; or (3) vasculopathy, characterized by immune complex deposition in vessel walls. Old lesions usually show nonspecific atrophy of the muscle fibers and diffuse interstitial fibrosis with relatively little inflammation. Changes in organs other than the skin and the striated muscles occur only rarely in dermatomyositis, in contrast to SLE and systemic scleroderma.
III. Disorders of the Superficial Cutaneous Reactive Unit

Conditions to consider in the differential diagnosis:

dermatomyositis
morbilliform viral exanthem
poikiloderma vasculare atrophicans
paraneoplastic pemphigus
erythema dyschromicum perstans
pinta, tertiary stage

IIIH3 Vacuolar Dermatitis, Variable Apoptosis

Vacuolar degeneration is associated with variable numbers of apoptotic cells in the epidermis. The dermis may have increased ground substance and there may be pigmented incontinence (see Section IIIH1).

Subacute Cutaneous Lupus Erythematosus

CLINICAL SUMMARY. Lupus erythematosus may affect multiple organ systems and has a broad range of clinical manifestations (107). It may take the form of an isolated cutaneous eruption or a fatal systemic illness. A combination of clinical and laboratory data has been set forth as “Criteria for the Classification of Systemic Lupus Erythematosus (SLE)” by the American Rheumatism Association (ARA). These criteria, developed for classification of patients with SLE as opposed to other rheumatic diseases, are also widely used to diagnose patients with lupus erythematosus. A person is judged to have SLE if any four or more of the 11 following criteria are present serially or simultaneously: Malar rash; Discoid rash; Photosensitivity; Oral ulcers; Arthritis involving two or more peripheral joints; Serositis (pleurisy or pericarditis); Renal disorder (nephritic or nephrotic); Neurologic disorders (seizures or psychosis); Hematologic disorders (hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia); Immunologic disorder (positive LE-cell test, anti-DNA abnormal titer, antibody to Sm nuclear antigen, or false-positive serologic test for syphilis); Antinuclear antibody. Furthermore, a diagnosis of SLE is indicated in any patient who has at least three of the following four symptoms: (1) a cutaneous eruption consistent with lupus erythematosus, (2) renal involvement, (3) serositis, or (4) joint involvement. A diagnosis of SLE requires confirmation by laboratory tests. Molecular and genetic markers including polymorphisms of HLA, TNF-a and complement molecules have been recently summarized (108).

Cutaneous changes of lupus erythematosus may be subdivided according to the morphology of the clinical lesion and/or its duration (acute, subacute, or chronic). Differentiation between LE subtypes is based upon the constellation of clinical, histologic, and immunofluorescence findings.

Subacute cutaneous lupus erythematosus (SCLE) represents about 9% of all cases of lupus erythematosus. Some cases are drug-induced and are indistinguishable from the idiopathic cases (109). It is characterized by extensive erythematosus, symmetric nonscarring and non-atrophic lesions that arise abruptly on the upper trunk, extensor surfaces of the arms, and dorsa of the hands and fingers.
This eruption has two clinical variants: (1) papulosquamous lesions and (2) annular to polycyclic lesions. Frequently both types of lesions are seen. In some instances, vesicular and discoid lesions with scarring may coexist. Patients with SCLE may have mild systemic involvement, particularly arthralgias.

**HISTOPATHOLOGY.** Histologic changes in SCLE consist of hydropic degeneration of the basilar epithelial layer, sometimes severe enough to form clefts and subepidermal vesicles, commonly with colloid (apoptotic) bodies in the lower epidermis and papillary dermis. There is often fairly prominent edema of the dermis, and there may be focal extravasation of erythrocytes and dermal fibrinoid deposits. Hyperkeratosis and inflammatory infiltrate are less prominent than in discoid lesions.

**Conditions to consider in the differential diagnosis:**
- cytotoxic drug eruptions
- SLE
- drug-induced lupus

**Clin. Fig. IIIH3.** Subacute cutaneous lupus erythematosus. Scaling papules and plaques on the back, shoulders, and forearms are characteristic of the papulosquamous variant.

**Fig. IIIH3.a.** Subacute lupus erythematosus, low power. There is a patchy orthokeratotic scale overlying a relatively unaltered epidermis. The papillary dermis is expanded, edematous and contains a moderate perivascular and diffuse lymphocytic infiltrate.

**Fig. IIIH3.b.** Subacute lupus erythematosus, medium power. The lymphocytic infiltrate in the papillary dermis obscures the dermal-epidermal interface and is exocytotic to the acanthotic epidermis. Melanophage pigment is seen within the upper reticular dermis. A rare apoptotic cell is present in the epidermis. (continues)
III. Disorders of the Superficial Cutaneous Reactive Unit

Vacuolar degeneration is associated with variable numbers of apoptotic cells in the epidermis. The basement membrane zone is thickened by deposition of eosinophilic hyaline material. Discoid lupus erythematosus is the prototype (110).

**Discoid Lupus Erythematosus**

**CLINICAL SUMMARY.** Characteristically, lesions of Discoid Lupus Erythematosus (DLE) consist of well-demarcated, erythematous, slightly infiltrated, “discoid” plaques that often show adherent thick scales and follicular plugging. The lesions are often limited to the face, where the malar areas and the nose are predominantly affected. In addition, the scalp, ears, oral mucosa, and vermilion border of the lips may be involved. In patients with disseminated discoid lesions, lesions are seen predominantly on the upper trunk and upper limbs, usually with lesions also on the head. Early and active lesions usually display surrounding erythema. Old lesions often appear atrophic and have hypo- or hyperpigmentation. Occasionally lesions may show verrucous hyperkeratosis, especially at their periphery. Hypopigmentation within previously affected areas is frequent.

**HISTOPATHOLOGY.** In most instances of discoid lesions, a diagnosis of lupus erythematosus is possible on the basis of a combination of histologic findings. Changes may be apparent at all levels of the skin, but all need not be present in every case. The findings may be summarized as follows:

1. **Stratum corneum:** hyperkeratosis with follicular plugging. Parakeratosis is not conspicuous, and it may be absent. Keratotic plugs are found mainly in dilated follicular openings, but they may occur in the openings of eccrine ducts as well.
2. **Epithelium:** thinning and flattening of the stratum malpighii, hydropic degeneration of basal cells, dyskeratosis and squamotization of basilar keratinocytes. The most significant histologic change in lupus erythematosus is hydropic degeneration of the basal layer, also referred to as liquefaction degeneration. In its absence, a histologic diagnosis of lupus erythematosus should be made with caution and only when other histologic findings greatly favor a diagnosis of LE. In addition to liquefaction degeneration, basilar keratinocytes may show individual cell necrosis (apoptosis) and acquire elongate...
Clin. Fig. IIIH4. Discoid lupus. A 29-year-old man developed pigmented plaques with central depression, atrophy and carpet tack plugging on the nose, auditory canals and scalp.

Fig. IIIH4.a. Discoid lupus erythematosus, low power. The epidermis is focally atrophic and effaced, and focally hyperplastic, with overlying hyperkeratosis. The reticular dermis is edematous and there is an infiltrate about dermal vessels that extends into the lower reticular dermis and the subcutaneous fat.

Fig. IIIH4.b. Discoid lupus erythematosus, medium power. The epidermis has basal layer vacuolar degeneration. An eosinophilic homogenized thickened basement membrane is at the dermal-epidermal interface. In the dermis is vascular ectasia, a lymphocytic infiltration and melanophage pigmentation.

Fig. IIIH4.c. Discoid lupus erythematosus, high power. The eosinophilic well defined thickened basement membrane is seen at the dermal-epidermal interface, along with the prominent vacuolar change.

Fig. IIIH4.d. Discoid lupus erythematosus, medium power. Deep perivascular and peri-adnexal inflammation are commonly seen.
contours like their superficial counterparts, rather than retaining their normal columnar appearance (squamotization). Frequently, the undulating rete ridge pattern is lost and is replaced by a linear array of squamotized keratinocytes.

3. Basement membrane: thickening and tortuosity. This change, which correlates with locations of immunoreactant deposits, is more apparent with PAS stains, and may be found along follicular-dermal junctions and capillary walls as well. In areas of pronounced hydropic degeneration of the basal cells, the PAS-positive subepidermal basement zone may be fragmented and even absent.

4. Stroma: a predominantly lymphocytic infiltrate (often with plasma cells), arranged along the dermal–epidermal junction, around hair follicles and eccrine coils, and in an interstitial pattern; interstitial mucin deposition; edema, vasodilatation, slight extravasation of erythrocytes.

5. Subcutaneous: slight extension of the inflammatory infiltrate may be present.

**Conditions to consider in the differential diagnosis:**

*discoid lupus erythematosus*
dermatomyositis

**References**

III. Disorders of the Superficial Cutaneous Reactive Unit


Keratinocytes may separate from each other on the basis of immunologic antigen–antibody mediated damage resulting in separation and rounding-up of keratinocyte cell bodies (acantholysis), on the basis of edema and inflammation (spongiosis), or perhaps on the basis of structural deficiencies of cell adhesion (Darier’s disease). These processes produce intra-epidermal spaces (vesicles, bullae, pustules).

### IV. Acantholytic, Vesicular, and Pustular Disorders

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Pemphigus Foliaceus

Usually developing in middle-aged individuals, pemphigus foliaceus may have a chronic generalized course or may rarely present as an exfoliative dermatitis. The disorder is caused by autoantibodies to a desmosomal protein, desmoglein 1, causing dyshesion in the outer spinous and granular epidermal layers. Some cases may be related to exposure to drugs such as penicillamine (4). Patients present with flaccid bullae that usually arise on an erythematous base. Erythema, oozing, and crusting are present. Because of their superficial location, the blisters break easily, leaving shallow erosions rather than the denuded areas seen in pemphigus vulgaris. Oral lesions do not occur. The Nikolsky sign is positive, and Tzanck preparation reveals acantholytic granular keratinocytes. Fogo selvagem (endemic pemphigus foliaceus which occurs in Brazil) is histologically and immunologically indistinguishable from pemphigus foliaceus.

HISTOPATHOLOGY. The earliest change consists of acantholysis in the upper epidermis, within or adjacent to the granular layer, leading to a subcorneal bulla in some instances, more commonly, enlargement of the cleft leads to detachment of the stratum corneum without bulla formation. The number of acantholytic keratinocytes is usually small, often requiring a careful search to identify them. Secondary clefts may develop, leading to detachment of the epidermis in its midlevel. These clefts may extend to above the basal layer, rarely giving rise to limited areas of suprabasal separation. In the setting of a subcorneal blister, dyskeratotic granular keratinocytes are diagnostic for this disorder. Eosinophilic spongiosis may be prominent with intraepidermal eosinophilic pustules. Thus the histologic features of pemphigus foliaceus may have three patterns: (1) eosinophilic spongiosis, (2) a subcorneal blister, often with few acantholytic keratinocytes, and (3) a subcorneal blister with dyskeratotic granular keratinocytes, diagnostic for this disorder. The character of the inflammatory infiltrate observed is variable. Most commonly the histologic differential diagnoses considered for pemphigus foliaceus are staphylococcal scalded skin and bullous impetigo.

Direct immunofluorescence in pemphigus foliaceus shows cell surface membrane staining with antibodies to IgG. The staining may be confined to the upper epidermal layers or it may involve all epidermal layers, indistinguishable from pemphigus vulgaris. Indirect immunofluorescence can also be utilized to detect circulating antibodies in the patient’s blood. In pemphigus foliaceus, normal human skin has a higher sensitivity as a substrate than monkey esophagus (5). Enzyme-linked immunosorbent assay (ELISA) testing provides a quantitative and very sensitive method for detecting serum anti-dsg-1 antibodies. Sensitivities and specificities have been reported in the range of 92% to 100% (6).

IVA

SUBCORNEAL OR INTRACORNEAL SEPARATION

There is separation within or just below the stratum corneum. Inflammatory cells may be sparse, or may consist predominantly of neutrophils.

1. Sub/Intracorneal Separation, Scant Inflammatory Cells
2. Sub/Intracorneal Separation, Neutrophils Prominent
3. Sub/Intracorneal Separation, Eosinophils Prominent

IVA1

Sub/Intracorneal Separation, Scant Inflammatory Cells

There is separation within or just below the stratum corneum, associated with scant inflammation, usually lymphocytic. Pemphigus foliaceus is prototypic (1–3).
IVA. Subcorneal or Intracorneal Separation

Acantholytic, Vesicular, and Pustular Disorders

IVClin.

Fig. IVA1

Clin. Fig. IVA1. *Pemphigus foliaceus*. A middle-aged male with crusted plaques required systemic corticosteroids and immunosuppressive therapy to control his blistering disease. (W. Witmer).

Fig. IVA1.a. *Pemphigus foliaceus*, low power. A blister forms in the superficial epidermis and there is a sparse dermal infiltrate.

Fig. IVA1.b. *Pemphigus foliaceus*, high power. The absence of a stratum corneum, and the presence of a few acantholytic cells, may be subtle clues to the diagnosis of pemphigus foliaceus. If there is an intact blister, it is seen as an intraepidermal blister within the granular cell layer and is devoid of an associated neutrophilic infiltrate. This feature is important in differentiating pemphigus foliaceus from impetigo/impetiginization.

Conditions to consider in the differential diagnosis:
- staphylococcal scalded skin
- bullous impetigo
- miliaria crystallina
- exfoliative dermatitis
- pemphigus foliaceus
- pemphigus erythematosus
- necrolytic migratory erythema
- pellagra
- acrodermatitis enteropathica

IVA2 Sub/Intracorneal Separation, Neutrophils Prominent

There is separation in or just below the stratum corneum. Neutrophils are prominent in the stratum corneum and in the superficial epidermis, and can often be found in the dermis. *Impetigo contagiosa* is a prototypic example (7,8).

Impetigo Contagiosa

CLINICAL SUMMARY. Impetigo contagiosa is primarily an endemic disease in preschool-age children, which may occur in epidemics. Very early lesions consist of vesicopustules that rupture quickly and are followed by heavy, yellow crusts. Most of the lesions are located in exposed areas. An occasional sequela is acute glomerulonephritis, which usually has a favorable long-term prognosis.

Impetigo contagiosa is clinically and histologically distinct from Staphylococcal scalded-skin syndrome (Ritter’s disease), which occurs largely in the newborn and in children younger than 5 years, and rarely in older individuals often in association with immunodeficiency or renal
insufficiency, and from bullous impetigo (9). The disease begins abruptly with diffuse erythema and fever. Large, flaccid bullae filled with clear fluid form and rupture almost immediately. Large sheets of superficial epidermis separate and exfoliate. The disease is rarely fatal in children. In neonates with generalized lesions, and in adults with severe underlying diseases, the prognosis is worse. Both bullous impetigo and staphylococcal scalded-skin syndrome are transmissible and can cause epidemics in nurseries, where they may occur together. The blisters in bullous impetigo and the scalded-skin syndrome are caused by exfoliative toxin (exfoliatin, types A or B) released by staphylococcus. In patients with bullous impetigo, the toxin produces blisters locally at the site of infection, whereas in cases of the scalded-skin syndrome, it circulates throughout the body, causing blisters at sites distant from the infection (3). In these two conditions, the bullae contain only few inflammatory cells, whereas in impetigo contagiosa, the blisters are filled with neutrophils.

An important difference between the two diseases is that no staphylococci can be grown from the bullae of the staphylococcal scalded-skin syndrome, in contrast to those of bullous impetigo. In staphylococcal scalded-skin syndrome, the staphylococci are present at a distant focus, often a purulent conjunctivitis, rhinitis, or pharyngitis or rarely a cutaneous infection or a septicemia.

**HISTOPATHOLOGY.** The vesicopustule of impetigo contagiosa arises in the upper layers of the epidermis above, within, or below the granular layer. It contains numerous neutrophils. Not infrequently, a few acantholytic cells can be observed at the floor of the vesicopustule. Often,
tests and lymphocyte transformation tests. Fever, leukocytosis, purpura, and occasionally clinical features suggesting erythema multiforme accompany the pustules. *In vitro* studies have shown this to be a drug-specific process effected by CD4+ T-cell mediated release of the neutrophil chemoattractant, IL-8 (11).

**HISTOPATHOLOGY.** Biopsies show subcorneal or intraepidermal pustules, papillary dermal edema, and a lymphohistiocytic perivascular infiltrate with some eosinophils and neutrophils. Vasculitis and/or single-cell keratinocyte necrosis may be present.

**Conditions to consider in the differential diagnosis:**

*impetigo contagiosa*
*bullous impetigo*
epidermis adjacent to folliculitis
impetiginized dermatitis
*candidiasis*
subcorneal pustular dermatosis (Sneddon–Wilkinson)
pustular psoriasis
IgA pemphigus
secondary syphilis
acropustulosis of infancy
transient neonatal pustular melanosis
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**HISTOPATHOLOGY.** Biopsies show subcorneal or intraepidermal pustules, papillary dermal edema, and a lymphohistiocytic perivascular infiltrate with some eosinophils and neutrophils. Vasculitis and/or single-cell keratinocyte necrosis may be present.

**Conditions to consider in the differential diagnosis:**
- *Impetigo contagiosa*
- *Bullous impetigo*
- Epidermis adjacent to folliculitis
- Impetiginized dermatitis
- Candidiasis
- Subcorneal pustular dermatosis (Sneddon–Wilkinson)
- Pustular psoriasis
- IgA pemphigus
- Secondary syphilis
- Acropustulosis of infancy
- Transient neonatal pustular melanosis

---

**Fig. IVA2.e.** Folliculitis with subcorneal pustule formation, low power. There is an intense, neutrophil-rich infiltrate which has obliterated the hair follicle. (J. Junkins-Hopkins).

**Fig. IVA2.f.** Folliculitis with subcorneal pustule formation, low power. There is a mixed inflammatory infiltrate in the dermis around the follicle.

**Fig. IVA2.g.** Folliculitis with subcorneal pustule formation, medium power. The epidermis above the follicle shows formation of a subcorneal pustule. If only a superficial shave biopsy is taken, the biopsy resembles other entities in this subgroup and the diagnosis may be missed. (J. Junkins-Hopkins).
Acantholytic, Vesicular, and Pustular Disorders

IV

Table IV.1  Acute Generalized Exanthematous Pustulosis, Pustular Psoriasis (von Zumbusch), Subcorneal Pustular Dermatosis (Sneddon–Wilkinson) and Bullous Impetigo Compared (11)

<table>
<thead>
<tr>
<th>AGEP</th>
<th>Pustular Psoriasis</th>
<th>Subcorneal Pustular Dermatosis</th>
<th>Bullous Impetigo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile pustules on erythematous base</td>
<td>Pinhead pustules in patches</td>
<td>Pustules coalescing in annular patterns</td>
<td>Small vesicles with clear yellow fluid</td>
</tr>
<tr>
<td>Fever, burning rash</td>
<td>Fever, chills</td>
<td>Oral lesions sometimes</td>
<td>Lymphangitis, adenopathy sometimes</td>
</tr>
<tr>
<td>Leukocytosis, eosinophilia</td>
<td>Leukocytosis, EST, CRP, ASO, Ig up</td>
<td>May be immune dysfunction</td>
<td>Gram positive cocci</td>
</tr>
<tr>
<td>Subcorneal intra-epithelial pustule, papillary dermal edema</td>
<td>Psoriasiform sometimes, spongiform pustules, papillary dermal edema</td>
<td>Neutrophils in pustules beneath stratum corneum</td>
<td>Subcorneal vesicles; spongiosis, few neutrophils, gram positive cocci</td>
</tr>
</tbody>
</table>

AGEP: Acute Generalized Exanthematous Pustulosis.

**Fig. IVA2.h.** Acute generalized exanthematous pustulosis, medium power. A subcorneal separation is seen associated with a superficial dermal infiltrate in which neutrophils are present.

**Figs. IVA2.i,j.** Acute generalized exanthematous pustulosis, high power. Neutrophils are seen in the upper epidermal layers as well as within the blister cavity. Differentiation from an early lesion of pustular psoriasis may require clinical correlation.

**Fig. IVA2.k.** Acute generalized exanthematous pustulosis, high power. Neutrophils and lymphocytes are present in the dermal infiltrate.
IV. Acantholytic, Vesicular, and Pustular Disorders

IVA3  **Sub/Intracorneal Separation, Eosinophils Predominant**

There is separation in or just below the stratum corneum, with (pemphigus) or without acantholytic keratinocytes. Eosinophils are present in the epidermis, and occasionally there is eosinophilic spongiosis. The separation is associated with a dermal infiltrate that contains eosinophils. *Erythema toxicum neonatorum* is a prototypic example (12), which however is rarely biopsied.

**Erythema Toxicum Neonatorum**

**CLINICAL SUMMARY.** A benign, asymptomatic eruption affecting about 40% of term infants usually within 12 to 48 hours after birth, erythema toxicum lasts 2 to 3 days and consists of blotchy macular erythema, papules, and pustules that tend to develop at sites of pressure. The eruption is associated with blood eosinophilia.

**HISTOPATHOLOGY.** The macular erythema is characterized by sparse eosinophils in the upper dermis, largely in a perivascular location, and mild papillary dermal edema. The papules show an accumulation of numerous eosinophils and some neutrophils in the area of a hair follicle and the overlying epidermis. Papillary dermal edema is more intense and eosinophils, more numerous. Mature pustules are subcorneal and are filled with eosinophils and occasional neutrophils. The pustules form as a result of the upward migration of eosinophils to the surface epidermis from within and around hair follicles.

**DIFFERENTIAL DIAGNOSIS.** The subcorneal pustules of impetigo and transient neonatal pustular melanosis are not follicular in origin and contain neutrophils rather than eosinophils. Although many eosinophils are present in the vesicles of incontinentia pigmenti, the vesicle is intraepidermal rather than subcorneal, and spongiosis is present. In addition, necrotic keratinocytes may be prominent in incontinentia pigmenti but are absent in erythema toxicum neonatorum.

**Conditions to consider in the differential diagnosis:**

- *erythema toxicum neonatorum*
- pemphigus foliaceus
- pemphigus erythematosus
- IgA pemphigus
- eosinophilic pustular folliculitis
- incontinentia pigmenti, vesicular
- exfoliative dermatitis, drug induced scabies

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Fig. IVA3.a

**Subcorneal collection of neutrophils and eosinophils**

Fig. IVA3.b

Fig. IVA3.c

- **Fig. IVA3.a.** Subcorneal pustule with eosinophils. There is a broad lesion characterized by increased cells in the stratum corneum with crust formation.

- **Fig. IVA3.b.** Subcorneal pustule with eosinophils. Subcorneal pustule and a mixed cell infiltrate in the superficial dermis.

- **Fig. IVA3.c.** Subcorneal pustule with eosinophils. The cells in the pustule are mostly eosinophils and also include neutrophils.
Scabies With Eosinophilic Pustulosis

An elderly patient with scabies had these unusual biopsy findings (Figs. IVA3.a.c). In an appropriate setting, the differential diagnosis could include erythema toxicum neonatorum.

Friction Blister

CLINICAL SUMMARY. Friction blisters are caused by mechanical shearing forces, resulting in disruption to keratinocytes or cytolysis. This occurs in the normal epidermis when the structural (keratin) matrix of the keratinocyte is overwhelmed by high levels of physical agents such as friction and heat. Friction (mechanical energy applied parallel to the epidermis) leads to the shearing of keratinocytes one from another and of the keratinocytes themselves, typically at the level of the stratum spinosum, giving the characteristic clear, fluid-filled blisters. The area of the separation fills due to hydrostatic pressure with a clear transudate with a low protein level. At about 24 hours, there is high mitotic activity in the basal cells; at 48 and 120 hours, new stratum granulosum and stratum corneum, respectively, can be seen (13). Minimal friction may lead to cytolysis in subjects whose keratinocytes do not have a normal structural matrix, such as in epidermolysis bullosa.

HISTOPATHOLOGY. Usual friction blisters show evidence of initial spongiosis and then disruption of the keratinocytes in the spinous layer. In lesions of the palms or soles, the blisters remain intact for a time because of the thick stratum corneum in these sites.

Intraspinous Keratinocyte Separation, Spongiotic

There are spaces within the epidermis (vesicles, bullae). There may be dyskeratosis or acantholysis, and a few eosinophils may be present in the epidermis.

1. Intraspinous Spongiosis, Scant Inflammatory Cells
2. Intraspinous Spongiosis, Lymphocytes Predominant
2a. Intraspinous Spongiosis, Eosinophils Present
3. Intraspinous Spongiosis, Neutrophils Predominant

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Intraspinous Spongiosis, Scant Inflammatory Cells

The infiltrate in the dermis is scant, lymphocytic, or eosinophilic. Transient acantholytic dermatosis is prototypic.

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IV. Acantholytic, Vesicular, and Pustular Disorders

Conditions to consider in the differential diagnosis:

- dyskeratosis
- epidermolytic hyperkeratosis
- epidermolytic acanthoma
- miliaria rubra
- transient acantholytic dermatosis
- bullous dermatitis of diabetes and of uremia
- comma bulla
- friction blisters

**IVB2  Intraspinous Spongiosis, Lymphocytes Predominant**

In the dermis, lymphocytes predominate. Eosinophils can be found in most examples of atopy, and in allergic contact dermatitis. The clinical manifestation of spongiotic dermatitis (a histologic pattern) is eczematous dermatitis. This is a T-cell-mediated inflammatory skin disease, where activated T cells may harm epidermal keratinocytes by direct cell–cell contact mediated cytotoxicity or by secreted proinflammatory cytokines, accounting for at least some of the features of intercellular edema or spongiosis formation. It has been shown that activated T cells infiltrating the skin induce apoptosis of single keratinocytes, as shown in situ, and in the lesional skin of atopic dermatitis and allergic contact dermatitis. Interestingly, in these studies, apoptosis of single keratinocytes was detected predominantly in suprabasal epidermal layers, concomitant with the predominantly observed suprabasal spongiosis formation in these conditions. This may be due to the existence of anti-apoptosis programs predominantly in basal keratinocytes (14).

**Dyshidrotic Dermatitis (Eczema)**

**CLINICAL SUMMARY.** This entity is characterized by recurrent, severely pruritic, deep-seated vesicles that classically involve the lateral aspects of the fingers and, in some cases, the toes. Emotional stress may exacerbate the eruption. In chronic cases, there may be more extensive involvement of the palms and soles. Although the eruption develops acutely, it may become chronic with erythema, lichenification, and fissuring. Secondary impetiginization (bacterial infection with neutrophils in the stratum corneum) is common.

**HISTOPATHOLOGY.** Spongiosis and intraepidermal vesiculation occur in acute lesions. There is a superficial perivascular lymphohistiocytic infiltrate with exocytosis of lymphocytes into spongiotic zones. The infiltration is usually mild. In acute lesions, the compact, thickened stratum corneum of acral skin remains intact, and the epidermal thickness is normal. With chronicity, spongiosis diminishes, acanthosis and parakeratosis predominate, and serum may be identified within the stratum corneum. Difficulty in diagnosis may occur because of the formation of vesiculopustules in older lesions.

**Conditions to consider in the differential diagnosis:**

- spongiotic (eczematous) dermatitis (see Section IIIB.1)
- atopic dermatitis
- allergic contact dermatitis
- photoallergic drug eruption
- irritant contact dermatitis
- nummular eczema
- dyshidrotic dermatitis
- “id” reaction

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**Fig. IVB2.a.** Spongiotic dermatitis, dyshidrotic eczema, low power. This biopsy of acral skin shows an intraepidermal vesicle and an associated superficial inflammatory infiltrate. A vesicle surrounded by spongiosis (spongiotic vesicle) is present beneath the intact acral-type stratum corneum.

**Fig. IVB2.b.** Dyshidrotic eczema, high power. There is diffuse spongiosis within the epidermis manifested by white spaces separating the keratinocytes. Several intraepidermal vesicles also form.
Intraspinous Keratinocyte Separation, Spongiotic Disorders

- seborrheic dermatitis
- stasis dermatitis
- miliaria rubra
- pityriasis rosea

**IVB2a Intraspinous Spongiosis, Eosinophils Present**

The number of eosinophils seen is variable from many in incontinentia pigmenti and pemphigus vegetans to few in atopic dermatitis. Eosinophilic spongiosis is a histopathologic reaction pattern that is a finding common in certain inflammatory skin diseases, including spongiotic dermatitis, arthropod bite reactions and scabies, occasionally viral vesicular disorders, incontinentia pigmenti, and immunobullous disorders, including especially bullous pemphigoid, pemphigus, and related disorders. Eosinophilic spongiosis can also be encountered occasionally in a variety of other unrelated disorders, including polycythemia vera, porokeratosis, and Meyerson's "inflammatory nevi." Although intraepithelial eosinophils can be found in biopsies of follicular disorders, such as Ofuji's disease or eosinophilic folliculitis, the term eosinophilic spongiosis is reserved for cases with eosinophils present in spongiotic areas of the epidermis (15).

**Acute Contact Dermatitis (See also Section IIIB1a)**

See Fig. IVB2a.a, Fig. IVB2a.b, and Fig. IVB2a.c.

**Bullous Pemphigoid, Urticarial Phase (See also Section IVE3)**

See Clin. Fig. IVB2a.a, Fig. IVB2a.d, and Fig. IVB2a.e.

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**Fig. IVB2a.a**. Spongiotic dermatitis (acute contact dermatitis), low power. In this acute lesion, the stratum corneum shows a basketweave pattern. Intraepidermal vesicles are seen associated with a perivascular inflammatory infiltrate.

**Figs. IVB2a.b and c**. Spongiotic dermatitis (acute contact dermatitis), high power. There is diffuse spongiosis with intraepidermal vesicles. The infiltrate is mixed but contains eosinophils in the dermis, and in the spongiotic epidermis.
Incontinentia Pigmenti

**CLINICAL SUMMARY.** Incontinentia pigmenti is an X-linked dominantly inherited disorder. Males with the abnormal gene on their single X chromosome are hemizygous for this condition and hence are so severely affected that they usually die in utero. The familial form of this disorder IP2 (or classical incontinentia pigmentosa) is localized to the Xq28 region. It is due to a mutation in the IKK-gamma gene, also called NEMO (16). While mostly a disorder of females, cases have been described in males with Klinefelter’s syndrome (XXY) and somatic mosaicism with a postzygotic NEMO mutation (17).

The disorder has four stages, beginning with a phase of erythema and bullae in infancy, progressing to linear, verrucous lesions which subside, leaving widely disseminated areas of irregular, spattered, or whorled pigmentation develop. In the fourth stage, seen in adult females, subtle, faint, hypochromic, or atrophic lesions in a linear pattern are most apparent on the lower extremities.

**HISTOPATHOLOGY.** The vesicles seen during the first stage arise within the epidermis and are associated with eosinophilic spongiosis, often with single dyskeratotic cells and whorls of squamous cells with central keratinization. Like the epidermis, the dermis shows an infiltrate containing many eosinophils and some mononuclear cells. The combination of eosinophilic spongiosis, spongiotic vesiculation, and dyskeratotic keratinocytes is virtually pathognomonic of incontinentia pigmenti, being seen also only
in Grover’s disease which is easily distinguishable on other grounds (15). In the second stage, there are acanthosis, irregular papillomatosis, and hyperkeratosis with intraepidermal keratinization, consisting of whorls of keratinocytes and of scattered dyskeratotic cells. The basal cells are vacuolated, and there is a decrease in their melanin content. The dermis shows a mild, chronic inflammatory infiltrate intermingled with melanophages. The areas of pigmentation seen in the third stage show extensive deposits of melanin within melanophages located in the upper dermis. In the hypopigmented/atrophic stage, there is epidermal atrophy, decreased melanin in the epidermal basal layer, apoptotic bodies, and absence of the pilosebaceous units and eccrine glands.

Conditions to consider in the differential diagnosis:
- spongiotic (eczematous) dermatitis
- atopic dermatitis
- allergic contact dermatitis
- photoallergic drug eruption
- Bullous pemphigoid, urticarial phase
- incontinentia pigmenti, vesicular stage
Neutrophils are seen in the epidermis, stratum corneum, and in the dermis. Aggregations of neutrophils in the superficial spinous layer constitute the spongiform pustules of Kogoj characteristic of psoriasis. Neutrophilic spongiosis has been less well characterized than eosinophilic spongiosis. It may be seen in a variety of conditions including psoriasis, acute generalized exanthematous pustulosis, intraepidermal blistering diseases including dermatitis herpetiformis, linear IgA bullous disease, and bullous lupus erythematosus (LE) which are all subepidermal immunobullous disorders in which neutrophils predominate in the inflammatory infiltrate, and in infections and infestations such as dermatophytosis, scabies, impetigo, and viral vesicular disorders (15).

**Dermatophytosis**

See Clin. Fig. IVB3 and Figs. IVB3.a–c.

**Conditions to consider in the differential diagnosis:**
- pustular psoriasis
- Reiter’s syndrome
- IgA pemphigus
- subcorneal pustular dermatosis (Sneddon–Wilkinson)

Clin. Fig. IVB3. *Dermatophytosis*. A large erythematous patch showing central clearing and a polycyclic scaling border, which is quite narrow and threadlike.

**Fig. IVB3.a.** *Dermatophytosis, low power*. There is a dense infiltrate in the dermis extending into the epidermis.

**Fig. IVB3.b.** *Dermatophytosis, high power*. The stratum corneum is separated and focally parakeratotic with numerous neutrophils. This pattern could mimic subcorneal pustular dermatosis or pemphigus foliaceus. Dermatophytes are often not readily identified in the H&E stain. This finding of “neutrophils in the horn” should prompt a stain for fungus.

**Fig. IVB3.c.** *Dermatophytosis, high power*. PAS stain reveals hyphae within the stratum corneum. The organisms are often much less numerous than here.
IVC. Intraspinous Keratinocyte Separation, Acantholytic

Intraspinous Keratinocyte Separation, Acantholytic, Vesicular, and Pustular Disorders

- Exanthemtic pustular drug eruptions
- Impetiginized dermatosis
- Dermatophytosis
- Rupial secondary syphilis
- Seborrheic dermatitis (see Section IIIB.1c)
- Epidermis adjacent to folliculitis
- Impetigo contagiosa
- Hydroa vacciniforme
- Mucocutaneous lymph node syndrome (Kawasaki disease, pustular variant)

IVC

INTRASPINOUS KERATINOCYTE SEPARATION, ACANTHOLYTIC

There are spaces within the epidermis (vesicles, bullae). The process of separation is acantholysis. Keratinocytes within the spinous layer detach or separate from each other or from basal keratinocytes. There may be dyskeratosis, and a few eosinophils may be present in the epidermis. The infiltrate in the dermis is variable, composed of lymphocytes with or without eosinophils.

1. Intraspinous Acantholysis, Scant Inflammatory Cells
2. Intraspinous Acantholysis, Predominant Lymphocytes
2a. Intraspinous Acantholysis, Eosinophils Present
3. Intraspinous Separation, Neutrophils or Mixed Cell types

IVC1 Intraspinous Acantholysis, Scant Inflammatory Cells

The infiltrate in the dermis is scant, lymphocytic, or eosinophilic. Hailey–Hailey disease and Grover’s disease are prototypic.

Familial Benign Pemphigus (Hailey–Hailey Disease)

**Clinical Summary.** Familial benign pemphigus is inherited as an autosomal dominant trait, with a family history obtainable in about two-thirds of the patients. It is characterized by a localized, recurrent eruption of small vesicles on an erythematous base (18). By peripheral extension, the lesions may assume a circinate configuration. The sites of predilection are the intertriginous areas, especially the axillae and the groin. Only very few instances of mucosal lesions have been reported. Mutations in ATP2Cl, encoding a calcium pump, are the cause of Hailey–Hailey Disease (19).

**Histopathology.** Although early lesions may show small suprabasal separations, so-called lacunae, in fully developed lesions, there are large separations, that is, vesicles and even bullae, in a predominantly suprabasal position. Villi, which are elongated papillae lined by a single layer of basal cells, protrude upward into the bullae, and, in some cases, narrow strands of epidermal cells proliferate

Clin. Fig. IVC1.a

*Hailey–Hailey Disease.* A 39-year-old woman presented with malodorous vegetating, erythematous crusted erosions, peripheral flaccid bullae, and scattered pustules in the axillae and groin.

Clin. Fig. IVC1.b

*Hailey–Hailey Disease.* The patient’s 43-year-old brother has similar macerated plaques with pustules in the intertriginous areas, characteristic of this autosomal dominant disorder. (continues)
downward into the dermis. Many cells of the detached stratum malpighii show loss of their intercellular bridges, so that acantholysis affects large portions of the epidermis. Individual cells and groups of cells usually are seen in large numbers in the bulla cavity. Some acantholytic cells may exhibit premature keratinization, resembling the grains of Darier’s disease. In spite of the extensive loss of intercellular bridges, the cells of the detached epidermis in many places are only slightly separated from one another because a few intact intercellular bridges still hold them loosely together. This quite typical feature gives the detached epidermis the appearance of a dilapidated brick wall.

**Transient Acantholytic Dermatosis (Grover’s Disease)**

**CLINICAL SUMMARY.** Transient acantholytic dermatosis is characterized by pruritic, discrete papules, and papulovesicles on the chest, back, and thighs (20,21). In rare instances, vesicles and even bullae are seen. Most patients are middle-aged or elderly men. Although the disorder is transient in the majority of patients, lasting from 2 weeks to 3 months, it can persist for several years. Despite histologic similarity to Darier’s disease, Grover’s disease does not share an abnormality in the ATP2A2 gene (22).

**HISTOPATHOLOGY.** Focal acantholysis and dyskeratosis (focal acantholytic dyskeratosis) are present. Because these foci are small, they are sometimes found only when step sections are obtained. The acantholysis may occur in five histologic patterns, resembling Darier’s disease, Hailey–Hailey disease, pemphigus vulgaris, superficial pemphigus, or spongiotic dermatitis. Two or more of these patterns may be found in the same specimen. In a recent study, a number of additional patterns were described, namely cases with porokeratosis-like oblique columns of parakeratosis, lesions showing a silhouette reminiscent of a lentiginous nevus, intraepidermal vesicular lesions, lichenoid changes with basal vacuolization and dyskeratosis, and dysmature foci with keratinocyte atypia. In addition, the dermal infiltrate was quite often composed not only of lymphocytes intermingled with eosinophils,
An elderly male presented with pruritic lesions on the chest and back. The lesions are discrete pruritic brown keratotic papules. At scanning magnification, multiple foci of intraepidermal separation are seen. There is a mild superficial, dermal inflammatory infiltrate. Multiple histologic changes can be seen in these areas of intraepidermal separation, including the most common pattern seen here which mimics Darier's disease, but also patterns of Hailey–Hailey disease, pemphigus vulgaris, pemphigus foliaceus, and spongiotic dermatitis.

There is hyperkeratosis and there is an inflammatory infiltrate in the dermis. There is suprabasal acantholysis with parakeratosis and corps ronds in the upper epidermal layer.
but also with neutrophils. Also, there was sometimes cytoplasmic edema of endothelial cells, and erythrocyte extravasation. In addition, involved areas were sometimes larger than 2 mm (23). The expression of Syndecan-1, a proteoglycan important for keratinocytes intercellular adhesion is markedly decreased in Grover's disease, as in other acantholytic conditions such as pemphigus and herpes simplex infection (24) (see also IVC1).

**Conditions to consider in the differential diagnosis:**

- Acantholytic dyskeratosis
- Darier's disease
- transient acantholytic dermatosis (Grover's disease)
- warty dyskeratoma (isolated keratosis follicularis)
- Others with Intraspinous Acantholysis, scant inflammatory cells
- epidermolytic hyperkeratosis
- epidermolytic acanthoma
- Hailey–Hailey disease
- focal acantholytic dyskeratosis
- acantholytic solar keratosis
- pemphigus erythematosus
- pemphigus foliaceus
- friction blister (cytolytic blister)

**IVC2 Intraspinous Acantholysis, Predominant Lymphocytes**

In the dermis, lymphocytes are predominant. In erythema multiforme and related lesions there is necrosis of individual cells (apoptosis) that may become confluent. *Herpes simplex and varicella-zoster* are prototypic examples (25).

**Herpes Simplex**

Two immunologically distinct viruses can cause herpes simplex: herpes simplex virus type 1 (orofacial type) and herpes simplex virus type 2 (genital type), often referred to as HSV-1 and HSV-2, respectively. Primary infection with HSV-1 is usually subclinical in childhood. In about 10% of the cases, acute gingivostomatitis occurs, usually in childhood and only rarely in early adult life. HSV-2 generally is acquired venereally. Occasionally, an infant contracts HSV-2 *in utero* or by direct contact in the birth canal. Recurrent infections of the oral cavity, the skin, or the genitals can result either from reactivation of a latent infection or from a new infection.

Both primary and recurrent herpes simplex, in their earliest stages, show one or several groups of vesicles on an inflamed base. If located on a mucous surface, the vesicles erode quickly, whereas, if located on the skin, they may become pustular before crusting.

**HISTOPATHOLOGY.** Herpes simplex of the skin produces profound degeneration of keratinocytes, resulting in acantholysis. Degeneration of epidermal cells occurs in two forms: ballooning degeneration and reticular degeneration, both of which are changes typical of viral vesicles. The earliest changes include nuclear swelling of keratinocytes. With hematoxylin and eosin stains, these nuclei appear slate gray and homogeneous. Ballooning degeneration (swelling of epidermal cells) then follows. Eosinophilic inclusion bodies are frequently observed in the centers of enlarged, round nuclei of balloon cells. Reticular degeneration is a process in which epidermal cells are distended by intracellular edema, so that cell walls rupture.
**Fig. IVC2.b.** *Herpes simplex infection, high power.* Multiple keratinocytes of the epithelium show typical nuclear changes of herpes viral infection, including peripheral rimming and a ground glass appearance; also several multinucleated keratinocytes are present.

**Fig. IVC2.c.** *Follicular herpes simplex infection, low power.* Occasionally, involvement is confined to a skin appendage, such as this follicle.

**Fig. IVC2.d.** *Follicular herpes simplex infection, medium power.* There is a perivascular and interstitial lymphocytic infiltrate around the follicle.

**Fig. IVC2.e.** *Follicular herpes simplex infection, high power.* Characteristic viral cytopathic changes are seen.
Through coalescence, a multilocular vesicle results, the septa of which are formed by resistant cellular walls. In older vesicles, the cellular walls disappear and the vesicle becomes unilocular. Reticular degeneration is not specific for viral vesicles, because it also occurs in the vesicles of dermatitis. The upper dermis beneath viral vesicles contains an inflammatory infiltrate of variable density. In some cases of herpes simplex, vascular damage is present, showing necrosis of vessel walls, microthrombi, and hemorrhage. In addition, eosinophilic inclusions may be found in endothelial cells and fibroblasts.

**Varicella-Zoster Infection**

See Clin. Fig. IVC2.b and Figs. IVC2.f, g.

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**Toxic Epidermal Necrolysis and Erythema Multiforme With Intraepidermal Vesiculation**

(See also Section IIIH1)

In toxic epidermal necrolysis (TEN, Lyell's syndrome), in bullous lesions of erythema multiforme, and in the central portion of target lesions of erythema multiforme, there are numerous necrotic keratinocytes, with full-thickness epidermal necrosis in TEN, and a subepidermal separation to form a bulla, or to result in extensive desquamation of the necrotic epithelium in TEN. The dermal inflammatory infiltrate is more sparse in TEN than in erythema multiforme. Extravasated erythrocytes are commonly found within the blister cavity. Melanophages within the papillary dermis occur in late lesions.

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**Clin. Fig. IVC2.b**

**Herpes zoster**. Lakes of umbilicated vesicles in a dermatomal distribution appeared in this HIV positive middle aged female.

**Fig. IVC2.f**

**Varicella-zoster infection, low power.** The epidermis shows diffuse spongiosis as well as necrosis. There is a moderately intense superficial and deep inflammatory infiltrate that may extend into the subcutaneous fat. Although varicella-zoster cannot always be distinguished from herpes simplex using histology, the infiltrate in varicella-zoster is generally more intense and extends more deeply into the dermis. Immunohistochemical staining provides specific differentiation of the two conditions.

**Fig. IVC2.g**

**Varicella-zoster infection, high power.** Similar to what is seen in herpes simplex infection, keratinocytes show multinucleation and the nuclei show peripheral rimming and ground glass change of the chromatin.
**Clin. Fig. IVC2.c.** Toxic epidermal necrolysis. The patient initially presented with a painful widespread erythematous rash which soon developed into sheets of peeling skin with erosions. This is a serious skin condition with a mortality of 25% to 50% and requires intensive medical care in a burn unit.

**Fig. IVC2.h.** Erythema multiforme/toxic epidermal necrolysis, low power. There is a focus of prominent epidermal spongiosis and necrosis. There is a sparse dermal infiltrate of lymphocytes.

**Fig. IVC2.i.** Erythema multiforme/toxic epidermal necrolysis, medium power. The intact, basketweave stratum corneum portrays the acute nature of this lesion. The epidermis shows multiple zones of intraspinous separation and blister formation.

**Fig. IVC2.j.** Erythema multiforme/toxic epidermal necrolysis, medium power. At the periphery of the lesion a few lymphocytes are seen tagging the dermal–epidermal interface and are associated with vacuolar alteration, the earliest change in this process. (continues)
Paraneoplastic Pemphigus

**CLINICAL SUMMARY.** This condition is associated with underlying neoplasms (26), most commonly lymphoma, chronic lymphocytic leukemia, Castleman’s disease, thymoma, spindle cell sarcoma, and Waldenström’s macroglobulinemia. Patient sera recognize multiple antigens of the plakin protein family that includes desmoplakin, bul- lous pemphigoid antigen 1 (BPAG1), envoplakin and periplakin, and desmogleins 1 and 3 (27). The cutaneous lesions are quite polymorphic. The most consistent clinical feature of PNP is the presence of intractable stomatitis mimicking Stevens–Johnson syndrome. Small airway occlusion, secondary to pulmonary epithelial injury can be fatal. Autoantibodies are deposited in the kidneys, bladder, and muscle, resulting in a paraneoplastic multiorgan syndrome (28). At least six different clinical variants are recognized: bullous pemphigoid-like, cicatricial pemphigoid-like, pemphigus-like, erythema multiforme-like, graft-versus-host disease-like, and lichen planus-like.

**HISTOPATHOLOGY.** The histologic features are variable, correlating with the various clinical presentations. The lesions show a unique combination of erythema multiforme-like, lichen planus-like, pemphigus vulgaris-like, and pemphigoid-like features. The principal findings are suprabasal acantholysis as seen in pemphigus vulgaris with, in addition, basal apoptosis, in association with a vacuolar interface dermatitis (erythema multiforme-like) with or without lichenoid inflammation (lichen planus-like). Paraneoplastic pemphigus (PNP) may also present exclusively with lichenoid interface dermatitis in the absence of acantholysis. In pemphigoid-like lesions, a sub-epidermal blister is present. Direct immunofluorescence demonstrates, in addition to keratinocyte cell surface IgG, C3 both in the intercellular space and at the dermal–epidermal junction. PNP sera also often stains other desmosome-containing tissues, such as bladder, heart and liver, unlike the other types of pemphigus, in which only stratified squamous epithelial substrates are stained (29).
Fig. IVC.2.k. Paraneoplastic pemphigus. In this lesion, the pattern is predominantly lichenoid.

Fig. IVC.2.l. Paraneoplastic pemphigus. A dense lichenoid mixed cell infiltrate with some suprabasal apoptotic cells.

Fig. IVC.2.m. Paraneoplastic pemphigus. From another case, a mixed picture like this of lichenoid inflammation with vacuolar change and apoptotic cells in the epidermis may suggest erythema multiforme and related disorders, or other lichenoid disorders.

Fig. IVC.2.n. Paraneoplastic pemphigus. In another area, there is suprabasal acantholysis similar to pemphigus vulgaris.

**Conditions to consider in the differential diagnosis:**

- *erythema multiforme* (with vacuolar and apoptotic changes)
- Stevens–Johnson syndrome
- toxic epidermal necrolysis (TEN, Lyell's syndrome)
- *herpes simplex, varicella-zoster*
- hydroa vacciniforme (epidermal necrosis)
- cowpox
- hand-foot-and-mouth disease (coxsackievirus)
- orf
- PNP
Intraspinous Acantholysis, Eosinophils Present

The number of eosinophils seen is variable from many in incontinentia pigmenti and pemphigus vegetans to few in atopic dermatitis. *Pemphigus vegetans* is a prototypic example (2,30).

**Pemphigus Vegetans**

CLINICAL SUMMARY. This is an uncommon variant of pemphigus vulgaris, which historically has been divided into the Neumann type and Hallopeau type. In the Neumann type, the disease begins and ends as pemphigus vulgaris, but many of the denuded areas heal with verrucous vegetations that may contain small pustules in early stages. The Hallopeau type is relatively benign, having pustules as the primary lesions instead of bullae. Their development is followed by the formation of gradually enlarging verrucous vegetations, especially in intertriginous areas.

HISTOPATHOLOGY. In the Neumann type, the early lesions consist of bullae and denuded areas that have the same histologic picture as that of pemphigus vulgaris (see Section IVD.3). As the lesions age, however, there is formation of villi and verrucous epidermal hyperplasia. Numerous eosinophils are present within the epidermis and dermis, producing both eosinophilic spongiosis and eosinophilic pustules. Acantholysis may not be present in older lesions.

In the Hallopeau type, the early lesions consist of pustules arising on normal skin with acantholysis and formation of small clefts, many in a suprabasal position. The clefts are filled with numerous eosinophils and degenerated acantholytic epidermal cells. Early lesions may reveal more eosinophilic abscesses than in the Neumann type. The subsequent verrucous lesions are histologically identical to the Neumann type. DIF examination reveals squamous intercellular IgG (29).

**Conditions to consider in the differential diagnosis:**
- *pemphigus vegetans*
- *pemphigus vulgaris*
- *incontinentia pigmenti*
- drug-induced pemphigus
- PNP
Inflammatory cells in the dermis include lymphocytes and plasma cells, with or without eosinophils, neutrophils, mast cells, and histiocytes. IgA pemphigus is a prototypic example (31).

**IgA Pemphigus**

**CLINICAL SUMMARY.** This is a pruritic vesiculopustular eruption characterized by squamous intercellular IgA deposits and intraepidermal neutrophils. It occurs primarily but not exclusively in middle-aged and elderly individuals. The clinical findings are similar to those in pemphigus foliaceus or subcorneal pustular dermatosis. There are flaccid vesicles, pustules, or bullae that arise on an erythematous base and may be annular. There may be mild leukocytosis, eosinophilia, and IgA kappa paraproteinemia. Two types have been distinguished: a subcorneal pustular dermatosis-like disorder or an intraepidermal pustular eruption. Direct immunofluorescence is positive for intercellular IgA in the upper layers of the epidermis in the former, and throughout the epidermis in the latter (32).

**HISTOPATHOLOGY.** Two patterns are observed that parallel the two clinical presentations. In the first, there are subcorneal neutrophilic vesicopustules or pustules with minimal acantholysis. In the second, intraepidermal vesicopustules or pustules contain small to moderate numbers of neutrophils. One case without neutrophil infiltration has been described.

**IMMUNOFLUORESCENCE TESTING.** DIF testing typically reveals IgA deposition in the squamous intercellular substance throughout the epidermis with increased intensity in the upper layers in some cases of the subcorneal pustular type. Complement and other immunoglobulins are usually absent. The antibodies are directed against neither the pemphigus vulgaris nor the foliaceus antigen, but bind with proteins in desmosomes (desmocollins).

**Conditions to consider in the differential diagnosis:**
- acantholytic solar keratosis
- acantholytic squamous cell carcinoma
- hydroa vacciniforme (epidermal necrosis)
- IgA pemphigus

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**Fig. IVC2a.b.** *Pemphigus vegetans, medium power.* At this magnification one can identify the characteristic intraepidermal abscesses. The intraepidermal abscesses are composed in this example of neutrophils and eosinophils, associated with areas of intraspinous acantholysis.

**Fig. IVC2a.c.** *Pemphigus vegetans, high power.* Foci of suprabasal acantholysis, similar to those seen in pemphigus vulgaris, are also seen.
There is separation between the keratinocytes of the basal layer and those of the spinous layer.

1. Suprabasal Vesicles, Scant Inflammatory Cells
2. Suprabasal Separation, Lymphocytes & Plasma Cells

**Suprabasal Vesicles, Scant Inflammatory Cells**

The suprabasal separation may be associated with scant inflammation, and frequently with dyskeratotic or atypical keratinocytes. Darier's disease (keratosis follicularis) and warty dyskeratoma (isolated keratosis follicularis) are prototypic (33).

**Keratosis Follicularis (Darier's Disease)**

**CLINICAL SUMMARY.** In this disease, which is usually transmitted in an autosomal dominant pattern, there is a more or less extensive, persistent, slowly progressive eruption consisting of hyperkeratotic or crusted papules or verrucous lesions often showing a follicular distribution. A sarco/endoplasmic reticulum Ca\(^{2+}\) transport ATPase (ATP2A2) has been identified as the defective gene, emphasizing the role of extracellular Ca\(^{2+}\) in cell-to-cell adhesion and in epidermal differentiation (34). The so-called seborrheic areas are the sites of predilection. The oral mucosa is involved occasionally. The nails can be affected. Special clinical variants are a hypertrophic type, a vesiculobullous type, and a linear or zosteriform type. In the hypertrophic type, widespread, markedly thickened, hyperkeratotic lesions are seen, especially in the intertriginous areas. In the vesiculobullous type, vesicles and small bullae are seen in addition to papules. In the linear or zosteriform type, usually limited to one side, there are either localized or widespread lesions that may occasionally be present at birth or may arise in infancy, childhood, or adult life. This type of lesion may represent a linear epidermal nevus with acantholytic dyskeratosis rather than Darier's disease, and the designation acantholytic dyskeratotic epidermal nevus has been suggested.

**HISTOPATHOLOGY.** The characteristic changes in Darier's disease are: (1) a peculiar form of dyskeratosis resulting in the formation of corps ronds and grains, (2) suprabasal acantholysis leading to the formation of suprabasal clefts or lacunae, and (3) irregular upward proliferation into the lacunae of papillae lined with a single layer of basal cells, so-called villi. There are also papillomatosis, acanthosis, and hyperkeratosis. The dermis shows a chronic inflammatory infiltrate. In some cases, there is downward proliferation of epidermal cells into the dermis. The corps ronds occur in the upper stratum malpighii, particularly in the granular and horny layers; grains are found in the horny layer and as acantholytic cells within the lacunae. Corps ronds possess a central homogeneous, basophilic, pyknotic nucleus that is surrounded by a clear halo, peripheral to which there is a shell of basophilic
dyskeratotic material. The grains resemble parakeratotic cells but are somewhat larger. Their nuclei are elongated and often grain-shaped and are surrounded by homogeneous dyskeratotic basophilic or eosinophilic material. The lacunae represent small, slit-like intraepidermal vesicles most commonly located directly above the basal layer, and containing acantholytic partial keratinized cells. The changes seen in particular lesions of Grover’s disease may be indistinguishable from Darier’s disease, but usually the lesions are smaller, and if multiple lesions are available from the same patient, the pattern typically varies from lesion to lesion.

**Clin. Fig. IVD1.a**  
Darier’s disease. A 54-year-old woman with this lifelong autosomal dominant disease presented with “dirty brown” papules on the neck and trunk.

**Clin. Fig. IVD1.b**  
Darier’s disease. The nails show characteristic changes of V shaped nicking, linear striations, onycholysis and subungual keratotic reaction.

**Fig. IVD1.a**  
Darier’s disease, low power. There is mild verrucous acanthosis of the epidermis and several foci of acantholysis are seen in the lower epidermal layers.

**Fig. IVD1.b**  
Darier’s disease, medium power. The acantholysis is suprabasal and several corps ronds are seen in the upper epidermal layers associated with a focus of parakeratosis.
Warty Dyskeratoma

CLINICAL SUMMARY. Warty dyskeratoma usually occurs as a solitary lesion, most commonly on the scalp, face, or neck (35). It often occurs as a slightly elevated papule or nodule with a keratotic umbilicated center, which after having reached a certain size, persists indefinitely.

HISTOPATHOLOGY. The center of the lesion is occupied by a large, cup-shaped invagination connected with the surface by a channel filled with keratinous material. The large invagination contains numerous acantholytic, dyskeratotic cells in its upper portion. The lower portion of the invagination is occupied by numerous villi, markedly elongated dermal papillae that are often lined with only a single layer of basal cells and project upward from the base of the cup-shaped invagination. Typical corps ronds can usually be seen in the thickened granular layer lining the channel at the entrance to the invagination.

Conditions to consider in the differential diagnosis:
- transient acantholytic dermatosis (Grover)
- benign familial pemphigus (Hailey–Hailey)
- Darier’s disease (keratosis follicularis)
- acantholytic solar keratosis
- acantholytic squamous cell carcinoma

Fig. IVD1.c. Warty dyskeratoma, low power. A solitary focus of verrucous epidermal hyperplasia with an invaginated architecture is seen in the center of this biopsy. There is a sparse dermal inflammatory infiltrate.

Figs. IVD1.d,e. Warty dyskeratoma, high power. There are multiple elongate finger-like projections of epithelium which show suprabasal acantholysis. There are also dyskeratotic cells and corps ronds. The pathology may be identical to Darier’s disease. However, the solitary nature, both clinically and histologically, allows easy differentiation between these two entities.
Suprabasal separation, associated with keratinocyte atypia, may be seen with a lymphoplasmacytic infiltrate in the dermis in an acantholytic actinic (solar) keratosis (36).

**Acantholytic Actinic Keratosis**

Five types of actinic (solar) keratosis can be recognized histologically: hypertrophic, atrophic, bowenoid, acantholytic, and pigmented (see also Section IIA.1). In all types, there is random atypia of basal keratinocytes, with hyperkeratosis intermingled with areas of parakeratosis. Keratinocytes in the stratum malpighii show a loss of polarity and thus a disorderly arrangement. Some of these cells show crowding, pleomorphism, and atypicality of their nuclei, which appear large, irregular, and hyperchromatic, and some of the cells are dyskeratotic or apoptotic; acantholytic keratoses show dyshesion of lesional cells that may simulate a glandular pattern. The acantholysis is usually suprabasal but may involve the full thickness of the epidermis.

**Conditions to consider in the differential diagnosis:**

- acantholytic solar keratosis (synonym)
- acantholytic squamous cell carcinoma

There is suprabasal separation with eosinophils in the epidermis (eosinophilic spongiosis), and in the dermis. The appearance of clinical disease appears to depend on the appropriate HLA background to permit an IgG4 response to desmoglein 3, a cell surface adhesion molecule. Autoreactive T cell responses may also be important in the pathogenesis. Pemphigus vulgaris is the prototype (1,2,37).

**Pemphigus Vulgaris**

**CLINICAL SUMMARY.** This condition develops primarily in older individuals, presenting with large and flaccid bullae. These break easily and leave denuded areas that tend to increase in size by progressive peripheral detachment of the epidermis (positive Nikolsky sign), leading in some cases to widespread cutaneous involvement. The lesions characteristically involve the oral mucosa, scalp, midface, sternum, and groin. Oral lesions are almost invariably present and are often the first manifestation of the disease. Before corticosteroids became available, the mortality of this disease was high because of fluid loss and superinfection.

**HISTOPATHOLOGY.** The earliest recognized change may be either eosinophilic spongiosis, or more commonly,
spongiosis in the lower epidermis. Acantholysis leads first to the formation of clefts, and then to blisters in a predominantly suprabasal location, although intraepithelial separation may occasionally be higher in the stratum spinosum. The basal keratinocytes, although separated from one another through the loss of attachment to each other, remain firmly attached to the dermis like a “row of tombstones” lining the blister base. The blister roof consists of the remaining intact squamous epithelium. Within the blister cavity, there are acantholytic keratinocytes that have rounded, condensed cytoplasm about an enlarged nucleus with peripherally palisaded chromatin and enlarged nucleoli. These may reside singularly or in clusters. They may be recognized cytologically in a Tzanck preparation which is a smear taken from the underside of the roof and from the base of an early, freshly opened bulla. Acantholysis may extend into adnexal structures. There is little inflammation in the early phase of blister formation. If

Clin. Fig. IVD3.a

Clin. Fig. IVD3.b

Clin. Fig. IVD3.a. *Pemphigus vulgaris*. A 52-year-old woman developed mouth erosions and fragile flaccid bullae with expanding erosions and skin denudation.

Clin. Fig. IVD3.b. *Pemphigus vulgaris*. The lesions progressed over the entire body requiring Burn Unit therapy. Indirect immunofluorescence was 1:5120 on guinea pig esophagus and 1:2560 on monkey esophagus.

Fig. IVD3.a. *Pemphigus vulgaris, low power*. At scanning magnification there is formation of an intraepidermal vesicle and an associated perivascular inflammatory infiltrate.

Fig. IVD3.b. *Pemphigus vulgaris, medium power*. There is intraspinous separation which is predominantly in the suprabasal region. The stratum corneum is intact and shows a basket weave pattern.
A solitary row of basal layer keratinocytes remain attached to the floor of the blister. The roof of the blister is composed of relatively intact superficial epidermal layers. The dermal infiltrate is composed of lymphocytes and eosinophils (not numerous in this case). Eosinophilic spongiosis may also be seen.

Another example shows a characteristic single-cell “tombstone layer” of basal keratinocytes at the floor of the blister.

There is cell surface (intercellular) IgG deposition. C3 deposition is also frequently seen in pemphigus vulgaris.

Using monkey esophagus as a substrate there is prominent cell surface (intercellular) staining with IgG.

Present, it is usually a sparse, lymphocytic perivascular infiltrate accompanied by dermal edema. If, however, eosinophilic spongiosis is apparent, numerous eosinophils may infiltrate the dermis, and as the lesions age, a mixed inflammatory cell reaction consisting of neutrophils, lymphocytes, macrophages, and eosinophils may develop. Because of the instability of the blister roof, erosion and ulceration may occur. Older blisters may also have several layers of keratinocytes at the blister base because of keratinocyte migration and proliferation, and there may be considerable downward growth of epidermal strands, giving rise to so-called villi.

**IMMUNOFLUORESCENCE TESTING.** DIF testing is a very reliable and sensitive diagnostic test for pemphigus vulgaris, in that it demonstrates IgG in the squamous intercellular substance in 80% to 95% of cases, including early cases and those with very few lesions, and in up to 100% of
cases with active disease. It remains positive, often for many years after the disease has subsided. Indirect testing is less specific than the direct test. Disease activity in pemphigus vulgaris can be correlated with antibody titers. Circulating IgG antibodies in patients with pemphigus vulgaris react with desmogleins, desmosomal proteins, resulting in release of plasminogen activator and activation of plasmin. This proteolytic enzyme acts on the intercellular substance and may be the primary mechanism of dyshesion. In the mucosal variant of pemphigus vulgaris, autoantibodies exclusively react with desmoglein 3, whereas patients with the mucocutaneous subtype raise antibodies against both desmoglein 3 and 1. Highly sensitive and specific ELISA have been developed for specific antibody testing (38).

**Conditions to consider in the differential diagnosis:**
pemphigus vulgaris
pemphigus vegetans

### IV. Acantholytic, Vesicular, and Pustular Disorders

**Porphyria Cutanea Tarda and Other Porphyrias**

**CLINICAL SUMMARY.** Three forms of the dominantly inherited disorder porphyria cutanea tarda can be distinguished: sporadic, familial, and hepatoerythropoietic. In the **sporadic form**, only the hepatic activity of uroporphyrinogen decarboxylase is decreased. Almost all patients are adults, and no clinical evidence of porphyria cutanea tarda is found in other members of the patient’s family. In most instances, in addition to the inherited enzymatic defect, an acquired damaging factor to liver function such as ethanol or estrogens is needed. Hepatitis C virus positivity and hemochromatosis gene mutations are also risk factors (40). In the **familial form**, in addition to the hepatic activity, the extrahepatic activity of uroporphyrinogen decarboxylase is decreased to about 50% of normal, and often, but not always, there is a family history of overt porphyria cutanea tarda. In the very rare **hepatoerythropoietic form**, the skin lesions appear in childhood, the activity of uroporphyrinogen decarboxylase in all organs is decreased to less than 10% of normal, and family studies suggest that these patients are homozygous for the causative gene.

Clinically, the sporadic form of porphyria cutanea tarda, by far the most common type of porphyria, shows blisters that arise through a combination of sun exposure and minor trauma, mainly on the dorsa of the hands but sometimes also on the face. Scarring and milia formation may result. The skin of the face and the dorsa of the hands often are thickened and sclerotic. Hypertrichosis of the face is common. In the familial and in the hepatoerythropoietic forms, the clinical picture is similar, but the changes are more pronounced. Evidence of hepatic cirrhosis with siderosis is regularly present in the sporadic form.

In **erythropoietic porphyria**, a very rare disease which typically develops during infancy or childhood, recurrent vesiculobullous eruptions in sun-exposed areas of the skin gradually result in mutilating ulcerations and scarring. In **erythropoietic protoporphyria**, the usual reaction to light is erythema and edema followed by thickening and

### SUBEPIDERMAL VESICULAR DERMATITIS

A subepidermal blister refers to separation of the epidermis from the dermis. The roof of the blister is composed of an intact or (partially) necrotic epithelium.

1. Subepidermal Vesicles, Scant/No Inflammation
2. Subepidermal Vesicles, Lymphocytes Predominant
3. Subepidermal Vesicles, Eosinophils Prominent
4. Subepidermal Vesicles, Neutrophils Prominent
5. Subepidermal Vesicles, Mast Cells Prominent

### Subepidermal Vesicles, Scant/No Inflammation

The infiltrate in the dermis in most of these conditions is scant (few lymphocytes, eosinophils, neutrophils). Porphyria cutanea tarda and other porphyrias are prototypic (39).

**Clin. Fig. IVE1.** Porphyria cutanea tarda. A 33-year-old man presented with intact vesicles and bullae and crusted erosions without milia on dorsal hands. His history of excessive alcohol intake and hepatitis C positivity is typical for the sporadic form of the disease.

**Fig. IVE1.a.** Porphyria cutanea tarda, low power. This biopsy of acral skin shows a subepidermal blister. There is little or no inflammation within the dermis.

**Fig. IVE1.b.** Porphyria cutanea tarda, medium power. At the edge of the blister, one can see that the roof of the blister is composed of full thickness epidermis and the floor of the blister is composed of underlying dermis. Again, almost no inflammation is seen at the periphery of the blister.

**Fig. IVE1.c.** Porphyria cutanea tarda, medium power. At the floor of the blister, the dermal papilla tend to retained their architecture, constituting festooning. A PAS stain may reveal basement membrane thickening of the blood vessels within this dermal papilla.

**Fig. IVE1.d.** Porphyria cutanea tarda, direct immunofluorescence, high power. There is smudgy, positive staining with IgG of the blood vessels in the papillary dermis.
Subepidermal Vesicular Dermatitis

Acantholytic, Vesicular, and Pustular Disorders

Clin. Fig. IVE1

Fig. IVE1.a

Fig. IVE1.b

Subepidermal vesicle

Festooning

Fig. IVE1.c

Fig. IVE1.d
superficial scarring of the skin. In rare instances, vesicles are present that may resemble those seen in hydroa vacciniforme. The protoporphyrin is formed in reticulocytes in the bone marrow and is then carried in circulating erythrocytes and in the plasma. In *porphyria variegata*, different members of the same family may have either cutaneous manifestations identical to those of porphyria cutanea tarda or systemic involvement analogous to acute intermittent porphyria, or both, or the condition may remain latent.

**HISTOPATHOLOGY.** The histologic changes in the skin lesions are the same in all six types of porphyria with cutaneous lesions. Differences are based on the severity rather than on the type of porphyria. Homogeneous, eosinophilic material is regularly observed, and bullae are present in some instances. In addition, sclerosis of the collagen is present in old lesions. In mild cases, homogeneous, pale, eosinophilic deposits are limited to the immediate vicinity of the blood vessels in the papillary dermis. These deposits are PAS-positive and diastase-resistant. In severely involved areas, which are most common in erythropoietic protoporphyria, the perivascular mantles of homogeneous material are wide enough in the papillary dermis to coalesce with those of adjoining capillaries. In addition, deeper blood vessels may show homogeneous material around them, and similar homogeneous material may be found occasionally around eccrine glands. In addition, the PAS-positive epidermal–dermal basement membrane zone may be thickened. In areas of sclerosis, which occur especially in porphyria cutanea tarda, the collagen bundles are thickened.

The bullae, which are most common in porphyria cutanea tarda, arise subepidermally. Some blisters are dermolytic and arise beneath the PAS-positive basement membrane zone; others form in the lamina lucida and are situated above the PAS-positive basement membrane zone. It is quite characteristic of the bullae of porphyria cutanea tarda that the dermal papillae often extend irregularly from the floor of the bulla into the bulla cavity. This phenomenon, referred to as “festooning,” is explained by the rigidity of the upper dermis induced by the presence of eosinophilic material within and around the capillary walls in the papillae and the papillary dermis. The epidermis forming the roof of the blister often contains eosinophilic bodies that are elongate and sometimes segmented. These “caterpillar bodies” are PAS-positive and diastase-resistant. There are only a few inflammatory cells in the dermis.

**Conditions to consider in the differential diagnosis:**
- *porphyria cutanea tarda* and other *porphyrias*
- Drug-induced pseudoporphyria
- Bullous pemphigoid, cell-poor
- Erythema multiforme bullosa, multiple types
- Erythema multiforme bullosa acquisita (classic)

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GVHD, acute
- Acute radiation dermatitis
- Bullous dermatosis of diabetes
- Bullous dermatosis of uremia
- Electrical burn (polarized epidermis)
- Thermal burn (epidermal necrosis)
- Suction blister
- Vibrio vulnificus septicemia (necrotic bullae)

**Subepidermal Vesicles, Lymphocytes Predominant**

The epidermis is separated from the dermis, predominantly due to liquefaction of the basal cell layer. In PMLE and bullous dermatophytosis massive papillary dermal edema is the cause. The infiltrate in the dermis is primarily lymphocytic. *Bullous lichen planus* is an example (41).

**Bullous Lichen Planus (See also Section IIIIF1)**

In lichen planus, a dense dermal infiltrate obscures the dermal–epidermal junction with vacuolar degeneration and necrosis of the basal cells. Necrotic keratinocytes, also referred to as apoptotic, colloid, hyaline, cytoïd, or Civatte bodies, are present in most of the cases in the lower epidermis and especially in the papillary dermis. Because of this disruption of the dermal–epidermal junction, small areas of artificial separation between the epidermis and the dermis, known as Max–Josef spaces, are occasionally seen. In some instances, the separation occurs in vivo and subepidermal blisters form (*vesicular or bullous lichen planus*). These vesicles form as a result of extensive damage to the basal cells. In bullous lichen planus, the blisters are limited to areas of lichen planus, while in lichen planus pemphigoides, blisters are seen in sites independent of the lesions of lichen planus (42).

**Polymorphous (Polymorphic) Light Eruption**

**CLINICAL SUMMARY.** This is a commonly occurring, transient, intermittent, sunlight-induced eruption of non-scarring, erythematous, itchy papules, plaques, or vesicles of exposed skin, most severe in spring and summer and commonest in young women (43). Attacks develop during sunny vacations and summer weather, often persisting or recurring, sometimes with gradual reduction in severity, from spring until fall. They typically follow around 15 minutes to a few hours of sun exposure, and last for hours, days, or rarely weeks.

**HISTOPATHOLOGY.** This may vary, but usually there is variable epidermal spongiosis and dermal, perivascular, predominantly mononuclear cell infiltration with papillary dermal edema, which in older lesions may extend into the deeper dermis and may be so severe as to occasionally result in an apparent subepidermal blister. This finding is
not unique to PMLE, being also occasionally seen in acute lupus and some discoid lupus lesions, and in dermatomyositis. The cells of the infiltrate are usually T lymphocytes, but occasionally eosinophils and neutrophils are present as well.

According to Pincus et al., the differential diagnosis of a lesion that has a perivascular lymphocytic infiltrate with papillary dermal edema should include PMLE, lupus, dermatomyositis, dermatophytosis, “dermal” contact dermatitis and an arthropod reaction, and occasionally lichen sclerosus and perniosis as well. Reliable histopathologic clues favoring a diagnosis of lupus over PMLE include significant vacuolar change with necrotic keratinocytes, the presence of dermal mucin deposition, a peridnexal infiltrate and CD123+ plasmacytoid dendritic cells in clusters amidst the dermal lymphocytic infiltrates (44).

**Bullous Dermatophytosis**

See Clin. Fig. IVE2.c and Figs. IVE2.e–h.

**Lichen Sclerosus et Atrophicus (See also Section III.C3)**

See Figs. IVE2.i.j.

**Conditions to consider in the differential diagnosis:**

- *bullous lichen planus* (more often histologic than clinical)
- erythema multiforme
- fixed drug eruption
- lichen sclerosus et atrophicus
- bullous erythematous, mononuclear type
- graft versus host disease
- polymorphous light eruption (PMLE)
- *Bullous dermatophytosis*
- epidermolysis bullosa acquisita (usually neutrophils)
Clin. Fig. IVE2.b. *Polymorphous light eruption*. Pruritic papules and vesicles developed on an intermittent basis several hours after sun exposure.

Fig. IVE2.c. *Polymorphous light eruption, low power*. There is both intraepidermal spongiosis and edema of the papillary dermis. There is an associated superficial and deep inflammatory infiltrate. The papillary dermal edema is frequently more intense, a helpful feature in making a diagnosis at low power.

Fig. IVE2.d and e. *Polymorphous light eruption, medium power*. The papillary dermal edema shows early subepidermal separation. The infiltrate may be mixed but is largely composed of lymphocytes.
Clin. Fig. IVE2.c. *Bullous tinea pedis.* Note denuded bulla, two intact bullae, and thickened toenail. KOH preparation confirmed diagnosis.

**Fig. IVE2.c.** *Bullous tinea corporis, low power.* There is marked papillary dermal edema, which is sometimes reminiscent of polymorphous light eruption. In addition, there is a moderately intense perivascular peridnexal and interstitial inflammatory infiltrate.

**Figs. IVE2.f,g.** *Bullous tinea corporis, low and medium power.* In addition to the marked papillary dermal edema, the epidermis shows spongiosis and parakeratosis. The infiltrate is mixed, containing neutrophils, eosinophils and mononuclear cells.

**Fig. IVE2.h.** *Bullous tinea corporis, high power.* Slightly basophilic dermatophyte organisms are seen in the stratum corneum on this hematoxylin and eosin stained section.
IV. Acantholytic, Vesicular, and Pustular Disorders

The subepidermal blister is associated with a dermal infiltrate rich in eosinophils. Eosinophils may extend into the overlying epidermis. Bullous pemphigoid is a prototypic example (45).

**Bullous Pemphigoid**

**CLINICAL SUMMARY.** First described by Lever in 1953 (46), bullous pemphigoid primarily affects elderly patients with large tense bullae arising on an urticarial erythematous base or on non-erythematous skin. The course is chronic and benign. In contrast to pemphigus, the Nikolsky sign is negative. The lesions involve the trunk, the extremities, and the intertriginous areas, with the oral mucosa involved in about one-third of the cases. Bullous pemphigoid may start as a nonspecific eruption suggestive of urticaria or dermatitis, and can persist for weeks or months.

**HISTOPATHOLOGY.** In early lesions, papillary dermal edema in combination with a variably cell-poor or cell-rich perivascular lymphocytic and eosinophilic infiltrate is present. The cell-poor pattern is observed when blisters develop on relatively normal skin, and the cell-rich pattern, when the blisters arise on erythematous skin. In the cell-poor pattern, there is usually scant perivascular lymphocytic inflammation with a few eosinophils, some scattered throughout the dermis and others near the epidermis. In the cell-rich pattern, eosinophilic dermal abscesses may develop with numerous perivascular and interstitial eosinophils intermingled with lymphocytes and neutrophils in the papillary and deeper dermis. Eosinophilic spongiosis may occur. The blister arises at the dermo-epidermal junction, although epithelial migration and regeneration may result in an intraepidermal location in older blisters. Similar to pemphigus vegetans, a pseudoepitheliomatous hyperplasia of the epidermis, subepidermal bullae, and accumulations of eosinophils and lymphocytes may be seen.

**Fig. IVE2.i.** *Lichen sclerosus et atrophicus, low power.* The epidermis shows atrophy and has lost the rete ridge architecture. The stratum corneum is thickened and orthokeratotic. There is pallor and homogenization of the expanded papillary dermis. Beneath the homogenized papillary dermis, there is a predominantly lymphocytic infiltrate which extends into the superficial reticular dermis.

**Fig. IVE2.j.** *Lichen sclerosus et atrophicus, medium power.* Early subepidermal separation is seen.

**IVE3 Subepidermal Vesicles, Eosinophils Prominent**

**Fig. IVE3.** *Bullous pemphigoid.* An elderly man presented with multiple tense bullae on an erythematous base and erosions, distributed primarily on the medial thighs and trunk.

**Fig. IVE3.a.** *Bullous pemphigoid, low power.* At scanning magnification, there is a subepidermal blister with an associated superficial inflammatory infiltrate.

**Fig. IVE3.b.** *Bullous pemphigoid, medium power.* The blister contains inflammatory cells and there is an associated superficial dermal inflammatory infiltrate.

**Fig. IVE3.c.** *Bullous pemphigoid, high power.* At the edge of the blister, eosinophils are seen within the blister and in the papillary dermis.

**Fig. IVE3.d.** *Bullous pemphigoid, low power.* In an early lesion, areas of subepidermal separation can be seen at scanning power, and there is an inflammatory infiltrate in the dermis.

**Fig. IVE3.e.** *Bullous pemphigoid, medium power.* In these early lesions, eosinophils are seen within the papillary dermis and focally extending into the overlying epidermis. (continues)
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Fig. IVE3.a

Fig. IVE3.b

Fig. IVE3.c

Fig. IVE3.d

Fig. IVE3.e
IMMUNOFLUORESCENCE TESTING. DIF testing of perilesional skin has shown linear C3 deposition at the dermoepidermal junction in virtually all of the cases and IgG in most. IIF studies reveal circulating anti-basement membrane zone IgG antibodies in most cases, with IgA and IgM in a minority. No correlation exists between the antibody titer and the clinical severity of the disease. The IgG is located within the lamina lucida, where it binds specifically most often to the noncollagenous domain NC16A of a transmembrane protein, collagen XVII (COL17, BP180), which is a type II transmembrane protein that spans the lamina lucida and projects into the lamina densa of the epidermal basement membrane zone (47). Autoantibodies against this protein are seen not only in bullous pemphigoid, but also in pemphigoid gestationis (PG), mucous membrane pemphigoid, linear IgA disease, lichen planus pemphigoides, and pemphigoid nodularis (48). The majority of bullous pemphigoid sera contain, in addition to IgG reactivity, IgA antibodies to BP180, and often also to another antigen BP230 (38). Specimens submitted for DIF examination may also be examined by the salt-split (direct salt-split) skin technique. When this technique is used in pemphigoid, IgG is present on the roof of the blister.

**Bullous Drug Eruption**

See Figs. IVE3.i,j.

**Pemphigoid Gestationis (Herpes Gestationis)**

CLINICAL SUMMARY. Pemphigoid gestationis is a self-limiting, autoimmune subepidermal bullous dermatosis of pregnancy resulting from the production of anti-placental...
Sub-epidermal edema forming blister

**Fig. IVE3.i.** Bullous drug eruption, low power. There is marked edema of the papillary dermis forming a sub-epidermal blister. This is associated with a superficial and deep inflammatory infiltrate.

**Fig. IVE3.j.** Bullous drug eruption, medium power. The subepidermal separation is associated with a mixed inflammatory infiltrate which contains eosinophils. Eosinophilic spongiosis, however, is less common than in pemphigoid. However, immunofluorescence may still be necessary for definitive diagnosis.

Numerous eosinophils in sub-epidermal blister

**Fig. IVE3.k.** Pemphigoid gestationis, low power. There is subepidermal blister formation and a superficial predominantly perivascular infiltrate.

**Fig. IVE3.l.** Pemphigoid gestationis, medium power. The subepidermal blister shows eosinophils within the blister cavity at the dermal–epidermal interface and within the epidermal layer. Scattered dyskeratotic cells may also be present. The histology is generally indistinguishable from that of bullous pemphigoid.
antibodies that cross-react with the same proteins in skin. The main antigen of PG is collagen XVII (BP180), present in both skin and placenta, which is exposed to the maternal immune system through an abnormal expression of MHC class II molecules in the placenta (49). Lesions usually develop during the second or third trimester. Lesions typically develop around the umbilicus and the extremities and can spread to other parts of the body.

HISTOPATHOLOGY. The appearances are exactly similar to those in bullous pemphigoid.

IMMUNOFLUORESCENCE TESTING. DIF findings are similar to those in bullous pemphigoid, with deposition of C3 along the interface in 100% of cases, and of IgG in 25% to 50%. ELISA testing can be helpful in establishing the diagnosis.

Conditions to consider in the differential diagnosis:
- bullous pemphigoid
- cicatricial pemphigoid
- bullous drug eruption
- herpes gestationis
- bullous insect bite reaction
- bullous scabies
- dermatitis herpetiformis (certain old bullae)

**IV4** Subepidermal Vesicles, Neutrophils Prominent

A neutrophilic infiltrate is seen often in dermal papillae at the dermal–epidermal junction adjacent to the subepidermal blister, or in the blister. *Dermatitis herpetiformis* is a prototypic example (50,51).

**Dermatitis Herpetiformis (Duhring’s Disease)**

CLINICAL SUMMARY. This is an intensely pruritic, chronic recurrent dermatitis that has a slight male predilection. The lesions usually develop in young to middle-aged adults as symmetrically grouped papulovesicles, vesicles, or crusts on erythematous bases. Oral lesions are absent. The elbows, knees, buttocks, scapula, and scalp are commonly involved. Most patients have asymptomatic gluten-sensitive enteropathy, and the pathogenesis appears to involve the development in susceptible individuals of IgA antibodies that cross-react between antigenically similar molecules in the skin and intestine (52). There is an increased but low risk of lymphoma.

HISTOPATHOLOGY. The typical histologic features are best observed in erythematous skin adjacent to early blisters. In these zones, neutrophils accumulate at the tips of dermal papillae. With an increase in size to microabscesses,
A significant admixture of eosinophils may be noted. As the neutrophilic or mixed microabscesses form, a separation develops between the tips of the dermal papillae and the overlying epidermis, so that early blisters are multiloculated. The presence of fibrin in the papillae may give them a bluish appearance. Within 1 to 2 days, the rete ridges lose their attachment to the dermis, and the blisters then become unilocular and clinically apparent. At this time, the characteristic papillary microabscesses may be observed at the blister periphery. The dermis beneath the papillae may have a relatively intense inflammatory infiltrate of lymphocytes, neutrophils, and some eosinophils. Apoptotic keratinocytes may be noted above the papillary microabscesses.

IMMUNOFLUORESCENCE TESTING. Granular deposits of IgA are found alone or in combination with other immune reactants within the dermal papillae in both lesional and nonlesional skin in most cases. A fibrillar pattern has also been described (53). Early in the course of the disease, IgA deposits may be absent, and repeat DIF is
necessary. False-negative results may occur when blistered or inflamed skin is evaluated. Circulating IgA antibodies that react against reticulin, smooth muscle endomysium, the dietary antigen gluten, bovine serum albumin, and b-lactoglobulin may be present. Using monkey or pig gut as substrate, IIF has been used to detect antiendomysial antibodies. The immune precipitates contain epidermal transglutaminase, an enzyme closely related to tissue transglutaminase, which appears to be a source of autoantibodies in celiac disease (52). Sensitive and specific commercial ELISA systems for IgA reactivity against epidermal and tissue transglutaminase are available (38).

**Linear Immunoglobulin A Dermatosis**

**CLINICAL SUMMARY.** Two relatively definitive clinical phenotypes are based on patient age and clinical features (54). These are adult linear IgA dermatosis and childhood linear IgA dermatosis (chronic benign bullous dermatosis of childhood) (55). Other cases may be associated with drug therapy at any age. In the adult type, vesicles and bullae are present, which are less symmetrical and less pruritic than those in dermatitis herpetiformis but are distributed in similar locations. Ocular and oral lesions may be present in up to 50% of cases. It is not infrequent for adult-type linear IgA dermatosis to be associated with drug therapy. Vancomycin, lithium, diclofenac, captopril, ciprofloxacin, and somatostatin have been associated with such presentations. Histologically, the changes are identical to idiopathic linear IgA dermatosis in most cases. In some cases, there is an associated lymphoepidermal infiltrate in combination with an interface neutrophilic infiltration.

The childhood type of linear IgA dermatosis, originally known as chronic bullous dermatosis of childhood, is a unique disorder that presents in prepubertal, often pre-school children, and rarely in infancy. Vesicles or bullae develop on an erythematous or normal base, occasionally giving rise to a so-called string of pearls, a characteristic lesion in which peripheral vesicles develop on a polycyclic plaque. They involve the buttocks, lower abdomen, and genitalia, and characteristically have a perioral distribution on the face. Oral lesions may occur. The disorder usually remits by age 6 to 8.

**HISTOPATHOLOGY.** The features are similar if not identical to dermatitis herpetiformis. According to some, there is less tendency for papillary microabscess formation and greater tendency for uniform neutrophil infiltration along the entire dermoepidermal junction and rete in inflamed skin. DIF reveals linear IgA along the basement membrane zone in perilesional skin in 100% of cases. If IgG as well as IgA are present, the differential diagnosis with bullous pemphigoid may be difficult or impossible (linear IgA/IgG dermatosis). In the great majority of patients, serum IgA autoantibodies target the cell-derived soluble ectodomain of BP180, LAD-1 (38). The antibodies are deposited principally within the lamina lucida and less commonly beneath the lamina densa. The histologic and immunofluorescent features of childhood linear IgA disease are similar to those of the adult-type disease.

**Bullous Lupus Erythematosus**

**CLINICAL SUMMARY.** Vesicles and bullae may develop in patients with systemic lupus erythematosus (56). In

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**Fig. IVE4.e.** *Linear IgA disease, low power.* There is a subepidermal blister associated with a superficial inflammatory infiltrate.

**Fig. IVE4.f.** *Linear IgA disease, medium power.* At the edge of the blister, where the dermal–epidermal junction is intact, inflammatory cells are seen tagging along the basal cell layer.
IN Acantholytic, Vesicular, and Pustular Disorders

**Neutrophils at DEJ**

*Fig. IVE4.g.*  *Linear IgA disease, high power.* At high magnification, one can see that the inflammatory cells are neutrophils and they are seen not only at the tips of papillae (as is seen in dermatitis herpetiformis) but they are also quite prominent along the tips of the rete ridges, a feature which may help distinguish linear IgA disease from dermatitis herpetiformis.

*Fig. IVE4.h.*  *Linear IgA disease, direct immunofluorescence, high power.* IgA is deposited in a linear fashion at the dermal–epidermal junction. Other immune reactants may be seen less commonly and intensely than IgA.

**Subepidermal vesicle, with neutrophils at DEJ**

*Fig. IVE4.i.*  *Bullous lupus erythematosus, medium power.* There is a large subepidermal bulla containing inflammatory cells.

*Fig. IVE4.j.*  *Bullous lupus erythematosus, high power.* There is an early lesion adjacent to the larger vesicle.
contrast to dermatitis herpetiformis, they are nonpruritic and neither symmetrical nor do they have a predilection for extensor surfaces of arms, elbows, or scalp. The lesions may be photodistributed. These patients rarely have classic lesions of discoid, systemic, or subacute cutaneous lupus erythematosus when they develop blisters.

**HISTOPATHOLOGY.** Three histologic patterns have been identified in such lesions. The first is striking basal layer vacuolization with subsequent blister formation. The second is vasculitis with subepidermal blister and pustule formation. The third and the most common is a dermatitis herpetiformis-like histologic pattern. Approximately 25% of cases are said to have a small-vessel, neutrophil-rich leukocytoclastic vasculitis beneath the blister. Histologic features more routinely identified with lupus erythematosus are not present, other than the presence of dermal mucin and hyaluronic acid in the dermis. By immunofluorescence, IgG and C3 deposits are demonstrated at the epidermal basement membrane zone. The pattern may be linear or “granular band-like.” A salt-split skin preparation using patient serum reveals localization to the split floor as in EBA. Antibodies to type VII collagen may be present. Immunoelectron microscopic examination reveals electron-dense deposits of IgG at the lower edge of the basal lamina and immediately subjacent dermis in an identical location to the antibody in EBA.

**Conditions to consider in the differential diagnosis:**
- dermatitis herpetiformis
- bullous lupus erythematous, neutrophilic type
- bullous vasculitis
- linear IgA dermatosis (adult, childhood, drug-associated)
- epidermolysis bullosa acquisita (inflammatory)
- vesiculopustular eruption of hepatobiliary disease
- toxic shock syndrome

**IVE5 Subepidermal Vesicles, Mast Cells Prominent**

The epidermis is separated from the dermis. There is an infiltrate in the superficial dermis composed almost entirely of mast cells, with or without a few eosinophils. This may be associated with separation of the epidermis from the dermis. *Bullous mastocytosis* is the only example (57).

**Bullous Mastocytosis**

**CLINICAL SUMMARY.** Vesicles or bullae may be seen in all of the types of cutaneous mastocytosis (urticaria pigmentosa) except telangiectasia macularis eruptiva perstans. The maculopapular type, which is the most common type, may be seen in children or adults and consists usually of dozens or even hundreds of brown lesions that urticate on stroking (Darier’s sign); the multinodular type exhibits multiple brown nodules or plaques, and, on stroking, shows urtication and occasionally blister formation. The nodular type seen almost exclusively in infants, is characterized by a usually solitary, large cutaneous nodule, which on stroking often shows not only urtication but also large bullae. The diffuse erythrodermic type always starts in early infancy and shows generalized brownish red, soft infiltration of the skin, with urtication on stroking. Multiple blisters may form during the first 2 years of life on stroking and also spontaneously. If bullae are a predominant clinical feature, the term *bullous mastocytosis* has been applied.
The bullae that may occur in infants with multiple or solitary nodules or with the diffuse erythrodermic type arise subepidermally. Because of regeneration of the epidermis at the base of the bulla, older bullae may be located intraepidermally. The bullous cavity often contains mast cells as well as eosinophils.

**Fig. IVE5.b.** Bullous mastocytosis, medium power. The subepidermal blister is associated with a diffuse, interstitial mononuclear cell infiltrate.

**Fig. IVE5.c.** Bullous mastocytosis, high power. The infiltrate is composed almost entirely of mast cells with small uniform oval nuclei. There are scattered eosinophils.

**Fig. IVE5.d.** Bullous mastocytosis, high power. Giemsa stain metachromatically stains the granules of mast cells purple. C-Kit immunostaining is a specific and reliable marker for mast cells.

**References**

The dermis serves as a reaction site for a variety of inflammatory, infiltrative, and desmoplastic processes. These include infiltrations of a variety of cells (lymphocytes, histiocytes, eosinophils, plasma cells, melanocytes, etc.); perivascular and vascular reactions; infiltration with organisms and foreign bodies; proliferations of dermal fibers and precursors of dermal fibers as reactions to a variety of stimuli.
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In some of the diseases considered here, the infiltrates are predominantly in the upper reticular dermis (urticarial eruptions), while others are both superficial and deep (gyrate erythemas). Most of these also involve the superficial plexus. A few diseases are mainly deep (some examples of lupus erythematosus, scleroderma).

1. Perivascular Infiltrates, Lymphocytes Predominant
2. Perivascular Infiltrates, Neutrophils Predominant
3. Perivascular Infiltrates, Lymphocytes and Eosinophils
4. Perivascular Infiltrates, with Plasma Cells
5. Perivascular Infiltrates, Mixed Cell Types

**VA1 Perivascular Infiltrates, Lymphocytes Predominant**

In the dermis, there is no vasculitis, only perivascular collections of lymphocytes as the predominant cell. Erythema annulare centrifugum (EAC) is prototypic (1,2).

**Erythema Annulare Centrifugum**

**CLINICAL SUMMARY.** Also known as gyrate erythema, this disorder represents a hypersensitivity reaction manifesting as arcuate and polycyclic areas of erythema. The condition has been categorized into superficial and deep variants. The deep form is characterized clinically by annular areas of palpable erythema with central clearing and absence of surface changes. The superficial variant differs only by the presence of a characteristic trailing scale, a delicate annular rim of scale that trails behind the advancing edge of erythema. Small vesicles may occur. The lesions may attain considerable size (up to 10 cm across) over a period of several weeks, may be mildly pruritic, and have a predilection for the trunk and proximal extremities. Erythema annulare centrifugum can be considered a reactive phenomenon, and has been associated with a variety of disparate conditions including pregnancy, surgical procedures, breast cancer, lymphoma, leukemia, herpes zoster, medication reactions, as well as others. Most cases resolve spontaneously within 6 weeks; however, the condition may persist for years.

**HISTOPATHOLOGY.** In the classic deep or indurated type, a perivascular lymphocytic infiltrate characterized by a tightly cuffed “coat-sleeve–like” pattern is present in the middle and lower portions of the dermis. In the superficial variant, there is a superficial perivascular tightly cuffed lymphohistiocytic infiltrate with endothelial cell swelling and focal extravasation of erythrocytes in the papillary dermis, and focal epidermal spongiosis and parakeratosis can be seen. Erythema chronicum migrans (ECM) is an important differential, but often presents with plasma cells as well as lymphocytes and is therefore discussed also in VA4.

**Erythema Chronicum Migrans (See also VA5)**

See Clin. Fig. VA1.c and Figs. VA1.d–f.

**Tumid Lupus Erythematosus**

The dermal form of LE without surface/epithelial changes is known as tumid LE. Clinically, affected patients display...
**Clin. Fig. V A1.a.** Erythema chronicum migrans. Note the central bite area and expanding border of erythema in a confirmed case of Lyme disease.

**Clin. Fig. V A1.b.** Erythema chronicum migrans, low power. Similar to EAC, there is a tight cuff of small cells around the vessels of the superficial and deep-dermal plexuses.

**Clin. Fig. V A1.c.** Erythema chronicum migrans, low power. A tight cuff of small round cells surrounds the vessels of the superficial and mid-dermal plexuses.

**Clin. Fig. V A1.b.** Erythema chronicum migrans, medium power. The vessels at the center of the infiltrates show no evidence of damage other than slight endothelial cell swelling.

**Clin. Fig. V A1.c.** Erythema chronicum migrans, high power. The infiltrate is composed almost entirely of mature small lymphocytes.

**Fig. VA1.c.** “Cuffing” of lymphocytes around blood vessel.
Superficial and Deep Perivascular Infiltrates Without Vasculitis

Conditions to consider in the differential diagnosis:
- pityriasis lichenoides et varioliformis acuta (PLEVA)
- stasis dermatitis
- acne rosacea

indurated papules, plaques, and nodules without erythema, atrophy, or ulceration of the surface. Histologically, superficial and deep dermal perivascular, interstitial, and periappendageal lymphoplasmacytic infiltrates associated with stromal mucin deposits are observed (3).

Clin. Fig. VA1.d. *Tumid lupus.* This is a deeper and more nodular form of lupus that presents with little to no scale. Some consider it a variant of subacute cutaneous lupus.

Fig. VA1.f. *Erythema chronicum migrans, high power.* Although plasma cells are usually present, in some instances, as here, the infiltrate is composed almost entirely of mature small lymphocytes.

Clin. Fig. VA1.e. *Erythema chronicum migrans, medium power.* The infiltrate surrounds vessels quite tightly, without a significant interstitial infiltrate.

Fig. VA1.g. *“Tumid” lupus erythematosus, low power.* A dense lymphocytic infiltrate is present around the vessels of the superficial, mid and deep dermal plexuses, and around adnexal structures. (continues)
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

discoid lupus erythematosus (DLE)
polymorphous light eruption
deep gyrate erythemas
erythema annulare centrifugum
erythema chronicum migrans
Jessner’s lymphocytic infiltrate
reticulated erythematous mucinosis (REM)
perioral dermatitis
papular acrodermatitis (Gianotti–Crosti)
leprosy, indeterminant
“tumid” lupus erythematosus
perniosis (chilblains)

Conditions to consider in the differential diagnosis:
acute febrile neutrophilic dermatosis (Sweet’s)
erysipelas
necrotizing fasciitis

VA2 Perivascular Infiltrates, Neutrophils Predominant

In this pattern, neutrophils are seen in perivascular or perivascular and diffuse patterns in the dermis. Edema is prominent in some instances. Sweet’s syndrome can present as a perivascular infiltrate, but is more often nodular and is therefore discussed in section VC2. Neutrophil-rich urticaria may present as a predominantly neutrophilic infiltrate, but eosinophils are usually also present (see section VA3). The other conditions listed are mostly infections. Biopsies from the periphery of a lesion may appear perivascular, but the fully developed center of these lesions will consist of diffuse infiltrates (section VA3).

Cellulitis

See Clin. Fig. VA2 and Figs.VA2.a,b.

Clin. Fig. VA2. Cellulitis. This middle-age female was admitted with septic shock secondary to her cellulitis. She had marked erythema and bullous changes and rapidly improved on IV antibiotics.
pyoderma gangrenosum (early)
ecthyma gangrenosum
neutrophil-rich urticaria
solar urticaria
rheumatoid arthritis
neutrophilic dermatosis of the dorsal hands
other neutrophilic dermatoses
Behçet disease
Bowel bypass syndrome (Bowel-associated dermatosis–arthritis syndrome)
Erythema elevatum diutinum

**VA3 Perivascular Infiltrates, Lymphocytes and Eosinophils**

Lymphocytes and eosinophils are mixed in the infiltrate. Lymphocytes are always seen, eosinophil numbers may vary being greatest in bite reactions and often (though variable and sometimes very few) in eosinophilic fascitis. Papular urticaria is a prototypic example (4).  

**Papular Urticaria**

**CLINICAL SUMMARY.** Also known as lichen urticatus, this condition is the result of hypersensitivity to bites from certain insects, especially mosquitoes, fleas, and bedbugs. One observes edematous papules and papulovesicles, which, because of severe itching, usually are excoriated. The eruption is more common in children than adults, and, if caused by mosquitoes, is limited to the summer months.

**HISTOPATHOLOGY.** The stratum malpighii shows intercellular and intracellular edema and occasionally a spongiotic vesicle. A predominantly lymphocytic infiltrate is present around the vessels of the dermis, often extending into the lower dermis and containing a significant admixture of eosinophils.

**Urticaria**

**CLINICAL SUMMARY.** Urticaria is characterized by the presence of abrupt onset, transient and recurrent wheals, which are raised erythematous and edematous areas of skin that are often pruritic. When large wheals occur and the edema extends to the subcutaneous or submucosal tissues, the process is referred to as angioedema. Acute episodes of urticaria generally last only several hours. When episodes of urticaria last up to 24 hours and recur over a period of at least six to eight weeks, the condition is considered chronic urticaria. The various causes of urticaria include soluble antigens in foods, drugs, insect venom; contact allergens; physical stimuli such as pressure, vibration, solar radiation, cold temperature; occult infections and malignancies; and some hereditary syndromes, but in many cases the cause remains undetermined.
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Loose perivascular and diffuse infiltrates

**Fig. VA3.a**

**Fig. VA3.b**

**Fig. VA3.c**

**Fig. VA3.d**

**Clin. Fig. VA3**. Urticaria. Edematous plaques with central clearing and geographic configuration are typical of urticaria.

**Fig. VA3.d**. Urticaria, low power. A patchy perivascular infiltrate of lymphocytes and eosinophils, which could be seen in "papular urticaria" or in idiopathic urticaria.
**Fig. VA3.e.** *Urticaria, medium power.* There is sparse dermal edema separating collagen fibers. Lymphatic channels are dilated (a clue to the presence of edema).

**Fig. VA3.f.** *Urticaria, high power.* The perivascular infiltrate includes mostly eosinophils and neutrophils. This density of infiltrate is compatible with chronic urticaria.

**Fig. VA3.g.** *Pruritic & urticarial papules & plaques of pregnancy (PUPPP), low power.* There is a tight perivascular infiltrate of lymphocytes and eosinophils about the superficial and mid plexuses.

**Fig. VA3.h.** *PUPPP, medium power.* As in usual urticaria, there is dermal edema separating collagen fibers, and lymphatic channels are dilated.

**Fig. VA3.i.** *PUPPP, high power.* The perivascular and interstitial infiltrate includes lymphocytes and eosinophils, which may not be numerous as in this case.
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

**Pruritic Urticarial Papules and Plaques of Pregnancy**

**CLINICAL SUMMARY.** Pruritic urticarial papules and plaques of pregnancy (PUPPP) is a fairly common entity that has a predilection for primigravidas in the third trimester of pregnancy (5). It can also occur directly post partum. PUPPP is associated with excessive maternal weight gain and multiple pregnancies. The rash usually starts on the abdomen and is composed of intensely pruritic erythematous urticarial papules, which may be surmounted by vesicles. The proximal parts of the extremities are also affected. There is no increased incidence of the rash in subsequent pregnancies. Typically lesions begin within striae distensae, and sparing of the umbilical area is a characteristic finding (as opposed to pemphigoid gestationis). The rash usually involutes spontaneously after delivery. Fetal outcome appears to be unaffected. The skin of the newborn child is unaffected (6).

**HISTOPATHOLOGY.** Microscopic findings most commonly show a superficial and mid-dermal perivascular lymphohistiocytic infiltrate with variable numbers of eosinophils and neutrophils together with edema of the superficial dermis. Epidermal involvement is variable and consists of focal spongiosis with exocytosis, parakeratosis, and mild acanthosis.

**Conditions to consider in the differential diagnosis:**
- urticaria/angioedema
- pruritic & urticarial papules & plaques of pregnancy (PUPPP)
- prurigo simplex
- papular urticaria
- morbilliform drug eruption
- photoallergic reaction
- eosinophilic fasciitis/scleroderma
- angiolymphoid hyperplasia with eosinophilia (AHLE)
- insect bite reaction

**Secondary Syphilis**

Secondary syphilis results from the hematogenous dissemination of Treponema Pallidum, resulting in widespread clinical signs accompanied by constitutional symptoms inclusive of fever, malaise, and generalized lymphadenopathy. A generalized eruption occurs, comprising brown-red macules and papules, and, rarely, pustules. Lesions may be follicular, annular, or serpiginous. Other skin findings include alopecia and condylomata lata, the latter comprising broad, raised, gray, confluent papular lesions arising in anogenital areas, and mucous patches composed of multiple shallow, painless ulcers. Scaling macules or papules on the palms and soles are a characteristic feature, and this is also known as a “copper penny” rash.

**HISTOPATHOLOGY.** The two fundamental pathologic changes in syphilis are (1) swelling and proliferation of endothelial cells and (2) a predominantly perivascular infiltrate composed of lymphoid cells and often plasma cells. However, plasma cells and endothelial swelling are not invariably present. Frank necrotizing vasculitis is distinctly unusual. In late secondary and tertiary syphilis,

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**Clin. Fig. VA4.a.** Secondary syphilis. This HIV positive male presented with annular papules on his penis.

**Clin. Fig. VA4.b.** Secondary syphilis. Brown-red macules were present on his palms. RPR was positive.
there are also granulomatos infiltrates of epithelioid histiocytes and giant cells.

Biopsies generally reveal psoriasiform hyperplasia of the epidermis with spongiosis and basilar vacuolar alteration, exocytosis of lymphocytes, and parakeratosis. The parakeratosis may be patchy or broad, with or without intracorneal neutrophilic abscesses. Scattered necrotic keratinocytes may be observed. Ulceration is not usual except in lues maligna. The dermal changes include marked papillary dermal edema and a perivascular and/or periadnexal and often lichenoid infiltrate that may be lymphocyte predominant, lymphohistiocytic, histiocytic predominant, or frankly granulomatous and that is of greatest intensity in the papillary dermis and extends as loose perivascular aggregates into the reticular dermis. In a few cases, atypical-appearing nuclei may be present and may suggest the possibility of lymphoma. Neutrophils are not infrequent and may permeate the eccrine coil to produce a neutrophilic eccrine hidradenitis. Granulomatous inflammation develops after a few months. A silver stain is positive for spirochetes in about a third of the cases. Silver stains can be difficult to interpret because of high background. In addition, positive results do not necessarily indicate the presence of Treponema Pallidum as a silver stain is not specific for this organism. Immunohistochemistry using antibodies directed against Treponema Pallidum Antigen have been shown to be more sensitive than silver stains and reflect a new standard for adjunct histological testing. PCR analysis is another technique which is valuable for the detection of Treponema
Pallidum (8,9,10). The organisms are seen in the epidermis, follicular epithelium, and blood vessels. Lesions of condylomata lata show all of the aforementioned changes, but with more florid epithelial hyperplasia and intraepithelial microabscess formation.

**Tertiary Syphilis**

See Clin. Fig. VA4.c.

**Morphea (See also VF)**

See Figs. VA4.e–h.

**Conditions to consider in the differential diagnosis:**

- primary syphilitic chancre
- erythema chronicum migrans
- acne rosacea
- perioral dermatitis
- scleroderma/morphea
- secondary syphilis
- Kaposi’s sarcoma, early lesions

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Clin. Fig. VA4.c

**Clin. Fig. VA4.c. Tertiary syphilis.** A bartender with positive syphilis serology presented with gummatous lesions characterized by subcutaneous swellings and ulceration.

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Fig. VA4.e

**Fig. VA4.e.** Morphea, low power. Scanning magnification reveals a perieccrine infiltrate associated with sclerosis of the lower portion of the reticular dermis. The eccrine glands appear “trapped” within the sclerotic collagen. In the inflammatory stage of morphea, sclerosis, although usually detectable as here, my not be as prominent as it is in later stages of the disease.

Fig. VA4.f

**Fig. VA4.f.** Morphea, medium power. Inflammatory stage morphea may present as a perivascular dermatitis.
**VA4** Superficial and Deep Perivascular Infiltrates Without Vasculitis

Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Lymphoplasmacytic infiltrate

**VA.** Morphea, high power. The infiltrate usually includes plasma cells as well as lymphocytes, and is frequently present at the dermal-subcutaneous junction.

**Perivascular Infiltrates, Mixed Cell Types**

In addition to lymphocytes, plasma cells and eosinophils are found in the dermal infiltrate. Erythema chronicum migrans is a prototypic example (11).

**Erythema Chronicum Migrans**

**CLINICAL SUMMARY.** Erythema chronicum migrans is the distinctive cutaneous manifestation of stage I Lyme disease and represents the site of primary tick inoculation. The lesion starts as an area of scaly erythema or a distinct

**Fig. VA5.a.** Erythema chronicum migrans, low power. There is a tight cuff of small round cells about the vessels of the superficial and mid-dermal plexuses.

**Fig. VA5.b.** Erythema chronicum migrans, high power. Lymphocytes, eosinophils, and mast cells (and often plasma cells) are present in the perivascular infiltrate.

**Clin. Fig. VA5.** Erythema chronicum migrans. A 17-year-old female presented with an expanding annular erythematous patch and a central violaceous papule on the posterior calf. Her Lyme titer was positive and she responded to antibiotic treatment.
red papule within 3 to 30 days after the tick bite, before spreading centrifugally with central clearing after a few weeks, occasionally reaching a diameter of 25 cm. Average lesional duration is a few weeks but in some cases, lesions may persist for as long as 12 months. The lesions may be solitary or multiple, the latter reflecting hematogenous dissemination of the spirochete, which may be accompanied by fever, fatigue, headaches, cough, and arthralgias.

**HISTOPATHOLOGY.** An intense superficial and deep angiocentric, neurotropic, and eccrinotropic infiltrate predominated by lymphocytes with a variable admixture of plasma cells and eosinophils is the principal histopathology. Plasma cells have been identified most frequently in the peripheries of lesions of erythema chronicum migrans, whereas eosinophils are identified in the centers of the lesions. Not infrequently, these florid dermal alterations are accompanied by eczematous epithelial alterations, and interstitial infiltration of the reticular dermis with a concomitant incipient sclerosing reaction. A Warthin-Starry stain may be positive, especially if taken from the advancing border of the lesion.

**Conditions to consider in the differential diagnosis:**
- secondary syphilis
- erythema chronicum migrans
- arthropod bite reaction

**VASCULITIS AND VASCULOPATHIES**

True vasculitis is defined by eosinophilic degeneration of the vessel wall (“fibrinoid necrosis”), infiltration of the vessel wall by neutrophils, with neutrophils, nuclear dust and extravasated red cells in the vessel walls and adjacent dermis. Some of the conditions mentioned here lack these prototypic findings, and may be termed “vasculopathies” (e.g., Degos disease).

1. Vascular Damage, Scant Inflammatory Cells
2. Vasculitis, Lymphocytes Predominant
3. Vasculitis, Neutrophils Prominent
4. Vasculitis, Mixed Cell Types and/or Granulomas
5. Thrombotic and Other Microangiopathies

**Fig. VB1.a**

**Degos’ Syndrome**

**CLINICAL SUMMARY.** The clinical manifestations include crops of asymptomatic, slightly raised, yellowish red papules that gradually develop an atrophic porcelain-white center. These papules tend to affect the trunk and proximal extremities. Degos initially described a cutaneous-intestinal syndrome, in which distinct skin findings (“drops of porcelain”) were associated with recurrent attacks of abdominal pain that often ended in death from intestinal perforations. He chose the name *malignant atrophic papulosis* (MAP) to emphasize the serious clinical course of the disease. It is nowadays believed that MAP is a clinicopathologic reaction pattern that can be associated with a number of conditions that are not always lethal. Lesions similar if not identical to MAP have been noted, in particular, in connective tissue diseases such as lupus erythematosus, dermatomyositis, and progressive systemic sclerosis, in atrophic blanche, and in Creutzfeldt–Jakob disease. On dermoscopy, a telangiectatic rim can be seen at the periphery of lesions, which can help differentiate this entity from other skin disorders (13).

**HISTOPATHOLOGY.** Although the pathogenesis of Degos’ syndrome is poorly understood, a thrombotic vasculopathy is a characteristic associated finding. A typical lesion shows a wedge-shaped area of altered dermis covered by atrophic epidermis with slight hyperkeratosis. Dermal alterations may include frank necrosis, but more common are edema, extensive mucin deposition, and slight sclerosis. There may be a sparse perivascular lymphocytic infiltrate but the vessel walls are not inflamed. Typically, vascular damage is noted in the vessels at the base of the “cone of necrobiosis.” This damage may be limited to endothelial swelling, but more characteristically, intravascular fibrin thrombi may be noted, suggesting that the dermal and epidermal changes result from ischemia.

**Conditions to consider in the differential diagnosis:**
- Degos’ syndrome (malignant atrophic papulosis)
- atrophic blanche
**Fig. VB1.b.** Degos lesion, medium power. Within the wedge, there is interstitial degeneration of collagen, and interstitial mucin deposition (R. Barnhill & K. Busam).

**Fig. VB1.c.** Degos lesion, high power. At the base of the lesion, there is a thrombosed vessel with a thickened wall. This lesion occurred in a patient with dermatomyositis (R. Barnhill & K. Busam).

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**VB2  Vasculitis, Lymphocytes Predominant**

The term “lymphocytic vasculitis” is controversial, but there are some conditions in which perivascular and intramural lymphocytes may be associated with some degree of vessel wall damage, not usually including frank fibrinoid necrosis. Most of these conditions are discussed elsewhere as “perivascular lymphocytic infiltrates.” In angiocentric lymphomas, the cells infiltrating the vessel walls are neoplastic, but the process may be mistaken for an inflammatory reaction. Pernio is a prototypic inflammatory example (14).

**Pernio**

**CLINICAL SUMMARY.** Pernio or chilblain usually consists of tender or painful, raised, violaceous plaques on the fingers or toes. Occasionally it is found at a more proximal portion of an extremity in a deeper location in the skin or subcutis. Pernio is caused in susceptible individuals by prolonged exposure to cold above the freezing point, especially in damp climates. It is important to distinguish idiopathic chilblains from chilblains in lupus erythematosus or chilblains associated with autoimmune disease.

**HISTOPATHOLOGY.** In pernio, intense edema of the papillary dermis is observed. A marked perivascular mononuclear cell infiltrate is seen in the upper dermis but sparing the edematous papillary dermis. The blood vessels are said to show a diffuse “fluffy” edema of their walls. The mononuclear infiltrate of the vascular walls is consistent with a lymphocytic vasculitis. The perivascular infiltrate can extend throughout the dermis into the subcutaneous fat. When comparing histology between idiopathic pernio and chilblains associated with autoimmune disease, it has been suggested that perieccrine distribution of lymphocytes is seen more with idiopathic pernio (15).

**Pityriasis Lichenoides**

Pityriasis lichenoides is an uncommon cutaneous eruption usually classified in two forms that differ in severity. Simultaneous appearance of the two types and transitions between them often occur, suggesting that they are variants of the same disease. Both present as usually non pruritic and painful self-healing lesions occurring in crops and affecting mainly young adults and occasionally children.

The milder form, pityriasis lichenoides chronica, is characterized by recurrent crops of brown-red papules, 4 to 10 mm in size, mainly on the trunk and extremities, that are covered with a scale and generally involute within three to six weeks with postinflammatory pigmentary changes. The more severe form, pityriasis lichenoides et varioliformis acuta (PLEVA), also referred to as Mucha-Habermann disease, consists of a fairly extensive eruption,
present mainly on the trunk and proximal extremities, and characterized by erythematous papules that develop into papulonecrotic, occasionally hemorrhagic or vesiculopustular lesions that resolve within a few weeks, usually with little or no scarring. Although the individual lesions follow an acute course, the disorder is chronic, extending over several months or even years with development of new lesions and variable periods of remission.

**HISTOPATHOLOGY.** In pityriasis lichenoides chronica, there is a superficial perivascular and lichenoid infiltrate composed of lymphocytes that extend into the epidermis, where there is vacuolar alteration of the basal layer, mild spongiosis, a few necrotic keratinocytes, and confluent parakeratosis. Melanophages and small numbers of extravasated erythrocytes are commonly seen in the papillary dermis. In PLEVA, there is a perivascular and dense band

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**Clin. Fig. VB2.** Perniosis. A 62-year-old male presented tender, edematous, erythematous macules and plaques with a hint of bullous change after spending a considerable time out in the cold. Lesions improved with avoidance and protection from the cold.

**Fig. VB2.a.** Pernio, low power. There is edema of the papillary dermis, with a superficial and deep perivascular and interstitial infiltrate.

**Fig. VB2.b.** Pernio, medium power. The infiltrate tends to be localized about and within the walls of vessels of the superficial plexus. Papillary dermal edema may be mild or pronounced, as seen here.

**Fig. VB2.c.** Pernio, high power. The vessel walls are edematous and are infiltrated by lymphocytes.
like predominantly lymphocytic infiltrate in the papillary dermis that extends into the reticular dermis in a wedge-shaped pattern. The infiltrate obscures the dermal-epidermal junction with pronounced vacuolar alteration of the basal layer, marked exocytosis of lymphocytes and erythrocytes, and intercellular and intracellular edema leading to variable degree of epidermal necrosis. Ultimately, erosion or ulceration may occur. The overlying cornified layer shows parakeratosis and a scaly crust with neutrophils in the more severe cases. Variable degrees of papillary dermal edema, endothelial swelling, and extravasated erythrocytes are seen. Severe vascular damage is rarely found except in a severe febrile ulceronecrotic variant of PLEVA where lymphocytic vasculitis with leukocytoclasis may be seen.

**Cytomegalovirus Infection**

See Figs. VB2.h–j.
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Fig. VB2.h. Cytomegalovirus infection of endothelial cells, low power. A biopsy of an oral lesion in a patient with AIDS shows a perivascular and diffuse infiltrate composed mainly of lymphocytes with a few plasma cells.

Fig. VB2.i. Cytomegalovirus, medium power. Endothelial cells are markedly swollen, and some contain inclusions (intranuclear and/or cytoplasmic).

Fig. VB2.j. Cytomegalovirus, high power. A fibroblast contains a characteristic large eosinophilic intranuclear inclusion body.

Fig. VB2.k. Erythema chronicum migrans, low power. A tight perivascular cuff of lymphocytes about the superficial and mid dermal vessels.

Fig. VB2.l. Erythema chronicum migrans, high power. In this example, the lymphocytes diffusely infiltrate the vessel wall. However, there is no vessel wall necrosis (see VB3).
**Erythema Chronicum Migrans**

See Figs. VB2.k,l.

**Conditions to consider in the differential diagnosis:**

- lymphocytic vasculitis
- lupus erythematosus
- lymphomatoid papulosis
- pityriasis lichenoides et varioliformis acuta (PLEVA)
- pityriasis lichenoides chronica
- purpura pigmentosa chronica
- morbilliform viral infections
- Lyme disease
- perniosis (chilblains)
- angiocentric mycosis fungoides
- angiocentric T-cell lymphoma/lymphomatoid granulomatosis
- cytomegalovirus inclusion disease
- Behcet’s syndrome

**VB3 Vasculitis, Neutrophils Prominent**

Neutrophils are prominent in the infiltrate, with fibrinoid necrosis and nuclear dust; eosinophils and lymphocytes are also found. Polyarteritis nodosa (PAN) is prototypic (16).

**Polyarteritis Nodosa and Microscopic Polyangiitis**

**CLINICAL SUMMARY.** *Classic polyarteritis nodosa* is a systemic vasculitic disorder in which large arteries are involved and in which ischemic glomerular lesions are

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**Fig. VB3.a.** *Polyarteritis nodosa, low power.* Vessels in the deep dermis and subcutis are thick-walled, and there is a diffuse subcutaneous infiltrate.

**Fig. VB3.b.** *Polyarteritis nodosa, high power.* The involved vessel is usually in the deep dermis or subcutaneous fat.

**Fig. VB3.c.** *Polyarteritis nodosa, high power.* There are areas of eosinophilic change (“fibrinoid necrosis”), with neutrophilic infiltration, in the walls of large vessels (small muscular arteries).
common but glomerulonephritis is rare. Microscopic polyarteritis nodosa, also termed microscopic polyangiitis (MPA) refers to a systemic small-vessel vasculitis primarily affecting arterioles and capillaries that is typically associated with focal necrotizing glomerulonephritis with crescents. The majority of patients with MPA are anti-MPO (p-ANCA) -positive. Some cases of vasculitis present with an overlapping syndrome affecting both small and medium-sized arteries.

The majority of patients with MPA are male and over 50 years of age. Prodromal symptoms include fever, myalgias, arthralgias, and sore throat. The most common clinical feature is renal disease manifesting as microhemaeturia, proteinuria, or acute oliguric renal failure. Although in classic PAN, cutaneous involvement is rare, 30% to 40% of patients with MPA exhibit skin changes. With cutaneous polyarteritis nodosa, the initial signs include livido reticularis, tender subcutaneous nodules, and ulcerations. Purpura, petechiae, and necrosis can be seen. The legs are most commonly affected (17) With MPA, the most common clinical sign is palpable purpura on the legs. MPA can also present with ulcers, cutaneous necrosis, splinter hemorrhages, and vesicles (18).

**HISTOPATHOLOGY.** The characteristic lesion of classic PAN is a panarteritis involving medium-sized and small arteries. Even though in classic PAN, the arteries show the characteristic changes in many visceral sites, affected skin often shows only small-vessel disease, and arterial involvement is typically focal. The changes affecting cutaneous small vessels are usually those of a necrotizing leukocytoclastic vasculitis (LCV). If there is a clinical presentation of cutaneous nodules, panarteritis similar to visceral lesions is usually detected. In classic PAN, the lesions typically are in different stages of development (i.e., fresh and old). Early lesions show degeneration of the arterial wall with deposition of fibrinoid material, and partial to complete destruction of the external and internal elastic laminae. An infiltrate present within and around the arterial wall is composed largely of neutrophils showing evidence of leukocytoclasis, although it often contains eosinophils. At a later stage, intimal proliferation and thrombosis lead to complete occlusion of the lumen with subsequent ischemia and possibly ulceration. The infiltrate also may contain lymphocytes, histiocytes, and some plasma cells. In the healing stage, there is fibroblastic proliferation extending into the perivascular area. The small vessels of the middle and upper dermis often exhibit a nonspecific lymphocytic perivascular infiltrate.

**Neutrophilic Small-Vessel Vasculitis (Leukocytoclastic Vasculitis)**

**CLINICAL SUMMARY.** Many different disease processes can be accompanied by small-vessel vasculitides with predominantly neutrophilic infiltrates. The clinical and histologic manifestations are thus fairly nonspecific. The majority of cases are idiopathic but associated diseases to be considered range from conditions limited to the skin such as most cases of drug-induced vasculitis to systemic conditions such as infections including hepatitis C, malignancies, Henoch-Schönlein purpura, connective tissue diseases, or ANCA-associated disorders such as Churg-Strauss syndrome, microscopic polyangiitis, or Wegener's granulomatosis (19).

**HISTOPATHOLOGY.** Neutrophilic small-vessel vasculitis is a reaction pattern of small dermal vessels, almost exclusively postcapillary venules, characterized by a combination of vascular damage and an infiltrate composed largely of neutrophils. Because there is often fragmentation of nuclei (karyorrhexis or leukocytoclasis), the term leukocytoclastic vasculitis (LCV) is frequently used. Depending on its severity, this process may be subtle and limited to the superficial dermis or be pandermal and florid and associated with necrosis and ulceration. If edema is prominent, a subepidermal blister may form. If the neutrophilic infiltrate is dense and there is pustule formation, the term pustular vasculitis may be applied. In a typical case of LCV, the dermal vessels show swelling of the endothelial cells and deposits of strongly eosinophilic strands of fibrin within and around their walls. The deposits of fibrin and the marked edema together give the vessel walls a “smudgy” appearance referred to as fibrinoid degeneration. The cellular infiltrate is present predominantly around the dermal blood vessels or within the vascular walls, so that the outline of the blood vessels may appear indistinct. The infiltrate consists mainly of neutrophils and of varying numbers of eosinophils and monoclonal cells. The infiltrate also is scattered throughout the upper dermis in association with fibrin deposits between and within collagen bundles. Extravasation of erythrocytes is commonly present. The appearance of the reaction pattern depends on the stage at which the biopsy is taken. In older lesions, the number of neutrophils may be decreased and the number of mononuclear cells increased so that mononuclear cells may predominate and a designation of a lymphocytic or even granulomatous vasculitis or vascular reaction might be made.

**Erythema Elevatum Diiutinum**

See Clin. Fig. VB3.b.

**Conditions to consider in the differential diagnosis:**

- small vessel leukocytoclastic vasculitis
- neutrophilic dermatoses
- Sweet’s syndrome
- granuloma faciale
- bowel-associated dermatosis–arthrosis syndrome
- septic/embolic lesions of gonococcemia/meningococccemia
- Rocky Mountain spotted fever (Rickettsia rickettsii)
- polyarteritis nodosa
Clin. Fig. VB3.a. Leukocytoclastic vasculitis. Hemorrhagic purpuric papules and plaques on the lower leg in a middle-aged female were felt to be secondary to a nonsteroidal anti-inflammatory drug (NSAID).

Fig. VB3.d. Leukocytoclastic vasculitis (LCV), low power. Although LCV is often confined to the superficial plexus, deeper small vessels including frequently those in the mid-dermis, are often involved, as in this example.

Fig. VB3.e. Leukocytoclastic vasculitis, medium power. The neutrophil-rich infiltrate is angiocentric with a less intense interstitial component.

Fig. VB3.f,g. Leukocytoclastic vasculitis, high power. There is fibrinoid necrosis of vessel walls, with neutrophilic infiltration and leukocytoclasia around the involved vessels.
characterized by vasculitis, eosinophilic infiltration of multiple organs, and peripheral eosinophilia. There is considerable overlap of this disease process with other systemic vasculitides, and with other inflammatory disorders exhibiting eosinophils, such as eosinophilic pneumonitis. The internal organs most commonly involved are the lungs, the gastrointestinal tract, and, less commonly, the peripheral nerves and the heart. In contrast to PAN, renal failure is rare. A slightly broader definition of CSS has been proposed requiring asthma, blood hypereosinophilia, and systemic vasculitis involving two or more extrapulmonary organs.

Two types of cutaneous lesions may occur: (1) hemorrhagic lesions similar to Henoch–Schönlein purpura varying from petechiae to extensive ecchymoses, often with areas of erythema and sometimes with necrotic ulcers, and (2) cutaneous–subcutaneous nodules. The extremities are the most common sites of skin lesions, but the trunk may also be involved and some cases are generalized. ANCA tests obtained during an active phase of the disease contain p-ANCA in the majority of cases. There is also a limited form, in which the lesions are confined to the conjunctiva, the skin, and the subcutaneous tissue.

**HISTOPATHOLOGY.** The areas of cutaneous hemorrhage typically show changes of LCV. Eosinophils may be conspicuous. In some instances, the dermis shows a granulomatous reaction composed predominantly of radially arranged histiocytes and, frequently, multinucleated giant cells centered around degenerated collagen fibers. The central portions of the granulomas contain not only degenerated collagen fibers but also dense aggregates of disintegrated cells, particularly eosinophils. These granulomas have been referred to as Churg–Strauss granulomas. However, they are not always present and similar findings can also be observed in other disease processes, such as connective tissue diseases (rheumatoid arthritis and lupus erythematosus), Wegener's granulomatosis, PAN, lymphoproliferative disorders, subacute bacterial endocarditis, chronic active hepatitis, and inflammatory bowel disease. The granulomas in the subcutaneous tissue may attain considerable size through expansion and confluence, thus giving rise to the clinically apparent cutaneous–subcutaneous nodules. They are embedded in a diffuse inflammatory exudate rich in eosinophils. Similar changes have also been observed in other diseases, such as PAN.

**Papulonecrotic Tuberculid**

See Figs. VB4.c, d.

**Conditions to consider in the differential diagnosis:**
- allergic granulomatosis (Churg–Strauss)
- Wegener's granulomatosis
- giant cell arteritis (temporal arteritis)
- erythema chronicum migrans
- erythema nodosum leprosum
- some insect bite reactions
- “secondary vasculitis” at the base of ulcers of diverse etiology
- Behçet's syndrome
- palisaded and neutrophilic granulomatosis
- interstitial granulomatous dermatitis

**Fig. VB4.c.** *Papulonecrotic tuberculid, low power.* Wedge-shaped infarction of the dermis and epidermis, caused by vasculitis (S. Lucas).

**Fig. VB4.d.** *Papulonecrotic tuberculid, high power.* Necrotizing vasculitis of a dermal artery, with surrounding granulomatous inflammation (S. Lucas).
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**Fig. VB4.c.** Papulonecrotic tuberculid, low power. Wedge-shaped infarction of the dermis and epidermis, caused by vasculitis (S. Lucas).

**Fig. VB4.d.** Papulonecrotic tuberculid, high power. Necrotizing vasculitis of a dermal artery, with surrounding granulomatous inflammation (S. Lucas).
**VB5 Thrombotic and Other Microangiopathies**

The dermal vessels contain fibrin, red cells and platelet thrombi, and/or eosinophilic protein precipitates. Coagulopathies of diverse etiologies may have similar histologic features (see section IIIG). Calciphylaxis is a microangiopathy that appears to be caused by calcification of the media of small arteries, followed by fibroplasia affecting the intima and occluding the lumen (12).

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**Clin. Fig. VB5.a.** Calciphylaxis. This elderly female with end stage renal disease and elevated parathyroid hormone level developed widespread induration of the lower extremities which led to purpuric and necrotic ulcerations.

**Fig. VB5.a.** Calciphylaxis, low power. Associated with fat necrosis and hemorrhage, there is a vessel in the subcutis with a calcified and thickened wall.

**Fig. VB5.b.** Calciphylaxis, medium power. There is necrosis of fat adjacent to the abnormal vessel. Necrosis is often much more extensive than in this example, and often involves the dermis.

**Fig. VB5.c.** Calciphylaxis, high power. The calcification affects the media of this small artery. In the same vessel, the intima is thickened by delicate fibroplasia, greatly compromising the lumen. The intimal fibrosis has retracted from the stiffened calcified wall due to fixation artifact.
**Calciphylaxis**

**CLINICAL SUMMARY.** Calciphylaxis is a life-threatening condition in which there is progressive calcification of small and medium-sized vessels of the subcutis with thickening of the intima by fibrosis and subsequent vascular compromise resulting in ischemia and necrosis. It most frequently arises in the setting of hyperparathyroidism associated with chronic renal failure, and is often, but not always, associated with an elevated serum calcium/phosphate product. Clinically, the lesions present as a panniculitis or vasculitis. Bullae, ulcerations, or a livedo reticularis-like eruption can be present. Lesions usually occur over areas with high fat content such as the abdomen, thighs, calves, and buttocks. The digits, breasts, tongue, and penis can also be affected. Early lesions appear as subcutaneous nodules or violaceous plaques. Later lesions with black central necrosis are seen. A biopsy from the center of an eschar will usually show characteristic changes (22).

**HISTOPATHOLOGY.** The histologic changes in calciphylaxis include calcium deposits in the subcutis, chiefly within the walls of small and medium-sized arteries. These deposits can be associated with endovascular fibrosis, thrombosis, or global calcific obliteration. Calcification can also be identified within the soft tissues. The vascular lesions result in ischemic and/or gangrenous necrosis of the subcutaneous fat and overlying skin.

**Livedo Reticularis**

See Clin. Fig. VB5.b.

**Conditions to consider in the differential diagnosis:**
- septicemia
- disseminated intravascular coagulation
- thrombotic thrombocytopenic purpura
- purpura fulminans
- coumarin necrosis
- lupus anticoagulant
- amyloidosis
- porphyria cutanea tarda and other porphyrias
- calciphylaxis
- thrombophlebitis and superficial migratory thrombophlebitis
- Lucio reaction

**Diffuse Infiltrates of the Reticular Dermis**

Diffuse infiltrates of the reticular dermis may show some relation to vessels or to skin appendages, or may be randomly distributed in the reticular dermis.

1. Diffuse Infiltrates, Lymphocytes Predominant
2. Diffuse Infiltrates, Neutrophils Predominant
3. Diffuse Infiltrates, “Histiocytoid” Cells Predominant
4. Diffuse Infiltrates, Plasma Cells Prominent
5. Diffuse Infiltrates, Mast Cells Predominant
6. Diffuse Infiltrates, Eosinophils Predominant
7. Diffuse Infiltrates, Mixed Cell Types
8. Diffuse Infiltrates, Pigment Cells
9. Diffuse Infiltrates, Extensive Necrosis

**Diffuse Infiltrates, Lymphocytes Predominant**

Lymphocytes are seen almost to the exclusion of other cell types. Jessner’s lymphocytic infiltration is prototypic (23).

**Jessner’s Lymphocytic Infiltration of the Skin**

**CLINICAL SUMMARY.** This poorly understood entity is characterized by asymptomatic papules or well-demarcated, slightly infiltrated red plaques, which may develop central clearing. In contrast to the lesions of chronic lupus erythematosus, the surface shows no follicular plugging or atrophy. The eruption may be precipitated or aggravated by sunlight. Lesions arise most often on the face, but may also involve the neck and upper trunk. Affected patients are usually middle-aged men and women. Variable

**Clin. Fig. VB5.b.** *Livedo reticularis.* Persistent red-blue mottling of the skin in a netlike pattern is a nonspecific sign of sluggish blood flow that may occur in association with a vasculitis or a vasculopathy in several different contexts, such as infection, atrophie blanche, cholesterol emboli, and connective tissue disease. A biopsy from a white area may show a thick walled vessel with the lumen occluded by a thrombus.
numbers of lesions (one to many) often persist for several months or several years. They may disappear without sequelae, or recur at previously involved sites or elsewhere. As a historical note, this lesion was one of Lever’s “Five L’s,” which may be slightly modified as: Lymphoma and Leukemia cutis, Lymphocytoma cutis, Jessner’s Lymphocytic infiltrate, Lupus erythematosus, polymorphous Light eruption, and Lepidoptera—the latter intended to signify assault by arthropods of various kinds.

**HISTOPATHOLOGY.** The epidermis may be normal but often appears slightly flattened. In the dermis, there are
Clin. Fig. VC1.b. Leukemia cutis. An elderly male with chronic lymphocytic leukemia developed recurrent ulcerated nodules on an infiltrated violaceous plaque. Local radiation therapy was successful.

Fig. VC1.d. Leukemia cutis, low power. In this example of acute myelogenous leukemia, there is a dense diffuse infiltrate in the reticular dermis.

Fig. VC1.e. Leukemia cutis, medium power. The infiltrate shows little tendency to perivascular or periadnexal orientation. There is no epidermal involvement.

Fig. VC1.f. Leukemia cutis, high power. The lesional cells tend to dissect between collagen bundles.

Fig. VC1.g. Leukemia cutis, high power. The lesional cells have ovoid or indented nuclei and an appreciable amount of eosinophilic cytoplasm, consistent with acute myelogenous leukemia. Phenotyping should be done on blood or bone marrow if possible.
moderately dense perivascular and diffuse infiltrates composed of small, mature lymphocytes admixed with occasional histiocytes and plasma cells. The infiltrate may extend around folliculo-sebaceous units and into subcutaneous adipose tissue.

**Leukemia Cutis**

See Clin. Fig. VC1.b and Figs. d–g.

**Conditions to consider in the differential diagnosis:**
- cutaneous lymphoid hyperplasia/lymphocytoma cutis
- Jessner’s lymphocytic infiltrate
- leukemia cutis (lymphocytic lymphoma, CLL)

**VC2 Diffuse Infiltrates, Neutrophils Predominant**

Neutrophils are the main infiltrating cells although lymphocytes can be found. Sweet’s syndrome is prototypic (24). Erysipelas is another good example (25).

### Acute Febrile Neutrophilic Dermatosis (Sweet’s Syndrome)

**CLINICAL SUMMARY.** Classic Sweet’s syndrome is characterized by acute onset of fever, leukocytosis, and erythematous plaques, vesicles or pustules infiltrated by neutrophils. This condition typically occurs in middle-aged women after nonspecific infections of the respiratory or gastrointestinal tract. In addition to the classic Sweet’s syndrome, sterile lesions with neutrophilic infiltrates that improve on steroid treatment can be found in a variety of other clinical conditions. Such infiltrates can be associated with inflammatory diseases such as autoimmune disorders or with recovery from infection. They may also develop in patients with hemoproliferative disorders or solid tumors, as well as in pregnant women.

**HISTOPATHOLOGY.** There is a dense perivascular infiltrate composed largely of neutrophils, often with leukocytoclasis. In addition, there are mononuclear cells, such as lymphocytes and histiocytes, and occasional eosinophils. The inflammatory cells typically assume a bandlike

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**Clin. Fig. VC2.** Sweet’s syndrome. A middle-aged man experienced the acute onset of fever and erythematous plaques on the face (Photo by William K. Witmer).

**Fig. VC2.a.** Sweet’s syndrome, low power. There is edema of the upper dermis, and a diffuse cellular infiltrate in the reticular dermis.

**Fig. VC2.b.** Sweet’s syndrome, medium power. The infiltrate infiltrate may involve the epidermis.
Diffuse Infiltrates of the Reticular Dermis

Perivascular, diffuse, and granulomatous infiltrates of the reticular dermis typically distribute throughout the papillary dermis. The density of the infiltrate varies and may be limited in a small proportion of cases. There is usually vasoconstriction and swelling of endothelium with moderate erythrocyte extravasation. The prominent edema of the upper dermis in some instances may result in subpidermal blister formation. Extensive vascular damage is not a feature of Sweet's syndrome. The histologic appearance varies depending on the stage of the process. In later stages, lymphocytes and histiocytes may predominate. It is important to realize that the composition and distribution of the infiltrate are not specific enough to histologically rule out an infectious process.

Neutrophilic Dermatosis of the Dorsal Hands

CLINICAL SUMMARY. Neutrophilic dermatosis of the dorsal hands is a recently described entity in the family of neutrophilic dermatoses which also include Sweet's syndrome, pyoderma gangrenosum, and rheumatoid neutrophilic dermatosis (26,27). These patients present with an eruption that is limited to the dorsal aspect of the hands. The lesions begin as tender plaques and nodules with edema and pustules and a violaceous rim. The pustules may become quite large and some lesions may ulcerate. There is preferential involvement for the radial aspect of the hand. Neutrophilic dermatosis of the dorsal hands most commonly occurs in women (76%) and in adults (mean age of 62 years). There may be an accompanying fever. Unlike classic Sweet's syndrome, neutrophilic dermatosis of the dorsal hands is generally not associated with an underlying systemic disease or malignancy. However, there have been rare patients with remote history of carcinoma and one with an unclassified type of arthritis.

HISTOPATHOLOGY. Biopsies of neutrophilic dermatosis of the dorsal hands reveal a dense neutrophilic infiltrate throughout the dermis which is abscess-like. There may be dermal edema and leukocytoclasia. Some cases have shown vasculitis and fibrinoid necrosis of small vascular channels, however, in many cases, the blood vessels are unaltered (28). This histopathology can be indistinguishable from Sweet's syndrome and pyoderma gangrenosum making clinical-pathologic correlation paramount. One must always exclude the possibility of an infectious process by the use of special stains for organisms as well as tissue culture. See images on next page.

Erysipelas

CLINICAL SUMMARY. Erysipelas is an acute superficial cellulitis of the skin caused by group A streptococci. It is characterized by a well-demarcated, slightly indurated, dusky red area with an advancing, palpable border. In some patients, erysipelas has a tendency to recur periodically in the same areas. In the early antibiotic era, the incidence of erysipelas appeared to be on the decline and most cases occurred on the face. More recently, however, there appears to have been an increase in the incidence, and facial sites are now less common whereas erysipelas of the legs is predominant. Obesity has been found to be an independent risk factor for local complications of erysipelas, including hemorrhage, bullous lesions, abscesses, and necrosis (29).
**HISTOPATHOLOGY.** The dermis shows marked edema and dilatation of the lymphatics and capillaries. There is a diffuse infiltrate, composed chiefly of neutrophils, that extends throughout the dermis and occasionally into the subcutaneous fat. It is loosely arranged around dilated blood and lymph vessels. If sections are stained with the Giemsa or Gram stain, streptococci may be found in the tissue and within lymphatics. In cases of recurring erysipelas, the lymph vessels of the dermis and subcutaneous tissue show fibrotic thickening of their walls with partial or complete occlusion of the lumen. Erysipelas and cellulitis must be distinguished from Sweet’s-like eruptions and vice versa. This distinction cannot always be made on histologic grounds alone.

**Conditions to consider in the differential diagnosis:**
- acute neutrophilic dermatosis (Sweet’s syndrome)
- erythema elevatum diutinum

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**Fig. VC2.e.** *Neutrophilic dermatosis of the dorsal hands, low magnification.* There is a dense inflammatory infiltrate in the upper and mid reticular dermis.

**Fig. VC2.f.** *Neutrophilic dermatosis of the dorsal hands, medium power.* The infiltrate in the dermis is diffuse and sometimes associated with dermal hemorrhage. The overlying epidermis may show edema or ulceration.

**Fig. VC2.g.** *Neutrophilic dermatosis of the dorsal hands, high power.* The infiltrate is composed predominantly of neutrophils. In this case, leukocytoclastic vasculitis is not seen, although vasculitis has been described in some cases of this entity.

**Fig. VC2.h.** *Neutrophilic dermatosis of the dorsal hands, high power.* The neutrophilic infiltrate is frequently associated with prominent leukocytoclasia.
Diffuse Infiltrates of the Reticular Dermis

Dermal edema (white spaces)

Neutrophils

Cellulitis, low power. The dermis is edematous and there is a patchy infiltrate in the reticular dermis.

Cellulitis, medium power. The infiltrate is partly perivascular, but also diffuse.

Cellulitis, high power. Most of the cells in the infiltrate are neutrophils. There is no necrosis, and bacteria are frequently not demonstrable in the dermis.

VC3 Diffuse Infiltrates, “Histiocytoid” Cells Predominant

Histiocytes or histiocytoid cells are found in great numbers in the dermal infiltrate. Some may be foamy, others may contain organisms. The leukemic cells of myeloid leukemia may be easily mistaken for histiocytes and may have histiocytic differentiation (myelomonocytic leukemia). Lepromatous leprosy is a good example (30).

Lepromatous Leprosy

Lepromatous leprosy (LL) initially has cutaneous and mucosal lesions, with neural changes occurring later. The lesions usually are numerous and are symmetrically
arranged. There are three clinical types: macular, infiltrative-nodular, and diffuse. In the macular type, numerous ill-defined, confluent, either hypopigmented or erythematous macules are observed. They are frequently slightly infiltrated. The infiltrative-nodular type, the classical and most common variety, may develop from the macular type or arise as such. It is characterized by papules, nodules, and diffuse infiltrates that are often dull red. Involvement of the eyebrows and forehead often results in a leonine facies, with a loss of lateral eyebrows and eyelashes. The lesions themselves are not notably hypoesthetic, although, through involvement of the large peripheral nerves, disturbances of sensation and nerve paralyses develop. The nerves that are most commonly involved are the ulnar, radial, and common peroneal nerves. The diffuse type of leprosy, called Lucio leprosy, most common in Mexico and Central America, shows diffuse infiltration of the skin without nodules. This infiltration may be quite inconspicuous except for the alopecia of the eyebrows and eyelashes it produce. Acral, symmetric anesthesia is generally present. Rarely, lepromatous leprosy can present as a single lesion, rather than as multiple lesions.

**Fig. VC3.a.** *Lepromatous leprosy, low power.* There is a diffuse to nodular infiltrate, nearly obliterating the architecture of the dermis.

**Fig. VC3.b.** *Lepromatous leprosy, medium power.* The infiltrate is composed of large histiocytes as well as small lymphocytes.

**Fig. VC3.c.** *Lepromatous leprosy, medium power, Fite stain.* Even at this magnification, the presence of acid-fast organisms can be appreciated.

**Fig. VC3.d.** *Lepromatous leprosy, high power, Fite stain.* The organisms are arranged in clumps within the cytoplasm of the histiocytes.
Langerhans cell Histiocytosis. An 18-month-old boy with a persistent scalp eruption characterized by closely set brownish papules covered with scales and crust required hospital admission for chemotherapy. A similar eruption was present in the diaper area.

Fig. VC3.e. Langerhans cell Histiocytosis low power. There is a diffuse infiltrate spanning the dermis.

Fig. VC3.f,g. Langerhans cell Histiocytosis, medium power. There are many pale staining monotonous large cells as well as many eosinophils. The lesional cells are focally epidermotropic.

Fig. VC3.h. Langerhans cell Histiocytosis. The lesional cells are large with abundant pink cytoplasm and reniform nuclei. There is an admixture of inflammatory cells including occasional eosinophils.
HISTOPATHOLOGY. In the usual macular or infiltrative-nodular lesions, there is an extensive cellular infiltrate that is almost invariably separated from the flattened epidermis by a narrow grenz zone of normal collagen. The infiltrate causes destruction of the cutaneous appendages and extends into the subcutaneous fat. In florid early lesions, the macrophages have abundant eosinophilic cytoplasm and contain a mixed population of solid and fragmented bacilli. There is no macrophage activation to form epithelioid cell granulomas. Lymphocyte infiltration is not prominent, but there may be many plasma cells. In time, and with antimycobacterial chemotherapy, degenerate bacilli accumulate in the macrophages constituting the so-called lepra cells or Virchow cells which then have foamy or vacuolated cytoplasm. The Wade-Fite stain reveals that the bacilli are fragmented or granular and, especially in every chronic lesions, disposed in large basophilic clumps called globi. In lepromatous leprosy, in contrast to tuberculoid leprosy, the nerves in the skin may contain considerable numbers of leprosy bacilli, but remain well preserved for a long time and slowly become fibrotic. The histopathology of Lucio (diffuse) leprosy is similar, but with a characteristic heavy bacillation of the small blood vessels in the skin.

**Langerhans Cell Histiocytosis (Histiocytosis X)**

Langerhans cell histiocytosis (LCH) or histiocytosis X is characterized by a proliferation of dendritic or Langerhans histiocytes (31). If LCH occurs during the first year of life, it is usually characterized by significant, potentially fatal visceral involvement and classified as acute disseminated LCH (Letterer–Siwe disease). If LCH develops during early childhood, the disease is manifested predominantly by osseous lesions with less extensive visceral involvement and known as chronic multifocal LCH or Hand—Schüller–Christian disease. In older children and adults, LCH is usually of the chronic focal type, often presenting one or few bone lesions known as eosinophilic granuloma. Cutaneous lesions are very commonly encountered in Letterer–Siwe disease and occur occasionally in the two other forms. The cutaneous lesions usually consist of petechiae and papules. In some cases, there are numerous closely set, brownish papules covered with scales or crusts, involving particularly the scalp, face, and trunk. The clinical course and the prognosis of LCH are difficult to predict.

HISTOPATHOLOGY. The key to diagnosis is identifying the typical Langerhans cell in the appropriate surroundings. The cell has a distinct folded or lobulated, often kidney-shaped nucleus. Nucleoli are not prominent, and the slightly eosinophilic cytoplasm is unremarkable. A typical clinical and light microscopic picture leads to a presumptive diagnosis; confirmation by typical S-100 or peanut agglutinin staining produces a diagnosis; a definite diagnosis requires either a positive CD1a stain or electron microscopic demonstration of Birbeck granules. Although three kinds of histologic reactions have been described in LCH histiocytosis—proliferative, granulomatous, and xanthomatous—only the first two are commonly seen. In general, the proliferative reaction with its almost purely histiocytic infiltrate is typical of acute disseminated LCH and a granulomatous reaction is usually present with chronic focal or multifocal LCH, as the name *eosinophilic granuloma* suggests. Xanthomatous lesions in the skin are decidedly rare. The proliferative reaction is characterized by the presence of an extensive infiltrate of histiocytes. The infiltrate usually lies close to or involves the epidermis, resulting in ulceration and crusting. Inflammatory cells are also present, most often lymphocytes but also eosinophils. The granulomatous reaction shows extensive aggregates of histiocytes often extending deep into the dermis, with variable eosinophils, multinucleated giant cells, neutrophils, lymphoid cells, and plasma cells may be present.

**Xanthelasma**

See Clin. Fig. VC3.b and Figs. VC3.h, i.

**Conditions to consider in the differential diagnosis:**
- xanthelasma, xanthomas (usually nodular)
- atypical mycobacteria
  - *Mycobacterium avium-intracellulare* (MAI)
- deep fungus infection
  - cryptococcosis
  - histoplasmosis
- paraffinoma
- silicone granuloma
- talc & starch granuloma
- annular elastolytic giant cell granuloma (actinc granuloma)
- *lepromatous leprosy*

**Clin. Fig. VC3.b**

**Clin. Fig. VC3.b. Xanthelasma.** Most often no underlying lipid abnormalities are present when patients present with these typical yellowish plaque on the eyelids.
Diffuse Infiltrates of the Reticular Dermis

Fig. VC3.i. Xanthelasma, low power. There is a diffuse infiltrate of pale-staining cells in the dermis.

Fig. VC3.j. Xanthelasma, high power. The lesional cells are large with abundant foamy cytoplasm. There is no admixture of inflammatory cells.

Histoid leprosy
Cutaneous leishmaniasis
Rhinoscleroma (Klebsiella rhinoscleromatis)
Histiocytosis-X
Leukemia cutis (myeloid, myelomonocytic)
Anaplastic large cell lymphoma (Ki-1)
Reticulohistiocytic granuloma
Malakoplakia

Diffuse Infiltrates, Plasma Cells Prominent

Plasma cells are found in the diffuse dermal infiltrate, though they may not be the predominant cell. Secondary syphilis may be predominantly perivascular and has been discussed as such in VA4. Other examples of this condition may present as a diffuse infiltrate.

Fig. VC4.a. Secondary syphilis, low power. There is a dense diffuse and perivascular infiltrate in the superficial and deep dermis.

Fig. VC4.b. Secondary syphilis, medium power. In this example, the infiltrate is bandlike in architecture and is composed mostly of plasma cells and lymphocytes.
Secondary Syphilis

See Figs. VC4.a, b.

Conditions to consider in the differential diagnosis:
- insect bite reaction
- plasmacytoma, myeloma
- circumorificial plasmacytosis
- Zoon’s balanitis
- syphilis, secondary or tertiary
- yaws, primary or secondary
- acne keloidalis nuchae

VC5 Diffuse Infiltrates, Mast Cells Predominant

Mast cells compose almost the entire dermal infiltrate. There may be an admixture of eosinophils. Urticaria pigmentosa is the prototype. (See sections IIIA2, IVE4, VIB10).

Urticaria Pigmentosa

See Figs. VC5.a–c.

Conditions to consider in the differential diagnosis:
- urticaria pigmentosa (nodular or diffuse) mastocytoma

Fig. VC5.a

Spindled mast cells and eosinophils

Fig. VC5.b

Metachromatic granules (different color)

Fig. VC5.c

Fig. VC5.a. Urticaria pigmentosa, medium power. There is a diffuse cellular infiltrate in the papillary and upper reticular dermis.

Fig. VC5.b. Urticaria pigmentosa, high power. The lesion cells have amphophilic cytoplasm with cytoplasmic granules, and a slightly eccentrically placed oval to round nucleus.

Fig. VC5.c. Urticaria pigmentosa, high power. The granules stain in a metachromatic (different color) manner with Giemsa (or toluidine blue). Staining for c-kit will also provide presumptive identification as mast cells.
Diffuse Infiltrates, Eosinophils Predominant

Eosinophils are prominent although not the only infiltrating cell. Lymphocytes are also found, and plasma cells may also be present. Eosinophilic cellulitis is a good example (32).

Eosinophilic Cellulitis (Wells’ Syndrome)

Clinical Summary. This rare dermatosis presents as a sudden eruption of a variable number of bright erythematos patches, which over a period of a few days expand into indurated erythematous plaques that may be painful. The overlying epidermis may produce vesicles or small blisters. The disease, if untreated, may persist for a few weeks or months and may be recurrent. Associated or provoking stimuli may include insect bites and cutaneous parasitosis, cutaneous viral infections and drug reactions, leukemic and myeloproliferative disorders, and atopic dermatitis and fungal infections. The patients are usually adults. Peripheral blood eosinophilia is usually present. The clinical appearance may mimic bacterial cellulitis (33).
Clin. Fig. VC6.b. *Insect bite.* A punch biopsy was required to remove the engorged tick embedded in an edematous erythematous papule on the lower back.

Fig. VC6.e. *Tick bite, low power.* A tick is seen above a re-epithelializing wound.

Fig. VC6.f. *Tick bite, medium power.* There is a diffuse mixed cellular infiltrate with eosinophils in the dermis.

Fig. VC6.g. *Tick bite, high power.* The infiltrate includes many eosinophils as well as lymphocytes and plasma cells.
HISTOPATHOLOGY. Early lesions demonstrate diffuse but dense dermal infiltrates of eosinophils; eosinophil degranulation is prominent. Infiltrates generally extend throughout the dermis and may involve the subcutaneous tissue or occasionally the underlying muscle. Where the epidermis is substantially involved, multilocular spongiform intraepidermal vesicles develop, but blistering is usually of subepidermal type. Eosinophils are found in the epidermis. Older lesions show more extensive eosinophil degranulation; the granular material aggregates focally around collagen fibers, forming the characteristic “flame figures.” These foci may develop a palisade of macrophages and sometimes giant cells. In florid lesions, necrobiosis may develop within the palisading histiocytic reaction.

Tick Bite

See Clin. Fig. VC6.b and Figs. VC6.e–g.

Conditions to consider in the differential diagnosis:
- eosinophilic cellulitis (Wells syndrome)
- insect bite reaction
- granuloma faciale

VC7 Diffuse Infiltrates, Mixed Cell Types

The diffuse infiltrate contains plasma cells, lymphocytes, histiocytes, and a variety of acute inflammatory cells. Leishmaniasis is a good example (34).

Cutaneous Leishmaniasis

CLINICAL SUMMARY. Leishmaniasis is transmitted by a number of different strains of the protozoan parasite Leishmania. Cutaneous leishmaniasis (CL) occurs initially as single or multiple erythematous papules on exposed areas of the body, weeks to months after the bite of an infected sandfly. The papules may enlarge to form indurated nodules, which frequently ulcerate to form a central crater. Cutaneous leishmaniasis can be placed along a clinical and immunopathologic spectrum in which the clinical features depend on the response of the host to the parasite. At one pole of the spectrum is the localized form (LCL), characterized by the occurrence of one or a few lesions with very few parasites and a well-developed immunologic response. These cases generally...
respond very well to treatment. At the other pole is the diffuse form (DCL), characterized by multiple lesions, large numbers of parasites, absence of immunologic response, and a poor response to treatment. More than 90% of cutaneous leishmaniasis cases can be placed in the localized end of the spectrum. There are intermediate forms called mucocutaneous, verrucous, or relapse cutaneous leishmaniasis which taken together account for about 8% of CL in the Americas. Diffuse cases are extremely rare. They are characterized by plaque-like or nodular lesions that can be localized in a single area of the body in the early stages and then extend until they cover most of the skin and start to slowly compromise nasal, buccal, and laryngeal mucous tissue. Clinically, these lesions can be confused with lepromatous leprosy or with cutaneous lymphomas.

**HISTOPATHOLOGY.** Early lesions of LCL are characterized by a macrophagic infiltrate with a slight tendency to epithelioid differentiation (related to time of evolution), with associated infiltration by lymphoid cells. In this stage, there are variably abundant parasites inside macrophages, facilitating diagnosis both through direct lesional touch smears and in biopsy sections. In the intermediate or late stages, most lesions are ulcerated. In the few lesions that are not ulcerated, the morphology is characterized by a tuberculoid-type granuloma with prominent lymphoid infiltration. When the lesions are ulcerated, they show a subacute or chronic mixed-cell reaction provoked by secondary infection. The latter may present with macrophagic infiltrates, formation of small abscesses, necrotic areas, plasma-cell infiltrates, and proliferation of small vessels. In this stage, parasites in lesions become

**Clin. Fig. VC7.b.** American cutaneous leishmaniasis. Lesion of localized cutaneous leishmaniasis presenting as an indurated nodule with an ulcerated crateriform center. (J. Convit).

**Fig. VC7.a.** Localized cutaneous leishmaniasis, low power. A diffuse infiltrate extends into the subcutis. The epidermis is ulcerated.

**Fig. VC7.b.** Localized cutaneous leishmaniasis, high power. The infiltrate is mixed, with many plasma cells and neutrophils but with histiocytes predominating. In this stage, many organisms are seen within the histiocytes.
increasingly difficult to find. The histopathology of acute lesions is usually characterized by epithelial loss, but in chronic lesions there can be a variable degree of epithelial hypertrophy.

The microscopic morphology of diffuse cutaneous leishmaniasis is a macrophagic infiltrate with sparse lymphocytes and with enormous numbers of parasites inside macrophages.

**Conditions to consider in the differential diagnosis:**

- B-Cell Cutaneous Lymphoid Hyperplasia
  - pseudolymphoma
  - lymphocytoma cutis
- syphilis, primary, secondary, or tertiary
- acrodermatitis chronica atrophicans
- cutaneous reactions to cytokines
- chronic actinic dermatitis (actinic reticuloid)
- rhinosporidiosis
- rhinoscleroma
- histoplasmosis
- dermal hematoPoiesis (extramedullary hematoPoiesis)
- cutaneous leishmaniasis
- granuloma inguinale
- granuloma gluteale infantum

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**VC8**  
**Diffuse Infiltrates, Pigment Cells**

The diffuse infiltrate contains bipolar, cuboidal, or dendritic cells with brown cytoplasmic pigment. Nevus of Ota is a well-known example (35).

**Nevus of Ota and Ito and Dermal Melanocyte Hamartoma**

**CLINICAL SUMMARY.** The nevus of Ota presents as a usually unilateral discolouration of the face composed of blue and brown, partially confluent macular lesions. The periorbital region, temple, forehead, malar area, and nose are usually involved, giving rise to the term nevus fusco-caeruleus ophthalmomaxillaris. There is frequently also a patchy blue discoloration of the sclera of the ipsilateral eye and occasionally also of the conjunctiva, cornea, and retina. In some instances, the oral and nasal mucosae are similarly affected. In a few cases, the lesions of the nevus of Ota are bilateral rather than unilateral. The involved areas of the skin show even a brown to slate-blue or mottled discoloration, usually without any infiltration. Occasionally, some areas are slightly raised, and sometimes discrete nodules of highly variable size up to a few centimeters and having the appearance of blue nevi are found within the

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*Clin. Fig. VC8*

*Nevus of Ota.* Mottled and even colored slate-blue discoloration with scleral involvement in the typical location of the periorbital area.

*Fig. VC8.a.* *Nevus of Ota, low power.* The melanocytic infiltrate is easily missed at scanning magnification. There is no melanocytic proliferation in the epidermis. Small areas of brown pigment are seen within the upper epidermis. (continues)
lesion. The nevus of Ito has a similar clinical appearance but differs by its location in the supravacicular, scapular, and deltoid regions. It may occur alone or in association with an ipsilateral or bilateral nevus of Ota. In the dermal melanocyte hamartoma, a single, very extensive area of gray-blue pigmentation may be present from the time of birth. The involvement may be nearly generalized, or there may be several coalescing blue macules that gradually extend within a circumscribed area from childhood.

**Histopathology.** The noninfiltrated areas of the nevus of Ota, as well as the nevus of Ito and the dermal melanocyte hamartoma, contain elongated, dendritic melanocytes scattered among the collagen bundles. Although most of the fusiform melanocytes lie in the upper third of the reticular dermis, they may also occur in the papillary layer, and may extend as far down as the subcutaneous tissue. Melanophages are uncommon. Slightly raised and infiltrated areas show a larger number of elongated, dendritic melanocytes than do noninfiltrated areas, thus approaching the histologic picture of a blue nevus, and nodular areas are indistinguishable histologically from a blue nevus. Malignant changes in lesions of nevus of Ota have been reported in a handful of cases. Malignant changes in lesions of nevus of Ito have been reported in a handful of cases. Rarely, a primary melanoma of the choroid, iris, orbit, or brain has developed in patients with a nevus of Ota involving an eye.

**Conditions to consider in the differential diagnosis:**
- Mongolian spot
- Nevus of Ota
- Nevus of Ito
- Dermal melanocytic hamartoma

**VC9 Diffuse Infiltrates, Extensive Necrosis**

Vascular and dermal necrosis are found secondary to vascular occlusion, or to destruction by organisms. Gangrenous ischemic necrosis is a good example (36).

**Gangrenous Ischemic Necrosis**

**Clinical Summary.** Gangrenous necrosis is usually seen in the distal extremity as a consequence of peripheral vascular disease, most often related to atherosclerosis. The onset is usually in old age. Diabetics are at especial risk, and tend to present at a younger age, with severe disease, which is more likely to be complicated by infection. In chronic ischemia, there may be evidence of atrophy, with thin, shiny skin and loss of skin appendages, or there may be hypertrophic changes with hyperkeratosis and thickening of the nails. The latter changes are especially likely
Clin. Fig. VC9. Gangrene. Severe peripheral vascular disease in a patient with a longstanding history of insulin dependent diabetes mellitus led to cold feet with dusky and black patches of necrosis.

Fig. VC9.a. Gangrene, low power. Full thickness coagulation necrosis of skin with loss of nuclear and fine cytologic detail is evident even at scanning magnification. The dermal vessels are acutely congested.

when there is associated venous stasis. When an extremity or a digit becomes necrotic, there may be initial pallor or duskyness, depending on the degree of occlusion and/or stasis. Ultimately, the affected portion will become black. If an ulcer develops, it is likely to be come infected, often with the development of osteomyelitis of the underlying digit.

HISTOPATHOLOGY. There may be evidence of chronic ischemia in the form of atrophy of skin, appendages, and muscle fibers. The early changes of acute ischemia, which may be seen at the edges of areas of infarction, include basal vacuolar change, coagulation necrosis of surface keratinocytes beginning superficially, and necrosis of appendages especially the metabolically active sweat glands. In established infarcts, the architecture may be evident as a ghostly outline, with loss of cell nuclei, but with some preservation of cell shape and connective tissue matrix. At the edge of the infarct, there is an inflammatory zone of neutrophils, with leukocytoclasia in the ischemic area itself. There may be occlusive thrombi in small and sometimes large vessels. In general, changes of severe atherosclerosis are confined to proximal vessels, which are not present in amputation specimens from the distal extremity.

Conditions to consider in the differential diagnosis:
- tertiary syphilis
- sporotrichosis
- deep fungus
- atypical mycobacteria
- infarcts
- vasculitis and deep vasculitis

Ill-defined nodules or diffuse infiltrates of inflammatory cells, usually including lymphocytes, plasma cells and neutrophils, are present in the dermis, and the epidermis is irregularly thickened.

VD DIFFUSE OR NODULAR INFILTRATES OF THE RETICULAR DERMIS WITH EPIDERMAL PROLIFERATION

VD Epidermal Proliferation With Mixed Cellular Infiltrates

There is a dermal inflammatory infiltrate composed of a variable mixture of lymphocytes, plasma cells, eosinophils, neutrophils, and histiocytes. There may be central necrosis forming an abscess, and there may be ill-defined or well-defined granulomas. The overlying epidermis is irregularly hyperplastic, with tongues of epithelium penetrating into the dermis. The epithelium in general shows evidence of good maturation from a well-defined basal layer to a thickened stratum corneum. Eruptions that may be associated with ingestion of halogens are a good example (37), as are the deep fungal infections such as blastomycosis (38).
North American Blastomycosis

**Clinical Summary.** North American blastomycosis, caused by *Blastomyces dermatitidis*, occurs in three forms: primary cutaneous inoculation blastomycosis, pulmonary blastomycosis, and systemic blastomycosis. Primary cutaneous inoculation blastomycosis is very rare and occurs almost exclusively as a laboratory or autopsy room infection. It starts at the site of injury on a hand or wrist as an indurated, ulcerated, chancreiform solitary lesion. Lymphangitis and lymphadenitis may develop in the affected arm. Small nodules may be present along the involved lymph vessel. Spontaneous healing takes place within a few weeks or months.

Pulmonary blastomycosis, the usual route of acquisition of the infection, may be asymptomatic or may produce mild to moderately severe, acute pulmonary signs, such as fever, chest pain, cough, and hemoptysis. The pulmonary lesions either resolve or progress to chronic pulmonary blastomycosis with cavity formation.

In systemic blastomycosis, the lungs are the primary site of infection. Granulomatous and suppurative lesions may occur in many different organs, but, aside from the lungs, they are most commonly found in the skin, followed...
by the bones, the male genital system, the oral and nasal mucosa, and the central nervous system. Cutaneous lesions are very common in systemic blastomycosis, occurring in about 70% of the patients. They may be solitary or numerous. They occur in two types, either as verrucous lesions, the more common type, or as ulcerative lesions. Verrucous lesions show central healing with scarring and a slowly advancing, raised, verrucous border that is beset by a large number of pustules or small, crusted abscesses. These lesions can clinically resemble basal cell carcinoma, squamous cell carcinoma, and keratoacanthoma. Ulcerative lesions begin as pustules and rapidly develop into ulcers with a granulating base. In addition, subcutaneous abscesses may occur; they usually develop as an extension of bone lesions.

**Histopathology.** In primary cutaneous inoculation blastomycosis, the primary lesion shows at first a nonspecific inflammatory infiltrate without epithelioid or giant cells. Numerous organisms, many in a budding state, are present. After a few weeks, occasional giant cells may be seen, and later on, the primary lesion may show the verrucous histologic pattern usually seen in skin lesions of systemic blastomycosis. In the verrucous lesions of systemic blastomycosis, in a biopsy taken from the active border, there is considerable downward proliferation of the epidermis, often amounting to pseudoeipitheliomatous hyperplasia. This can resemble a squamous cell carcinoma. Intraepidermal abscesses are often present. Occasionally, multinucleated giant cells are completely enclosed by the proliferating epidermis. There is a polymorphous dermal infiltrate dominated by neutrophils which often form small abscesses. Multinucleated giant cells are scattered throughout the dermis, with only occasional ill-formed granulomas. The spores of *B. dermatitidis* are found in histologic sections often only after a diligent search, usually in clusters of neutrophils or within giant cells. The spores have a thick wall, which gives them a double-contoured appearance. They measure 8 to 15 μm in diameter (average, 10 μm). In immunocompromised hosts, many organisms can be seen in tissue sections with minimal inflammation. Classically, multinucleate yeast forms with broad-based buds are seen.

**Deep Fungal Infections-General**

**Histopathology.** Histologic reactions in deep cutaneous fungal infections, including primary cutaneous aspergillosis, chromomycoses, phaeohyphomycosis, phaeomycetoma, rhinosporidiosis, and lobomycosis, typically consist of a mixed dermal infiltrate that is often associated with pseudoeipitheliomatous hyperplasia and occasionally with dermal fibrosis. Incidental cutaneous infections by fungi that usually primarily involve other organs, such as blastomycosis or coccidioidomycosis, typically show a pattern similar to that seen with the deep primary cutaneous fungi: a mixed dermal infiltrate with multinucleated giant cells associated with pseudoeipitheliomatous hyperplasia (39). A similar reaction pattern of pseudoeipitheliomatous hyperplasia is seen in eruptions associated with halogen ingestion—bromoderma, fluoroderma, iododerma. A few organisms, such as *Histoplasma* and *Loboa loboi* are more likely to be associated with epidermal thinning than with hyperplasia, and other systemic fungal infections, such as disseminated candidiasis with its microabscess formation, cryptococcosis with its gelatinous and granulomatous reaction patterns, or zygomycosis and aspergillosis with their tendency for vascular invasion and infarction, show special tissue reaction patterns.

**Conditions to consider in the differential diagnosis:**

- squamous cell carcinoma
- pseudoeipitheliomatous hyperplasia
- halogenodermas
- **deep fungal infections**
  - North American blastomycosis
  - paracoccidioidomycosis
  - chromoblastomycosis
  - coccidioidomycosis
  - rhinosporidiosis
  - protothecosis
  - verrucous cutaneous leishmaniasis
  - North American blastomycosis
  - verrucous lupus vulgaris
  - tuberculosis verrucosa cutis
  - Mycobacterium marinum
  - granuloma inguinale (Calymmatobacterium granulomatis)
  - pyoderma vegetans
  - verruciform xanthoma
  - verrucose sarcoidosis
  - granuloma gluteale infantum
  - verrucous lupus erythematosus

**Nodular Inflammatory Infiltrates of the Reticular Dermis—Granulomas, Abscesses, & Ulcers**

A granuloma may be defined as a localized collection of histiocytes, which may have abundant cytoplasm and confluent borders (“epithelioid histiocytes”), often with Langhans type giant cells. Granulomas may be associated with necrosis or may palisade around the areas of necrobiosis, may be mixed with other inflammatory cells, may include foreign-body giant cells, and may contain ingested foreign material or pathogens (acid-fast bacilli, fungi). An abscess is a localized area of suppurative necrosis, containing abundant neutrophils mixed with necrotic debris,
and usually surrounded by a reaction of granulation tissue and fibrosis.

1. Epithelioid Cell Granulomas without Necrosis
2. Epithelioid Cell Granulomas with Necrosis
3. Palisading Granulomas
4. Mixed Cell Granulomas
5. Inflammatory Nodules with Prominent Eosinophils
6. Inflammatory Nodules with Mixed Cell Type
7. Inflammatory Nodules with Necrosis and Neutrophils (Abscesses)
8. Inflammatory Nodules with Prominent Necrosis
9. Chronic Ulcers & Sinuses Involving the Reticular Dermis

**VE1 Epithelioid Cell Granulomas Without Necrosis**

Large epithelioid histiocytes are common in the infiltrate as well as giant cells. The infiltrate may also contain a few plasma cells as well as lymphocytes. Sarcoidosis is prototypic (40).

**Sarcoidosis**

**CLINICAL SUMMARY.** Sarcoidosis is a systemic granulomatous disease of undetermined etiology. A distinction is made between the rare subacute, transient type of sarcoidosis and the usual chronic, persistent type. In subacute, transient sarcoidosis, which subsides in almost all patients within a few months without sequelae, cutaneous manifestations other than erythema nodosum do not occur.

In chronic, persistent sarcoidosis, cutaneous lesions are quite common and may be the only manifestation. The most common type of cutaneous lesion consists of brown-red or purple papules and plaques. Through central clearing, annular or circinate lesions may result. When the papules or plaques are situated on the nose, cheeks, and ears, the term *lupus pernio* is applied. Rare manifestations of sarcoidosis include the lichenoid form, in which small, papular lesions are found, as well as the very rare erythodermic, ichthyosiform, atrophic, ulcerating, verrucous, angiolupoid, hypopigmented, and alopecic forms. Subcutaneous nodules of sarcoidosis are infrequent.

**HISTOPATHOLOGY.** Like lesions in other organs, the cutaneous lesions of chronic, persistent sarcoidosis are characterized by the presence of circumscribed granulomas of epithelioid cells, so-called epithelioid cell tubercles showing little or no necrosis. Occasionally, a slight degree of necrosis showing eosinophilic staining is found in the center of some of the granulomas. Classically, sarcoid has been associated with only a sparse lymphocytic infiltrate, particularly at the margins of the epithelioid cell granulomas. Because of this sparse infiltrate of lymphocytes, the

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**Clin. Fig. VE1.a**

*Clin. Fig. VE1.a. Sarcoidosis. A 39-year-old male with pulmonary sarcoidosis developed several fleshy subcutaneous nodules on his palmar digits. The lesions resolved with intralesional steroids.*

**Fig. VE1.a.** *Sarcoidosis, low power. A multi-nodular infiltrate diffusely involves the superficial and deep reticular dermis.*
VE. Nodular Inflammatory Infiltrates of the Reticular Dermis—Granulomas, Abscesses, & Ulcers

Well defined granulomas

Fig. VE1.b

Sparse lymphocytes

Fig. VE1.c

Asteroid body

Fig. VE1.d

Granulomas, giant cells and lymphocytes

Fig. VE1.e

Granuloma with many lymphocytes

Fig. VE1.f

**Fig. VE1.b.** Sarcoidosis, medium power. The nodules are granulomas composed of epithelioid histiocytes, with relatively sparse surrounding lymphocytes.

**Fig. VE1.c.** Sarcoidosis, medium power. The granulomas contain epithelioid histiocytes, occasional giant cells, and they are generally noncaseating.

**Fig. VE1.d.** Sarcoidosis, high power. A giant cell contains a prominent asteroid body. Although characteristic, these are not diagnostic of sarcoidosis.

**Fig. VE1.e.** Lupus vulgaris, low power. Near-confluent non-necrotizing granulomas in the dermis. The lymphocytic infiltrate is more intense than in sarcoidosis. (S. Lucas).

**Fig. VE1.f.** Lupus vulgaris, high power. Same lesion as VE1.e, showing an epithelioid cell granuloma, and interstitial lymphocytes (S. Lucas).
granulomas have been referred to as “naked” tubercles. However, lymphocytic infiltrates in sarcoid may occasionally be dense, as in tuberculosis.

In typical lesions of sarcoidosis of the skin, the well-demarcated islands of epithelioid cells contain only few, if any, giant cells, usually of the Langhans' type (with their nuclei arranged at the periphery of the cytoplasm). A moderate number of giant cells can be found in old lesions. These may contain asteroid bodies or Schaumann bodies, which are star-shaped eosinophilic structures or round/oval, laminated, partly calcified blue structures respectively. Neither of the two bodies is specific for sarcoidosis.

The papules, plaques, and lupus pernio-type lesions show variously sized aggregates of epithelioid cells scattered irregularly through the dermis with occasional extension into the subcutaneous tissue. In the erythrodernmic form, the infiltrate shows rather small granulomas of epithelioid cells in the upper dermis intermingled with numerous lymphocytes and rare giant cells. Typical epithelioid cell tubercles are found in the ichthyosiform lesions. Verrucous sarcoid shows prominent acanthosis and hyperkeratosis. Subcutaneous sarcoidosis (also known as Darier-Roussy sarcoidosis) is a form of sarcoidosis where the granulomatous infiltrates are limited to the subcutaneous adipose tissue (41,42).

In the common form of tuberculosis of the skin, lupus vulgaris, epidermal involvement is often a feature, and there is often a more prominent lymphocytic infiltrate between the granulomas.

Lupus Vulgaris

The granulomas of lupus vulgaris, which is a form of cutaneous tuberculosis due to hematogenous spread, are usually non-necrotizing (see also Section VE2).

Conditions to consider in the differential diagnosis:
- sarcoidosis (lupus pernio and other types)
- granulomatous granuloma annulare
- foreign body granulomas
- syphilis, secondary or tertiary
- granulomatous rosacea
- cheilitis granulomatosa (Miescher-Melkersson-Rosenthal)
- tuberculoid leprosy
- tuberculosis
  - lupus vulgaris
  - lichen scrofulosorum
- Crohn's disease
- allergic granulomatous reactions to chemical agents
  - silica, zirconium, aluminum, beryllium (may have necrosis)
- collagen implant granuloma
- granulomatous mycosis fungoides
- chronic cutaneous leishmaniasis

### Epithelioid Cell Granulomas With Necrosis

The presence of necrosis in an epithelioid cell granuloma of the skin strongly suggests cutaneous tuberculosis except in lesions of the face. Further, some cutaneous tuberculous eruptions do not contain prominent necrosis. However, tuberculosis is prototypic of necrotizing granulomas (43).

**Tuberculosis**

**CLINICAL SUMMARY.** Infection of the skin and subcutis by *Mycobacterium tuberculosis* occurs by three routes: (1) by direct inoculation into the skin (causing a primary chancre, or tuberculosis verrucosa cutis, or tuberculosis cutis orificialis lesions); (2) by hematogenous spread from an internal lesion (causing lupus vulgaris, miliary tuberculosis, and tuberculous gumma lesions); and (3) from an underlying tuberculuous lymph node by direct extension (causing scrofuloderma). In clinical practice, many cases do not readily fit into these clinical and histologic categories. The necrotic granuloma is typical of tuberculosis and other mycobacterial infections, but it is not specific.

**HISTOPATHOLOGY.** In *lupus vulgaris*, tuberculous granulomas composed of epithelioid cells and giant cells are present. Caseation necrosis within the tubercles is slight or may be absent. The giant cells usually are of the Langhans' type, with peripheral arrangement of the nuclei, but some can be of the foreign-body type. There is an associated infiltrate of lymphocytes, which are sometimes more prominent than the granulomatous component. There is destruction of the cutaneous appendages. In areas of healing, extensive fibrosis may be present. Tubercle bacilli may be difficult to demonstrate. In *miliary tuberculosis*, the center of the papular lesions is necrotic constituting a microabscess containing neutrophils, cellular debris, and numerous tubercle bacilli, surrounded by a zone of macrophages with occasional giant cells. In *scrofuloderma*, the center of the lesion usually exhibits nonspecific acute inflammatory changes, but in the deeper portions and at the periphery of the lesion, there are tuberculoid granulomas with considerable necrosis and inflammation. *Tuberculosis verrucosa cutis* represents inoculation infection in an individual with prior immunity. There is epithelial hyperkeratosis and acanthosis, and in the dermis, there are epithelioid cell granulomas with necrosis. The lesions of *tuberculosis cutis orificialis* are shallow ulcers with a granulating base occurring near mucosal orifices due to the spread by direct contamination from an internal lesion that is excreting bacilli. In most instances, tuberculoid granulomas with pronounced necrosis are found deep in the dermis. Tubercle bacilli are usually readily demonstrated in the sections, even when the histologic appearance is nonspecific. In a *tuberculous gumma*, most of the lesion is caseation necrosis with a rim of epithelioid cells and giant cells. Acid-fast bacilli are scant.
**Fig. VE2.a.** *Inoculation tuberculosis, low power.* A prosector’s wart from inoculation of a finger from an infected cadaver. There is central caseation necrosis with dense surrounding macrophages and lymphocytes (S. Lucas).

**Fig. VE2.b.** *Inoculation tuberculosis, medium power.* An epithelioid cell granuloma at left, a Langhans giant cell at left lower, and a granuloma with central necrosis and acute inflammation. Occasional acid-fast bacilli were observed in this case (S. Lucas).

**Fig. VE2.c.** *Tuberculous gumma, low power.* A tuberculoma-like appearance with extensive caseation necrosis in the dermis, with a surrounding cellular infiltrate (S. Lucas).

**Fig. VE2.d.** *Tuberculous gumma, high power.* The edge of the necrosis (right) with histiocytes, lymphocytes, and a Langhans giant cell at left of the image.
Secondary changes in the epidermis are common, and are most pronounced in tuberculosis verrucosa cutis. The epidermis may undergo atrophy and subsequent destruction, causing ulceration, or it may become hyperplastic, showing acanthosis, hyperkeratosis, and papillomatosis. At the margins of ulcers, pseudoepitheliomatous hyperplasia often exists. In rare instances, squamous cell carcinoma supervenes.

**Tuberculoid Leprosy (See also Section VC3)**

See Figs. VE2.e—g.

**Lupus Miliaris Disseminatus Facei**

**CLINICAL SUMMARY.** Although now considered a variant of rosacea, lupus miliaris disseminatus faciei has its own distinct clinical presentation Characteristic lesions are discrete papules—single papules or small groups of flesh-colored or mildly erythematous papules—involving the face but specifically involving the eyelids and upper lip, areas where rosacea lesions are uncommon, and lacking the erythema and telangiectasia of rosacea.

**HISTOPATHOLOGY.** Biopsy specimens sectioned through the central portion of a papular lesion demonstrate one of the most highly characteristic patterns of cutaneous histopathology. Surrounding a usually large area of caseous necrosis, aggregates of epithelioid histiocytes and occasional multinucleate giant cells form a substantial "tubercle." There are sparse lymphoid infiltrates peripheral to the granulomas. The lesions are the size of a millet seed or half a rice grain. The etiology is unclear and some have speculated that it is caused by a foreign body reaction to hair follicles and their decomposition products (44).

**Conditions to consider in the differential diagnosis:**

* tuberculosis
* tuberculosis verrucosa cutis
* miliary tuberculosis
* lupus vulgaris (necrosis usually slight or absent)
non-tuberculosis mycobacteria (e.g., *M. ulcerans*)
type 1 reaction in tuberculoid leprosy
lupus miliaris disseminatus facei granulomatous
rosacea
tertiary syphilis
epithelioid sarcoma
cryptococcosis
histoplasmosis

**VE3 Palisading Granulomas**

There are foci of altered collagen (“necrobiosis”) surrounded by histiocytes and lymphocytes. Histiocytic giant cells are also seen in the infiltrate. The lesions of epithelioid sarcoma are associated with true tumor necrosis, but may superficially resemble rheumatoid nodules. Granuloma annulare is the prototype (45).

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**Granuloma Annulare**

**CLINICAL SUMMARY.** The lesions of granuloma annulare consist of small, firm, asymptomatic papules that are flesh-colored or pale red and are often grouped in a ring-like or circinate fashion, found most commonly on the hands and feet. Though chronic, they subside after a number of years. Unusual variants of granuloma annulare include (1) a generalized form, consisting of hundreds of papules that are either discrete or confluent but only rarely show an annular arrangement; (2) perforating granuloma annulare, with umbilicated lesions that may be local or generalized; (3) erythematous granuloma annulare, showing large, slightly infiltrated erythematous patches, with a palpable border, on which scattered papules may subsequently arise; and (4) subcutaneous granuloma annulare, in which subcutaneous nodules similar to rheumatoid
nodules occur, especially in children, either alone or in association with intradermal lesions.

**HISTOPATHOLOGY.** Histologically, granuloma annulare is characterized by an infiltrate of histiocytes and lymphocytes, which may be present in an interstitial pattern without organization, or in a well-developed palisade completely surrounding areas with prominent mucin. Patterns between these two extremes occur. Although degenerated collagen and small quantities of fibrin may be present, it is the increased mucin (hyaluronic acid) that is the hallmark of granuloma annulare (though it may be absent from some lesions, especially those that lack good palisading). The increased mucin is usually apparent on routinely stained sections as faint blue material with a stringy and finely granular appearance. Stains such as colloidal iron and alcian blue can be used to highlight it. Plasma cells are present rarely, and a sparse to moderately dense infiltrate of eosinophils can occur. Multinucleated histiocytes are present more often than not, but they are usually few and often subtle. They can occasionally be seen to have engulfed short,
Fig. VE3.c

**Granuloma annulare, low power.** The hypocellular center of the palisaded granuloma may show mucinous ground substance.

Necrobiosis Lipoidica Diabeticorum (NLD)

**Clinical Summary.** Most patients with necrobiosis lipoidica have or will have diabetes, abnormal glucose tolerance, or a family history of diabetes, although of all patients with diabetes, less than 1% develop necrobiosis lipoidica. The lesions present as one or several sharply but irregularly demarcated patches or plaques often with central telangiectases, usually on the shins, elsewhere on the lower extremities, or occasionally elsewhere (46).

**Histopathology.** The epidermis may be normal, atrophic, or hyperkeratotic, or ulcerated. Usually the entire thickness of the dermis or its lower two thirds is affected by variable degrees of granulomatous inflammation, degeneration of collagen, and sclerosis. Giant cells are usually of the Langhans’ or foreign-body type occasionally with Touton cells or asteroid bodies. There may or may not be histiocytes arranged in a palisade, which may tend to be somewhat horizontally oriented and vaguely tiered. Histiocytes may encircle altered connective tissue, particularly degenerated collagen, referred to as “necrobiosis,” and differing from normal collagen tinctorially by having a paler grayer hue and structurally by appearing more fragmented and more haphazardly arranged, or more compact. Increased mucin is usually inapparent or just subtle, in contrast to granuloma annulare. Other findings include a sparse to moderately dense, primarily perivascular lymphocytic infiltrate, plasma cells in the deep dermis in some biopsies, involvement of the upper subcutis with thickened fibrous septa, and lipids in foamy histiocytes or in cholesterol clefts. Older lesions show telangiectases superficially. Blood vessels, particularly in the middle and lower dermis, often exhibit thickening of their walls with PAS-positive, diastase-resistant material and proliferation of their endothelial cells. The process may lead to partial and rarely to complete occlusion of the lumen.

**Differential Diagnosis.** Although it is true that histologic distinction between necrobiosis and granuloma annulare may be difficult or impossible, usually it can be accomplished by using the following criteria: (1) Necrobiosis lipoidica rarely involves just one focus of the dermis or predominantly the upper half of the dermis, whereas granuloma annulare commonly does. (2) Histiocytes in palisades that completely encircle altered connective tissue are more common in granuloma annulare, whereas histiocytes in linear array that are horizontally oriented in a somewhat tiered fashion are more typical of necrobiosis lipoidica. (3) Abundant mucin is typical of granuloma annulare and distinctly uncommon in necrobiosis lipoidica. (4) Necrobiosis lipoidica often shows dermal sclerosis and thickened subcutaneous septa, whereas granuloma annulare does not (the sclerosis often produces a straight edge to the sides of a punch biopsy, in contrast to the inward retraction and/or more irregular edge seen in biopsies without sclerosis). Other features that are more characteristic of necrobiosis lipoidica include more numerous giant cells, more pronounced vascular changes such as thickened blood vessel walls, and prominent plasma cells in the deep dermis, and occasionally extensive deposits of lipids or nodular lymphocytic infiltrates in the deep dermis or subcutis.

Necrobiotic Xanthogranuloma With Paraproteinemia

**Clinical Summary.** A rare disorder, necrobiotic xanthogranuloma with paraproteinemia presents with large, often yellow, indurated plaques with atrophy, telangiectasia, and occasionally also ulceration (47). The most common location is peri-orbital, and the thorax is also commonly involved. In most patients, serum protein electrophoresis shows an IgG monoclonal gammopathy that usually consists of kappa light chains. Bone marrow examination may reveal multiple myeloma. The skin lesions of necrobiotic xanthogranuloma are reactive and are not associated with monoclonal plasma cells or multiple myeloma (48).
**Clin. Fig. VE3.c.** *Necrobiosis lipoidica.* A solitary plaque of the anterior tibial region shows a pink-brown color, atrophy, and telangiectasia. (W. Witmer).

**Fig. VE3.d.** *Necrobiosis lipoidica (NLD), low power.* The presence of fibrosis can be identified because of the straight edges of the biopsy. The infiltrate involves the full thickness of the dermis and is arranged in a tier-like fashion.

**Fig. VE3.e.** *Necrobiosis lipoidica, medium power.* Histiocytes and lymphocytes on the left surround degenerated collagen. Compared to the normal collagen above it, the degenerated collagen has a more compact appearance and appears more gray-blue than pink.

**Fig. VE3.f–h.** *Necrobiosis lipoidica, high power.* Epithelioid granulomas in the deep dermis and lymphocytes and plasma cells at the dermal-subcutaneous junction are features that favor NLD over granuloma annulare.
**HISTOPATHOLOGY.** Granulomatous masses are present either as focal aggregates or as large, intersecting bands occupying the dermis and subcutaneous tissue. The intervening tissue separating the granulomas shows extensive necrobiosis. The granulomas contain histiocytes, foam cells, and often also an admixture of inflammatory cells, often arranged as lymphoid follicles. A distinctive feature is the presence of numerous large giant cells, both of the Touton type with a peripheral rim of foamy cytoplasm and of the foreign-body type. Aggregates of cholesterol clefts are also common.

**Rheumatoid Nodules**

**CLINICAL SUMMARY.** Rheumatoid nodules vary in size from a few millimeters to 5 cm and may be solitary or numerous. They occur in patients with rheumatoid arthritis, particularly over extensor surfaces (49), and rarely in extracutaneous sites. *Pseudorheumatoid nodule* refers to nodules in the subcutis that mimic rheumatoid nodules histologically but that develop in the absence of rheumatoid arthritis (or systemic lupus erythematosus). The subsequent development of rheumatoid arthritis occurs infrequently in adults and rarely, if ever, in children. These nodules have been considered to represent a subcutaneous variant of granuloma annulare.

**HISTOPATHOLOGY.** Rheumatoid nodules occur in the subcutis and lower dermis and show one or several areas of fibrinoid degeneration of collagen that stain homogeneously red. Nuclear fragments and basophilic material may be present, but mucin is almost always

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**Clin. Fig. VE3.d.** *Necrobiotic xanthogranuloma.* A 65 year old woman developed asymmetric periorbital induration with violaceous color change.

**Fig. VE3.i.** *Necrobiotic xanthogranuloma, low power.* A diffuse infiltrate spans the dermis and subcutaneous tissue.

**Fig. VE3.j.** *Necrobiotic xanthogranuloma, low power.* The infiltrate is vaguely granulomatous, with intersecting bands of acellular necrosis and cellular infiltrates which are present either as focal aggregates or as large, intersecting bands occupying the dermis and subcutaneous tissue.

**Fig. VE3.k.** *Necrobiotic xanthogranuloma, high power.* The granulomatous infiltrate contains histiocytes, foam cells, and an admixture of lymphocytes and plasma cells, with numerous large giant cells of the Touton type with a peripheral rim of foamy cytoplasm, or of foreign-body type. (continues)
minimal or absent. These areas are surrounded by histiocytes in a palisaded arrangement, often with scattered foreign-body giant cells. In the surrounding stroma, there is a proliferation of blood vessels, with fibrosis and a fairly sparse infiltrate of other inflammatory cells including predominantly lymphocytes and a few neutrophils, but also mast cells, plasma cells, and eosinophils occasionally.

**Palisaded Neutrophilic and Granulomatous Dermatitis**

**CLINICAL SUMMARY.** Palisaded neutrophilic and granulomatous dermatitis (PNGD) is an inflammatory reactive process in the skin that is generally associated with underlying immune mediated systemic disease (50–52). Clinically, the patients present with papules, plaques and linear bandlike lesions. The lesions favor the extremities especially the extensor surfaces. The papules may have a central crust, umbilication, or ulceration. They may be asymptomatic or painful. Among all, 74% of the reported cases have occurred in women and PNGD generally occurs in middle-aged adults. It has been associated with the following underlying systemic diseases: rheumatoid arthritis, systemic lupus erythematosus, Wegener’s granulomatosis, CSS, Takayasu’s aortitis, sarcoidosis, and lymphoproliferative disorders (53). It has also been induced by medications, including allopurinol (54). There is overlap of clinical and histopathologic findings with an entity called interstitial granulomatous dermatitis (IGD). This entity also occurs in patients with a history of arthritis and/or arthralgias and characteristically has linear plaques in intertriginous and extremity areas that has been described as the “rope sign.”

**HISTOPATHOLOGY.** The characteristic histopathologic finding in PNGD is the Churg–Strauss granuloma,
which was initially described in lesions of allergic granulomatosis (Churg–Strauss syndrome). There is an area of neutrophilic inflammation with leukocytoclastic debris and prominent basophilia surrounded by poorly defined palisaded histiocytic inflammation. The inflammatory infiltrate is mixed showing neutrophils, eosinophils, and mononuclear cells. Some cases may reveal leukocytoclastic vasculitis. In interstitial granulomatous dermatitis, similarly, there may be an interstitial and/or palisaded histiocytic infiltrate with collagen alteration. Neutrophilic inflammation with vasculitis leukocytoclasia and basophilic debris are much less intense. PNGD and IGD may show overlapping histologic features.

**Conditions to consider in the differential diagnosis:**
- granuloma annulare
- rheumatoid nodule
- necrobiosis lipoidica
- subcutaneous granuloma annulare
- leukocytoclastic vasculitis
- granuloma annulare-like medication reactions
- interstitial granulomatous dermatitis (IGD)
- necrobiotic xanthogranuloma with paraproteinemia
- annular elastolytic giant cell granuloma (actinic granuloma)
- rheumatic nodule
- epithelioid sarcoma
- occasional examples of deep fungus infections
<table>
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<td><strong>Granuloma Annulare</strong></td>
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PNGD: Palisaded neutrophilic and granulomatous dermatitis  
NXG: Necrobiotic xanthogranuloma with paraproteinemia  
GA: Granuloma annulare  
NL: Necrobiosis Lipoidica
Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Fig. VE3.r. Palisaded neutrophilic and granulomatous dermatitis, low power. In the dermis, there is edema associated with a diffuse infiltrate which is both perivascular and interstitial.

Fig. VE3.s. Palisaded neutrophilic and granulomatous dermatitis, medium power. Characteristically one sees granular basophilic material within the reticular dermis associated with a mixed inflammatory infiltrate.

Fig. VE3.t.u. Palisaded neutrophilic and granulomatous dermatitis, high power. In some areas, neutrophils predominate in the infiltrate and may show vasculitis. In these images, one also sees the characteristic basophilic material. Eosinophils are also present.

Fig. VE3.v. Interstitial granulomatous dermatitis, low power. There is a superficial and deep perivascular and interstitial infiltrate without involvement of the epidermis. (continues)
Mixed Cell Granulomas

Lymphocytes and plasma cells are present in addition to epithelioid histiocytes, which may form loose clusters, and giant cells, which may be quite inconspicuous. In many of these granulomatous infiltrates, organisms are found. Keratin granuloma is the most common mixed granuloma. Flakes of keratin may be appreciated as fibers, often gray rather than pink, in the cytoplasm of giant cells. Foreign-body reactions may present as mixed-cell granulomas (55).

Foreign-Body Reactions

**Clinical Summary.** Foreign substances, when injected or implanted accidentally into the skin, can produce a focal, nonallergic foreign-body reaction, or in persons specifically sensitized to them, a focal allergic response. In addition, certain substances formed within the body may produce a nonallergic foreign-body reaction when deposited in the dermis or the subcutaneous tissue. Such endogenous foreign-body reactions are produced, for instance, by urates in gout and by keratinous material in pilomatrixoma, as well as in ruptured epidermoid and trichilemmal cysts.

**Histopathology.** A nonallergic foreign-body reaction typically shows a granulomatous response with histiocytes and giant cells around the foreign material. Often, some of the giant cells are of the foreign-body type, in which the nuclei are in haphazard array. In addition, lymphocytes are usually present, as may be plasma cells and neutrophils, constituting a mixed-cell granuloma. Frequently, some of the foreign material is seen within macrophages and giant cells, a finding that of course is of great diagnostic value. The most common cause of a foreign-body granuloma is rupture of a hair follicle or follicular cyst, and sometimes only the cyst content, rather than residual cyst wall, is identifiable. Exogenous substances producing nonallergic foreign-body reactions are, for instance, silk and nylon sutures, wood, paraffin and other oily substances, silicone gel, talc, surgical glove starch powder, and cactus spines. Some of these substances—nylon sutures, wood, talc, surgical glove starch powder, and sea-urchin spines—are doubly refractile on polarizing examination. Double refraction often is very helpful in localizing foreign substances.

An allergic granulomatous reaction to a foreign body typically shows a sarcoidal or tuberculoid pattern consisting of epithelioid cells with or without giant cells. Phagocytosis of the foreign substance is slight or absent. Substances that in sensitized persons produce an allergic granulomatous reaction are, for instance, zirconium, beryllium, and certain dyes used in tattoos. Some substances that at first act as foreign material may later on, after sensitization has occurred, act as allergens, as in the case of sea-urchin spines and silica.

**Conditions to consider in the differential diagnosis:**
- keratin granuloma
- ruptured cyst
- folliculitis
- Foreign body granulomas
- sporotrichosis
persistent arthropod bite
syphilis, secondary and tertiary
cryptococcosis
candidal granuloma
non-tuberculous mycobacteria
cat-scratch disease
North American blastomycosis
South American blastomycosis
chromomycosis
phaeohyphomycosis
coccidioidomycosis

**VES** Inflammatory Nodules With Prominent Eosinophils

The nodular dermal infiltrates contain many eosinophils often admixed with lymphocytes. Angiolymphoid hyperplasia is the best example (56).

**Angiolymphoid Hyperplasia With Eosinophilia, and Kimura’s Disease**

**CLINICAL SUMMARY.** Lesions of angiolymphoid hyperplasia with eosinophilia (ALHE) may arise superficially in
The dermis, or in the subcutaneous or deeper tissues. Superficial lesions, which have been referred to as pseudo-
pyogenic granuloma, present often in young to middle-aged women with pruritic papules and plaques often at or
around the external ear or elsewhere in the head and neck. Lesions of subcutaneous and deeper tissues typically pres-
ent as a solitary, slowly growing, firm, subcutaneous swell-
ing up to 10 cm in size usually in the head and neck region
with some predilection for the pre- or postauricular sites.
Blood eosinophilia and modest enlargement of neighboring
lymph nodes and salivary tissue may occur. The conditions
are chronic, but serious complications do not occur.

When ALHE was first described in Western Europe,
similarities to Kimura’s disease as reported in the Far East
were noted. However, more recently most authorities
emphasize differences between the two entities. Angiolym-
phoid hyperplasia and Kimura’s disease occur most com-
monly in the head and neck region in adults and both
share the histologic features of extensive lymphoid prolif-
eration, tissue eosinophilia, and evidence of vascular
hyperplasia. Kimura’s disease, however, demonstrates a
wider age span with male predominance and a tendency
for more extensive lesions to occur, often with involve-
ment of salivary tissue and lymph nodes and at sites dis-
 tant from the head and neck region.

HISTOPATHOLOGY. The main components of the
pathology are: (1) Proliferation of small to medium-sized
blood vessels often showing a lobular architecture and
lined by greatly enlarged (epithelioid) endothelial cells; (2)

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**Fig. VE5.a.** Kimura’s disease, low power. A nodular cluster of lymphoid follicles in the deep dermis and sub-
cutaneous tissue.

**Fig. VE5.b.** Kimura’s disease, medium power. The follicles are surrounded by fibrosis and separated by a mesh-
work of prominent small vessels.

**Fig. VE5.c.** Kimura’s disease, medium power. Eosinophils are often abundant.

**Fig. VE5.d.** Kimura’s disease, high power. The endothelial cells lining the small vessels are swollen and may
protrude into the lumen, imparting a cobblestone appearance.
A perivascular inflammatory cell infiltrate composed mainly of lymphocytes and eosinophils; (3) Nodular areas of lymphocytic infiltrate occurring with or without follicle formation; and (4) Inflammatory vascular occlusive changes in medium-sized arteries associated with endothelial cell proliferation.

In superficial lesions, there is variable vascular hyperplasia that can include areas in which the proliferation is almost angiomatous. A distinctive feature is the “cobblestone”, or “hob-nail” appearance of enlarged endothelial cells that project into the lumina of some vessels. These cells lack atypia or mitotic activity. Affected vessels often contain endothelial cells with intracytoplasmic vacuoles, the so-called “histiocytoid hemangioma” pattern. In subcutaneous lesions, the inflammatory cell infiltrate is usually more massive, with a central, poorly circumscribed nodule that replaces the fat. The nodule is composed of confluent sheets of small lymphocytes and eosinophils in which a network of poorly canalized thick-walled capillaries is embedded. Satellite smaller islands of lymphoid cells with lymphoid follicles usually surround the central nodule. Commonly, there is involvement of medium- to large-sized arteries, with infiltration of the vessel wall by inflammatory cells and occlusion of the lumen.

Histologic differences between AHLE and Kimura’s disease include the lesser degree of exuberant vascular hyperplasia lacking prominent eosinophilic endothelial cells and the absence of uncanalized blood vessels in Kimura’s
disease. Other points of difference are eosinophilic abscesses and marked fibrosis around the lesions in Kimura's disease and the absence of lesions centered around damaged arteries. There is an important association between Kimura's disease and nephrotic syndrome.

**Scabetic Nodule**

See Figs. VE5.e–h.

**Conditions to consider in the differential diagnosis:**

- angiolympoid hyperplasia with eosinophils
- Kimura's disease
- scabetic nodule

**VE6 Inflammatory Nodules With Mixed Cell Types**

A variety of cells are present in the infiltrate, including neutrophils, histiocytes, plasma cells, giant cells, and lymphocytes. Sporotrichosis is a good example (57).

**Sporotrichosis**

**CLINICAL SUMMARY.** Clinical sporotrichosis usually occurs as one of the two primary cutaneous forms, either the fixed cutaneous or the lymphocutaneous form. Both result from direct inoculation at a site of minor trauma. Systemic sporotrichosis is rare and more commonly follows pulmonary infection in association with immunosuppression. The lymphocutaneous form of sporotrichosis starts with a painless papule that grows into an ulcer, usually on a finger or hand. Subsequently, a chain of asymptomatic nodules appears along the lymph vessel draining the area, in a pattern of “lymphangitic” or “sporotrichoid” spread. These lymphatic nodules may undergo suppuration with subsequent ulceration. In the fixed cutaneous form, a solitary plaque or occasionally a group of lesions is seen, most commonly on an arm or the face. It may show superficial crusting or a verrucous surface. There is no tendency toward lymphatic spread.

**HISTOPATHOLOGY.** Early lesions of primary cutaneous sporotrichosis usually show a nonspecific inflammatory infiltrate composed of neutrophils, lymphoid cells, plasma cells, and histiocytes. In an older lesion with an elevated border or a verrucous appearance, small abscesses are often found in the hyperplastic epidermis, and the dermis contains small abscesses and granulomas often associated with asteroid bodies and scattered through a lymphoplastic infiltrate with eosinophils and giant cells. Later, through coalescence, a characteristic arrangement of the infiltrate in three zones may develop. These include a central “suppurative” zone composed of neutrophils; a “tuberculoid” zone with epithelioid cells and multinucleated histiocytes; and peripherally, a “round cell” zone of lymphoid cells and plasma cells.

The nodules of sporotrichosis at first show scattered granulomas within an inflammatory infiltrate, predominantly in the deep dermis and the subcutaneous fat. These enlarge and coalesce to form irregularly shaped suppurative granulomata, and eventually a large abscess surrounded by zones of histiocytes and lymphocytes as described for primary lesions.

In many instances, it is not possible to recognize the causative organisms of *S schenckii* in tissue sections. Immunohistochemical staining may increase the yield. In a recent study of 119 samples of confirmed cutaneous sporotrichosis, the fungus was not seen in 65% of the specimens. The authors note that histopathological changes related to older lesions or to a more developed immune response were directly associated with absence of the organism (58). If present, the spores of *S schenckii* appear as round to oval bodies 4 to 6 μm in diameter that stain more strongly at the periphery than in the center. Single or occasionally multiple buds are present. In some instances, small, cigar-shaped bodies up to 8 μm long are also present. Asteroid bodies in sporotrichosis consist a central spore 5 to 10 μm in diameter surrounded by radiating elongations of a homogeneous eosinophilic material, known as the Splendore-Hoepli phenomenon and thought to represent deposition of antigen-antibody complexes and host debris.

**Atypical Mycobacteria**

**CLINICAL SUMMARY.** Among the nontuberculosis, nonleprosy mycobacterial infections of the skin, those caused by *Mycobacterium marinum* are the most common among non-immunosuppressed people (59). Unlike *M tuberculosis*, which is transmitted from person to person, nontuberculosis mycobacteria are abundant in nature, in soil and water, and contact is frequent in most zones of the world.

These skin infections may be acquired by direct inoculation into the skin or by hematogenous spread from a visceral focus. Increased use of immunosuppression in medicine (e.g., for transplantation and cancer chemotherapy) and the pandemic of HIV/AIDS have resulted in many more mycobacterial skin infections. The cell-mediated immune system is a major defense against such organisms and is affected or destroyed during the course of these immunosuppressive conditions. The clinical and histopathologic patterns are also altered, with organisms being found in greater density than in immunocompetent persons.

**HISTOPATHOLOGY.** The histopathologic picture in nontuberculosis mycobacterioses is just as variable as the clinical picture and may present nonspecific acute and chronic inflammation, suppuration and abscess formation, or tuberculoid granulomas with or without caseation (60). In some instances, both tissue reactions occur concurrently. The presence or absence of acid-fast bacilli depends
Clin. Fig. VE6.a. *Sporotrichosis.* An ulcerated nodule developed after the area was pricked by a rose bush.

Clin. Fig. VE6.b. *Sporotrichosis.* Subsequently nodules along the draining lymph vessels appeared (a “sporotrichoid” pattern of spread).

Fig. VE6.a. *Sporotrichosis, low power.* A patchy to diffuse infiltrate spanning the dermis.

Fig. VE6.b. *Sporotrichosis, medium power.* Focal areas of necrosis can be appreciated within the infiltrate, which in some areas is granulomatous.

Fig. VE6.c. *Sporotrichosis, high power.* PAS stain. A rare small spore is identified in the area of inflammation. (S. Lucas).
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

on the tissue reaction. In suppurative lesions, numerous acid-fast bacilli often can be found.

**Conditions to consider in the differential diagnosis:**
- sporotrichosis
- rhinoscleroma (Klebsiella rhinoscleromatis)
- atypical mycobacteria
  - Mycobacterium avium-intracellulare
  - Mycobacterium marinum
- nocardiosis
- lobomycosis
- protothecosis

**Fig. VE6.d.** *Atypical mycobacteria.* There is an ill-defined cellular lesion in the dermis.

**Fig. VE6.e.** *Atypical mycobacteria.* The inflammatory infiltrate constituting the lesion is comprised of a mixed population of cells including neutrophils (which may predominate in some cases), plasma cells, histiocytes and giant cells.

**Fig. VE6.f.** *Atypical mycobacteria.* Some foamy histiocytes are present in the infiltrate. These may predominate in some lesions with a high load of organisms.

**Fig. VE6.g.** *Atypical mycobacteria.* Acid-fast bacilli are often readily demonstrable, usually within the cytoplasm of histiocytes.
**VE7** Inflammatory Nodules With Necrosis and Neutrophils (Abscesses)

Inflammatory nodules characterized by central supplicative necrosis, with neutrophils adjacent to the necrosis, and often with granulation tissue, mixed inflammatory cells including epithelioid histiocytes and giant cells, and fibrosis at the periphery. Botryomycosis is prototypic (61).

**Botryomycosis**

**CLINICAL SUMMARY.** Botryomycosis is a chronic supplicative infection of skin (and other organs such as lungs and meninges) in which pyogenic bacteria form granules similar to those seen in mycetoma. Most patients have no known immune defect. The skin lesions are local nodules, ulcers, or sinuses communicating with deep abscesses. They occur mainly on the extremities.

**HISTOPATHOLOGY.** The dermal inflammation is predominantly that of neutrophilic abscesses with surrounding granulation tissue and fibrosis. Within the abscesses are granules (grains) shaped like a bunch of grapes, hence the name of the disease. The grains, which may range up to 2 mm in diameter, are composed of closely aggregated non-filamentous bacteria with a peripheral, radial deposition of intensely eosinophilic material—a Hoepppli-Splendore (HS) reaction. The bacteria are usually *Staphylococcus aureus*, but streptococci and certain Gram-negative bacilli such as *Proteus*, *Pseudomonas*, and *E. coli* are sometimes

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**Fig. VE7.a.** Botryomycosis, low power. There is pseudoepitheliomatous hyperplasia of the epidermis, and there are small abscesses in the dermis (S. Lucas).

**Fig. VE7.b.** Botryomycosis, medium power. An abscess within which is a basophilic bacterial colony with a surrounding eosinophilic Hoepppli-Splendore phenomenon. (S. Lucas).

**Fig. VE7.c.** Botryomycosis, high power. A staphylococcal lesion showing Gram-positive coccis (centrally they are degenerate and non-staining) (S. Lucas).
found. The overlying epithelium often exhibits pseudoepi-
epitheliomatous hyperplasia. Transepithelial elimination of
grains may be observed.

**Chromoblastomycosis**

**CLINICAL SUMMARY.** Chromoblastomycosis is a slowly
progressive cutaneous mycosis caused by pigmented
(dematiaceous) fungi that occur as round, nonbudding
forms in tissue sections. Inasmuch as budding is absent,
the designation chromoblastomycosis is somewhat inap-
propriate. The causative fungi are saprophytes that can be
found growing in soil, decaying vegetation, or rotten wood
in subtropical and tropical countries. The primary lesion is
thought to develop as a result of traumatic implantation of
the fungus into the skin. The lesions are most common on
the lower extremities and consist of verrucous papules,
nodules, and plaques that may itch. The most common
cause of chromoblastomycosis is *Fonseca pedrosoi*.

**HISTOPATHOLOGY.** The cutaneous type of chromo-
blastomycosis resembles North American blastomycosis
in histologic appearance with a lichenoid-granulomatous
inflammatory pattern, with pseudoepitheliomatous
epidermal hyperplasia and an extensive dermal infiltrate

**Clin. Fig. VE7.** *Chromoblastomycosis*. Skin biopsy in the center of this ulcerated, crusted plaque revealed the
characteristic, dark-brown spores.

**Fig. VE7.d.** *Chromoblastomycosis, low power*. An ulcerated epidermis overlies a mixed-cell inflammatory
infiltrate in the dermis.

**Fig. VE7.e.** *Chromoblastomycosis, medium power*. The infiltrate includes lymphocytes and epithelioid cells
with giant cells but without well-formed epithelioid cell granulomas.

**Fig. VE7.f.** *Chromoblastomycosis, high power*. The organisms appear as dark brown, thick-walled, ovoid or
spheric spores lying within giant cells as well as free in the tissue.
VE. Nodular Inflammatory Infiltrates of the Reticular Dermis—Granulomas, Abscesses, & Ulcers

composed of many epithelioid histiocytes, as well as multinucleated giant cells, small abscesses with clusters of neutrophils, and variable numbers of lymphocytes, plasma cells, and eosinophils. Tuberculoid formations may be present, but caseation necrosis is absent. The causative organisms are found within giant cells as well as free in the tissue, especially in the abscesses. They appear as conspicuous, dark brown, thick-walled, ovoid or spheric spores varying in size from 6 to 12 μm and lying either singly or in chains or clusters. In a study of 27 cases of chromoblastomycosis from Brazil, sclerotic bodies were noted in 92.5% of cases (62). Fontana staining and the use of unstained and destained sections can be helpful in identifying the causative organism (63).

**Conditions to consider in the differential diagnosis:**

- acute or chronic bacterial abscesses
- deep fungal infections
- phaeohyphomycotic cyst
- North American blastomycosis
- chromoblastomycosis
- cutaneous alternariosis
- paracoccidioidomycosis
- coccidioidomycosis
- sporotrichosis
- atypical mycobacteria

botryomycosis
actinomycosis
nocardiosis
cat scratch disease
erythema nodosum leprosum (Type 2 leprosy reaction)
scrofuloderma
tuberculoid gumma
protothecosis

**VE** | **Inflammatory Nodules With Prominent Necrosis**

Necrosis is a striking feature along with variable but sometimes sparse infiltrates of inflammatory cells, that may include plasma cells, epithelioid histiocytes, neutrophils, lymphocytes and hemorrhage. Organisms may be demonstrable. Aspergillosis is prototypic (64).

**Aspergillosis**

**CLINICAL SUMMARY.** Cutaneous aspergillosis may occur as a primary infection or may be secondary to disseminated aspergillosis. The lesions of primary cutaneous aspergillosis are usually found at an intravenous infusion site. One observes either one or several macules, papules, plaques, or hemorrhagic bullae, which may rapidly progress

**Fig. VE8.a**
*Cutaneous aspergillosis, low power.* There is an extensive dermal inflammatory infiltrate throughout most of the field, with a less cellular area of necrosis at the lower left of the image. The epidermis has separated due to ischemic changes of basal keratinocytes.

**Fig. VE8.b**
*Cutaneous aspergillosis, medium power.* At the periphery of the necrotic area (lower left), there is an inflammatory infiltrate in the viable dermis. Both areas are extensively infiltrated by fungal hyphae. (continues)
Thrombosed vessel

Septate hyphae

Vessel wall

Organisms in transit through vessel wall

45 degree branching

**Fig. VE8.c.** Cutaneous aspergillosis, high power. A thrombosed vessel surrounded by acute inflammatory cells, with fungal hyphae of Aspergillus organisms in typical pose spanning the vessel wall.

**Fig. VE8.d.** Cutaneous aspergillosis, medium power, silver stain for fungi. Black-stained fungal hyphae in the vessel lumen, wall and surrounding tissue.

**Fig. VE8.e.** Cutaneous aspergillosis, high power, silver stain for fungi. The hyphae are narrow, fairly uniform, septate, and tend to branch at acute angles.

into necrotic ulcers that are covered by a heavy black eschar. Death often results from secondary systemic dissemination of the aspergillosis. Primary cutaneous infection has been seen in patients with AIDS. In addition, *Aspergillus* may colonize burn or surgical wounds and subsequently invade viable tissue; in these cases the prognosis is generally good. Secondary cutaneous aspergillosis, usually associated with invasive lung disease, shows multiple scattered lesions as a result of embolic, hematogenous spread, and has a poor prognosis.

**HISTOPATHOLOGY.** Unlike most deep cutaneous fungal infections, cutaneous aspergillosis is not characteristically associated with pseudoepitheliomatous epidermal hyperplasia. In the more serious primary forms and in the secondary disseminated form, numerous *Aspergillus* hyphae are seen in the dermis with hematoxylin-eosin–stained sections, or with PAS or silver methenamine staining. The 2 to 4 μm hyphae are often arranged in a radiate fashion, are septate, and branch at an acute angle. Hyphae characteristically invade blood vessels giving rise to areas of ischemic necrosis with very little inflammation in some instances. In other cases, there may be an acute inflammatory reaction with polymorphonuclear leukocytes in addition to lymphocytes and histiocytes. In patients with primary cutaneous or subcutaneous aspergillosis who are otherwise in good health, the number of hyphae present is relatively small, and there may be a well-developed granulomatous reaction.

**Conditions to consider in the differential diagnosis:**
- tertiary syphilis
- tertiary yaws
- aspergillosis
- zygomycosis (mucormycosis)
- tuberculosis
- atypical mycobacteria
- infarcts
- deep vasculitis
- deep thrombosis
- calciphylaxis
- frostbite
- necrobiotic xanthogranuloma with paraproteinemia
- gangrenous ischemic necrosis
- epithelioid sarcoma
Chronic Ulcers & Sinuses Involving the Reticular Dermis

A chronic ulcer is characterized by central suppurative necrosis, with neutrophils adjacent to the necrosis, and often with granulation tissue, fibrosis, and reactive epithelium at the periphery. A sinus extends deeper into the dermis than most ulcers, in a serpentine fashion. A fistula is an abnormal communication between two epithelial-lined surfaces. The histologic architecture of fistulas and sinuses is similar to that of chronic ulcers. Chancroid is a good example of a chronic ulcer (65).

Chancroid

CLINICAL SUMMARY. Chancroid, caused by *Haemophilus ducreyi*, is a sexually transmitted disease leading to one or several ulcers, chiefly in the genital region. The ulcers exhibit little if any induration and often have undermined borders. They are usually tender. Inguinal lymphadenitis, either unilateral or bilateral, is common and, unless treated, often results in an inguinal abscess.

HISTOPATHOLOGY. The histologic changes beneath the ulcer are sufficiently distinct to permit a presumptive diagnosis of chancroid in many instances. The lesion consists of three zones overlying each other and shows characteristic vascular changes. The surface zone at the floor of the ulcer is rather narrow and consists of neutrophils, fibrin, erythrocytes, and necrotic tissue. The next zone is fairly wide and contains many newly formed blood vessels showing marked proliferation of their endothelial cells. As a result of the endothelial proliferation, the lumina of the vessels are often occluded, leading to thrombosis. In addition, there are degenerative changes in the walls of the vessels. The deep zone is composed of a dense infiltrate of plasma cells and lymphoid cells. Demonstration of bacilli

Clin. Fig. VE9.a. *Chancroid*. Multiple, painful, nonindurated ulcers require investigation for this venereal disease.

Fig. VE9.a. *Chancroid, low power*. Cutaneous ulcer with the characteristic three-zone pattern of inflammation—superficial acute inflammatory exudate, a midzone of granulation tissue, and a deep zone of plasma cells and lymphocytes. (S. Lucas).

Fig. VE9.b. *Chancroid, medium power*. The superficial necrotic zone, and underlying granulation tissue (S. Lucas).

Fig. VE9.c. *Chancroid, high power*. A Giemsa stained image from the superficial necrotic zone, containing bacilli lying in parallel chains. (S. Lucas, courtesy of A. Freinkel).
in tissue sections stained with Giemsa stain or Gram stain is occasionally possible. The bacilli are most apt to be found between the cells of the surface zone. *H. ducreyi* is a fine, short, Gram-negative coccobacillus, measuring about 1.5 by 0.2 μm, often arranged in parallel chains.

**Pyoderma Gangrenosum**

**CLINICAL SUMMARY.** The lesions begin as tender papulopustules or as folliculitis that eventually may ulcerate. In the fully developed stage, the lesions have a raised, undermined border, which has a dusky purple hue. Pyoderma gangrenosum may occur as an isolated cutaneous phenomenon or may be a cutaneous manifestation associated with various systemic disease processes, such as inflammatory bowel disease, connective tissue diseases, and lymphoproliferative lesions (66). Trauma is a common inciting factor, with surgical incisions being a frequently reported instigator. Commonly the lesions are located on the legs, and breast, abdomen, and peristomal areas may also occur. Pyoderma gangrenosum often heals with a cribriform scar. The condition has been recently reviewed (67).

**HISTOPATHOLOGY.** The histologic findings are nonspecific and the diagnosis is primarily clinical. Most authors

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**Clin. Fig. VE9.b.** *Pyoderma gangrenosum.* A 25-year-old man with ulcerative colitis developed a fluctuant calf nodule which broke down into a painful enlarging ulcer with purple-red undermined borders.

**Fig. VE9.d.** *Pyoderma gangrenosum, low power.* A punched-out ulcer with an undermined edge extending deeply into the dermis.

**Fig. VE9.e.** *Pyoderma gangrenosum, medium power.* The ulcer base is lined by an intense infiltrate of neutrophils.

**Fig. VE9.f.** *Pyoderma gangrenosum, high power.* Neutrophils are present in a vessel walls without true vasculitis, which requires fibrinoid necrosis. Necrotizing vasculitis that may be seen at the surface of acute ulcers may be secondary to the ulcer, and should not necessarily be considered pathogenic.
Nodular Inflammatory Infiltrates of the Reticular Dermis—Granulomas, Abscesses, & Ulcers

studying early lesions have reported a primarily neutrophilic infiltrate, which frequently involves follicular structures, but is also often diffuse, and may overlap with a Sweet's reaction. Others, however, have stated that the lesions begin with a lymphocytic reaction. Degrees of vessel involvement range from none to fibrinoid necrosis. In the majority of lesions, a neutrophilic infiltrate is present with some, but limited, vascular damage. Outright vasculitis has been reported and has led to speculations about its possible role in the etiology of pyoderma gangrenosum. Focal vasculitis is often observed in fully developed lesions, but appears secondary to the inflammatory process. The infiltrate tends to

Clin. Fig. VE9.c

Chondrodermatitis nodularis helicis. This tender, crusted nodule on the superior helix requires biopsy to distinguish from skin carcinoma.

Fig. VE9.g

Chondrodermatitis nodularis helicis. Hyperkeratosis and a hyperplastic epithelium are associated with a focal ulcer and an inflammatory reaction that extends to the cartilage of the ear.

Fig. VE9.h

Chondrodermatitis nodularis helicis. Beneath the focal ulcer there is a characteristic zone of eosinophilic fibrinoid degeneration of collagen extending to the cartilage.

Fig. VE9.i

Chondrodermatitis nodularis helicis. Around the zone of eosinophilic fibrinoid degeneration, there is a proliferation of small mature vascular channels with inflammatory cells.
be deeper and more extensive than that in classic Sweet's syndrome. Fully developed lesions exhibit ulceration, necrosis, and a mixed inflammatory cell infiltrate. The pattern of breakdown of tissue that results from these processes has been termed "pathergy". Involvement of the deep reticular dermis and subcutis may exhibit primarily mononuclear cell and granulomatous inflammatory reactions. The key histologic differential diagnosis is an infectious process.

**Chondrodermatitis Nodularis Helicis**

See Clin. Fig. VE9.c and Figs. VE9.g–i.

**Conditions to consider in the differential diagnosis:**

- pyoderma gangrenosum
- erythema gangrenosum
- deep fungal infection
  - North American blastomycosis
  - eumycetoma
- tuberculosis cutis orificialis
- enterocutaneous fistula
- chondrodermatitis nodularis helicis
- erythema
- papulonecrotic tuberculid
- Buruli ulcer (M. ulcerans)
- chancroid (Haemophilus ducreyi)
- granuloma inguinale (Calymmatobacterium granulomatis)
- lymphogranuloma venereum (Chlamydia trachomatis)
- follicular occlusion disorder
  - pilonidal sinus
  - hidradenitis suppurativa
  - acne conglobata
  - perifolliculitis capitis abscedens et suffodiens (dissecting cellulitis of the scalp)
- Anthrax (Bacillus anthracis)
- Tularemia (Francisella tularensis)
- cutaneous leishmaniasis
- necrotizing sialometaplasia of hard palate
- eosinophilic ulcer of the tongue

**VF Fiber Disorders, Collagen Increased**

Dermal collagen is increased with production at the dermal subcutaneous interface. Inflammation is seen at this site. The inflammatory cells are lymphocytes, plasma cells, and eosinophils. Fibroblasts in some instances are increased. Scleroderma is the prototype (68).

**Scleroderma**

**CLINICAL SUMMARY.** Scleroderma is a connective tissue disorder characterized by thickening and fibrosis of the skin. Two types of scleroderma exist: circumscribed scleroderma (morphea), and systemic scleroderma (progressive systemic sclerosis). In morphea, the lesions usually are limited to the skin and to the subcutaneous tissue beneath the cutaneous lesions. Morphea may be divided according to morphology and distribution of lesions into six types: guttate, plaque, linear, segmental, subcutaneous, and generalized. The underlying cause of morphea is unknown, but its development is thought to require a predisposition and a trigger from the environment. Known triggers include trauma, radiation, medications, and infections. Autoimmunity is also suspected to play a role (69).

Lesions of the plaque type, the most common, are indurated, with a smooth surface, and an ivory color with a violaceous border in growing lesions, the so-called lilac ring. Guttate lesions are small and superficial. Linear lesions may have the configuration of a saber-cut (coup de sabre). Segmental morphea occurs on one side of the face, resulting in hemiatrophy. In subcutaneous morphea (morphea profunda) the involved skin is thickened and bound to the underlying fascia and muscle. Generalized morphea comprises very extensive cases showing a combination of several of the five types just described.

In systemic scleroderma, visceral lesions are present in addition to involvement of the skin and the subcutaneous tissue, leading to death in some patients. The indurated lesions of the skin are not sharply demarcated or "circumscribed,” as in morphea. Facial changes include a mask-like expressionless face, and tightening of the skin around the mouth associated with radial folds. There may be diffuse hyperpigmentation, mainly in diffuse systemic scleroderma. The hands show nonpitting edema involving the dorsa of the fingers, hands, and forearms. Gradually the fingers become tapered, the skin becomes hard, and flexion contractions form. These changes, referred to as acrosclerosis, are associated with Raynaud's phenomenon. Macular telangiectasias on the face and hands, calcinosis cutis on the extremities, and ulcerations, especially on the tips of the fingers, over the knuckles, and on the lower extremities, occur predominantly in acrosclerosis.

Systemic sclerosis with limited scleroderma, known as CREST syndrome is a variant of acrosclerosis that consists of several or all of the following manifestations: Calcinosis cutis, Raynaud's phenomenon, involvement of the Esophagus with
dysphagia, Sclerodactyly and Telangiectases. Death from visceral lesions is rather infrequent in the CREST syndrome.

Multiple autoantibodies, many directed against intranuclear antigens such as anticentromere (ACA, anti-CENP-B), anti-topoisomerase I (anti-topo I), anti-RNA polymerase I/III, and anti-Th/To, are present in patients with scleroderma; there is controversy as to whether and to what extent these may be pathogenic (70). A recent study has shown an association between the presence of specific autoantibodies and the phenotypic expression of disease as well as clinical outcome in scleroderma (71).

**HISTOPATHOLOGY.** The different types of morphea cannot be differentiated histologically. Early inflammatory and late sclerotic stages can be distinguished. In the early inflammatory stage, particularly at the active violaceous border, the reticular dermis collagen bundles are thickened and there is a moderately intense interstitial and perivascular

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**Clin. Fig. VF1.a.** Morphea. Asymptomatic, indurated depressed plaques with white-appearing sclerotic centers are seen on the back of an otherwise healthy elderly male.

**Fig. VF1.a.** Morphea, low power. A late inflammatory lesion, with a patchy interstitial and perivascular inflammatory infiltrate, and partial sclerosis of dermal collagen.

**Fig. VF1.b.** Morphea, medium power. The infiltrate tends to be especially pronounced at the dermal-subcutaneous junction.

**Fig. VF1.c.** Morphea, high power. Lymphocytes and plasma cells are admixed in the infiltrate. (continues)
inflammatory infiltrate, which is predominantly lympho-cytic admixed with plasma cells. A much more pronounced inflammatory infiltrate often involves the subcutaneous fat and extends upward toward the eccrine glands. Trabeculae subdividing the subcutaneous fat are thickened by an inflammatory infiltrate and deposition of new collagen. Large areas of subcutaneous fat are replaced by newly formed collagen composed of fine, wavy fibers. Vascular changes in the early inflammatory stage may consist of endothelial swelling and edema of the walls of the vessels.

In the late sclerotic stage, as seen in the center of old lesions, the inflammatory infiltrate has disappeared almost completely, except in some areas of the subcutis. The epidermis is normal. The collagen bundles in the reticular dermis appear thickened, closely packed, hypocellular, and hyper-eosinophilic. In the papillary dermis, homogeneous collagen may replace the normal loosely arranged fibers. The eccrine glands are atrophic, have few or no adipocytes surrounding them, and are surrounded by newly formed collagen. Few blood vessels are seen within the sclerotic collagen; they often have a fibrotic wall and a narrowed lumen. Hair follicles and sebaceous glands are absent. The fascia and striated muscles underlying lesions of morphea may be affected in the linear, segmental, subcutaneous, and generalized types, showing fibrosis and sclerosis similar to that seen in subcutaneous tissue. The muscle fibers appear vacuolated and separated from one another by edema and focal collections of inflammatory cells.

The histologic appearance of the skin lesions in systemic scleroderma is similar to that of morphea so that their histologic differentiation is not possible. However, in early lesions of systemic scleroderma the inflammatory reaction is less pronounced than in morphea. The vascular changes in early lesions are slight, as in morphea. In contrast, in the late stage, systemic scleroderma shows more pronounced vascular changes than morphea, particularly in the subcutis. These changes include a paucity of blood vessels, thickening and hyalinization of their walls, and narrowing of the lumen. Even in late lesions, the epidermis usually appears normal. Aggregates of calcium may also be seen in the late stage within areas of sclerotic, homogeneous collagen of the subcutaneous tissue.
Clin. Fig. VF1.b. *Radiation dermatitis.* Chronic radiation changes of atrophy, hypopigmentation, hyperpigmentation, and telangiectases developed many years after radiation therapy for acne.

Fig. VF1.g. *Late radiation dermatitis, low power.* The dermal collagen is homogenized, telangiectatic vessels are apparent, and there are irregular down-growths of the epidermis. Adnexal structures are markedly diminished.

Fig. VF1.h. *Late radiation dermatitis, medium power.* Stellate fibroblasts are prominent in the sclerotic collagen.

Fig. VF1.i. *Late radiation dermatitis, high power.* Randomly scattered fibroblasts exhibit nuclear enlarged and hyperchromatic nuclei. There are no mitoses, and there is no contiguous proliferation of the atypical cells.
Radiation Dermatitis

CLINICAL SUMMARY. Early or acute radiation dermatitis develops after large doses of x-rays or radium. Erythema develops within about a week, and may heal with desquamation and pigmentation. If the dose was high enough, painful blisters may develop at the site of erythema. In that case, healing usually takes place with atrophy, telangiectasia, and irregular hyperpigmentation. Subsequent to very large doses ulceration occurs, generally within two months. Such an ulcer may heal ultimately with severe atrophic scarring, or it may not heal.

Late (chronic) radiation dermatitis occurs from a few months to many years after the administration of fractional doses of x-rays or radium. The skin shows atrophy, telangiectasia, and irregular hyper- and hypopigmentation. Ulceration, as well as foci of hyperkeratosis, may be seen within the areas of atrophy. Squamous cell carcinomas or

Clin. Fig. VF1.c

Clin. Fig. VF1.d

Fig. VF1.j

Fig. VF1.k

Clin. Fig. VF1.c. Nephrogenic fibrosing dermopathy. Skin tightening led to decreased range of motion.

Clin. Fig. VF1.d. Nephrogenic fibrosing dermopathy. Yellow plaque in sclera is a characteristic finding.

Fig. VF1.j. Nephrogenic fibrosing dermopathy, low power. Scanning magnification reveals subtle increased cellularity within the reticular dermis. This may be seen either in the upper or lower reticular dermis, and it may extend into the subcutaneous septa.

Fig. VF1.k. Nephrogenic fibrosing dermopathy, medium power. There is an increased number of spindled cells within the reticular dermis.
basal cell carcinomas may develop. Minimally invasive procedures are becoming more common and pathologists should consider fluoroscopy induced chronic radiation dermatitis when such histologic features are identified. Usually a history of radiation exposure is not provided. Characteristic sites of involvement include the axilla, scapula, and mid back. Lesions can develop days to years after exposure. The clinical appearance is that of an atrophic plaque that can have ulceration and telangiectasia (72).

**HISTOPATHOLOGY.** In early radiation dermatitis, there is intracellular edema of the epidermis with pyknosis of the nuclei of epidermal and adnexal cells. An inflammatory infiltrate is present throughout the dermis and may permeate the epidermis. Some of the blood vessels are dilated, whereas others, especially large ones in the deep dermis, show edema of their walls, endothelial proliferation, and even thrombosis. The collagen bundles are edematous. In cases with blisters, the degenerated epidermis is detached from the dermis, and there may be ulceration, with necrosis and neutrophilic infiltration.

In late radiation dermatitis, the epidermis is irregular, with variable atrophy and hyperplasia, often with hyperkeratosis. The cells of the stratum malpighii may be disordered, with individual cell keratinization, and some of the nuclei may be atypical. The epidermis may also show irregular downward growth and may even grow around telangiectatic vessels, nearly enclosing them. In the dermis, the collagen bundles are swollen and often hyalinized. Large, bizarre, stellate “radiation fibroblasts” may be found, with nuclei that are enlarged, irregular, and hyperchromatic. This “radiation atypia” differs from that seen in neoplasms because the cellularity is low and the atypical nuclei are scattered among other, less atypical cells. Thus, the atypia is “random” rather than “uniform.” Also, there is typically no mitotic activity. Blood vessels in the deep dermis often show fibrous thickening of their walls, nearly or entirely occluding the lumen. Some of the vessels show thrombosis and recanalization. In contrast, the vessels of the upper dermis may be telangiectatic, and there may be lymphedema in the subepidermal region. Hair structures and sebaceous glands are absent, but the sweat glands usually are preserved at least in part, except in areas of severe injury.

**Nephrogenic Systemic Fibrosis**

**CLINICAL SUMMARY.** Nephrogenic systemic fibrosis (NSF) was initially recognized in 1997, described in 2000, and was called nephrogenic fibrosing dermopathy in 2001. The name was subsequently changed to NSF to reflect the systemic involvement of the disease. Development of NSF is linked to the use of gadolinium containing magnetic resonance imaging contrast agents in patients with renal dysfunction (73). Early lesions develop with erythema, edema, and indurated plaques of the trunk or extremities. There are large poorly defined plaques with irregular borders that become firm and indurated. The induration can become severe and disabling. The thickened fibrotic skin which develops eventually can lead to joint contractures and immobility. Early on there are edema and indurated plaques of the trunk or extremities. There are large poorly defined plaques with irregular borders that become firm and indurated. The induration can become severe and disabling. The thickened fibrotic skin which develops eventually can lead to joint contractures and immobility. Early on there are edema and indurated plaques of the trunk or extremities. There are large poorly defined plaques with irregular borders that become firm and indurated. The induration can become severe and disabling. The thickened fibrotic skin which develops eventually can lead to joint contractures and immobility. Early on there are edema and indurated plaques of the trunk or extremities. There are large poorly defined plaques with irregular borders that become firm and indurated. The induration can become severe and disabling.

**Pathogenesis.** Yellow scleral plaques can also occur. The pathogenesis of...
NSF relates to increased collagen deposition and fibrosis that affects multiple organ systems including the lungs and heart. Skeletal muscle, the kidney, testes, and dura have also been affected. Development of NSF has been linked to decreased renal function (acute and chronic) and proinflammatory events such as surgical procedures (74). It clinically has overlap features with scleroderma and scleromyxedema. However, the patients lack antibodies to Scl-70 and they also lack the paraproteinemia that is associated with scleromyxedema. The etiology is unclear but some studies have suggested that a circulating fibrocyte may play a role in the formation of the extensive fibrosing plaques.

HISTOPATHOLOGY. The histopathologic findings are essentially indistinguishable from those seen in scleromyxedema (75). There is a proliferation of spindled cells within the dermis and occasionally extending into the subcutaneous tissue. The epidermis is unaffected. The degree of cellularity and mucin deposition is variable depending on the age of the lesion. Calcification and osseous metaplasia may occur in longstanding lesions. Characteristically, the spindle cells are positive with antibodies to CD34 and procollagen I. Early lesions show collagen bundles with edema and varying amounts of mucin. Elastic fibers are increased. Later lesions show thickened collagen bundles and there are smaller clefts between collagen bundles, but the clefts are maintained (76,77). Since these findings are indistinguishable from scleromyxedema, that diagnosis must be differentiated based on clinical findings. Scleroderma and scleredema fail to reveal the spindle cell hyper-cellularity as one sees in nephrogenic systemic fibrosis.

**Regressing Melanoma**

See Clin. Fig. VF1.e and Figs. VF1.n, o.

**Clin. Fig. VF1.e.** Regressing melanoma. The gray to skin colored area in the center of this asymmetrical variegated pigmented plaque is an area of partial regression. Note the lack of symmetry in this lesion compared to benign nevi including halo nevi.

**Fig. VF1.n.** Regression within a melanoma, low power. The papillary dermis is widened by fibroplasia which represents an area of regression of a portion of the radial growth phase of the tumor. This area of regression was part of a larger lesion, however occasionally an entirely of sub totally regressed melanoma can present with this histology.

**Fig. VF1.o.** Regression within a melanoma, medium power. Regression in melanoma is characterized by an expanded papillary dermis which shows delicate fibroplasia as well as edema. There is an increased number of small mature vascular channels, with a variable lymphocytic infiltrate and usually with pigment-laden macrophages.
**VF. Dermal Matrix Fiber Disorders**

Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Superficial Scar (e.g., Biopsy Site Reaction)

It is important to recognize a scar in the dermis, because this can be a clue to a prior biopsy for example of a neoplasm at the site.

**Conditions to consider in the differential diagnosis:**
- scar, keloid
- scleroderma/morphea
- sclerodermoid graft versus host disease
- scleromyxedema
- scleredema
- nephrogenic fibrosing dermopathy
- phytonadione-induced pseudoscleroderma
- necrobiosis lipoidica
- eosinophilic fasciitis
- radiation fibrosis
- regressing lesion (melanoma, other tumors)
- fibromatosis
- acrodermatitis chronica atrophicans

facial hemiatrophy
chronic lymphedema
necrobiosis lipoidica
acro-osteolysis
Scleroderma

**VF2 Fibers Disorders, Collagen Reduced**

Collagen may be reduced focally or diffusely as part of an inborn error of collagen fiber metabolism, or as an acquired phenomenon. Focal dermal hypoplasia is a prototypic example (78).

**Focal Dermal Hypoplasia (Goltz Syndrome)**

**CLINICAL SUMMARY.** Focal dermal hypoplasia syndrome, or Goltz syndrome, an X-linked dominant syndrome lethal in homozygous males. Therefore, the syndrome occurs largely in females. It is caused by mutations in the PORCN gene located on chromosome...
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Xp11.23. This gene encodes an O-acyltransferase that affects Wnt signaling proteins required for fibroblast proliferation and osteogenesis. The cutaneous manifestations include widely distributed linear areas of hypoplasia of the skin resembling striae distensae; soft, yellow nodules, often in linear arrangement; and large ulcers due to congenital absence of skin that gradually heal with atrophy. The skin lesions often follow Blaschko’s lines. The presence of fine, parallel, vertical striations in the metaphysis of long bones on radiography, referred to as osteopathia striata, is a reliable diagnostic marker of Goltz’s syndrome. Ocular and dental malformations can also occur (79).

**HISTOPATHOLOGY.** The linear areas of hypoplasia of the skin show a marked diminution in the thickness of the dermis, the collagen being present as thin fibers not united into bundles. The soft, yellow nodules represent accumulations of fat that largely replace the dermis, so that the subcutaneous fat extends upward to the epidermis, partially separated only by a few wisps of collagen.

**Conditions to consider in the differential diagnosis:**
- Ehlers–Danlos syndrome
- Marfan’s syndrome
- Penicillamine-induced atrophy
- Striae distensae
- Aplasia cutis
- Focal dermal hypoplasia (Goltz)
- Atrophoderma (Pasini and Pierini)
- Relapsing polychondritis (type II collagen degeneration of cartilage)

**Fig. VF2.a.** Focal dermal hypoplasia syndrome (Goltz), low power. The dermis is essentially absent. The epidermis in this example shows reactive changes.

**Fig. VF2.b.** Focal dermal hypoplasia syndrome (Goltz), medium power. Lobules of the subcutaneous fat extend up to the basal layer of the epidermis, partially separated only by a few wisps of collagen.

**Clin. Fig. VF2.** Atrophoderma. Sharply demarcated brown plaques with cliff-drop borders on the trunk are typical.
Abnormal elastic fibers are increased focally in the dermis and may become calcified as in pseudoxanthoma elasticum, or there is diffuse elastosis in the superficial reticular dermis of sun-exposed skin. Pseudoxanthoma elasticum is a good example.

**Pseudoxanthoma Elasticum**

In this disorder, genetically abnormal elastic fibers with a tendency toward calcification occur in the skin and

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**Clin. Fig. VF3.a.** *Pseudoxanthoma elasticum.* An ophthalmologist detected angioid streaks in the retina of a middle-aged woman.

**Clin. Fig. VF3.b.** *Pseudoxanthoma elasticum.* Referral to dermatology confirmed the diagnosis of PXE with multiple yellowish waxy papules present in her axillae as shown here as well as in her antecubital fossae and neck region.

**Fig. VF3.a.** *Pseudoxanthoma elasticum, low power.* In this example, there is little calcification. The architecture of the reticular dermis appears subtly altered at scanning magnification.

**Fig. VF3.b.** *Pseudoxanthoma elasticum, medium power.* The collagen fibers are not arranged in their normal interlacing pattern. (continues)
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Calcified elastic fibers

Fig. VF3.c

Fig. VF3.d

Bramble bush pattern

Fig. VF3.f

Fig. VF3.c. *Pseudoxanthoma elasticum, high power.* At this power, the abnormal fibers, here staining a bright pink color, can be appreciated.

Fig. VF3.d. *Pseudoxanthoma elasticum, low power.* An elastic stain reveals the tangle of abnormal elastic fibers in the dermis.

Fig. VF3.e. *Pseudoxanthoma elasticum, medium power.* The fibers are abnormally short, swollen, and irregularly clumped.

Fig. VF3.f. *Pseudoxanthoma elasticum, high power.* In penicillamine-induced pseudoxanthoma elasticum, the elastic fibers are coarse and fragmented with a “bramble-bush” appearance (Verhoeff-van Gieson stain).

frequently also in the retina and within the walls of arteries, particularly the gastric mucosal arteries, coronary arteries, and large peripheral arteries. The inheritance is autosomal recessive. Pseudoxanthoma elasticum is caused by mutations in the ABCC6 gene, which encodes a putative transmembrane efflux transporter that is primarily expressed in the liver (81). The cutaneous lesions usually appear first in the second or third decade of life and are generally progressive in extent and severity. They consist of soft, yellowish, coalescing papules, and the affected skin appears loose and wrinkled. The sides of the neck, the axillae, and the groin are the most common sites of lesions. In the eyes, so-called angioid streaks of the fundi may cause progressive impairment of vision. Involvement of the arteries of the gastric mucosa may lead to gastric hemorrhage; coronary artery involvement may result in attacks of angina pectoris; involvement of the large peripheral arteries may cause intermittent claudication. Radiologic examination in such cases reveals extensive calcification of the affected arteries.
HISTOPATHOLOGY. Histologic examination of the involved skin reveals in the middle and lower thirds of the dermis considerable accumulations of swollen and irregularly clumped fibers staining like elastic fibers with orcein or Verhoeff’s stain. With routine hematoxylin-eosin, the altered elastic fibers in stain faintly basophilic because of their calcium imbibition, and staining for calcium with the von Kossa method shows them well. In the vicinity of the altered elastic fibers, there may be accumulations of a slightly basophilic mucoid material, which stains strongly positive with the colloidal iron reaction or with alcian blue. In some cases with pronounced elastic tissue calcification, a macrophage and giant cell reaction may be present.

The angioid streaks occur in Bruch’s membrane, which is located between the retina and the choroid and possesses numerous elastic fibers in its outer portion, the lamina elastica. Calcification of these fibers causes fissures to form in the lamina elastica. These fissures result in repeated hemorrhages and exudates, which in turn cause scarring and pigment shifting in the retina. Gastric bleeding is the result of calcification of elastic fibers in the thin-walled arteries located immediately beneath the gastric mucosa. The internal elastic lamina is particularly affected. In muscular arteries, such as the coronary arteries and the large peripheral arteries, calcification begins in the internal and external elastic laminae, leading to their fragmentation, and subsequently extends to the media and intima.

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channel, they maintain their normal staining characteristics, but as they approach the epidermal surface they may not stain as expected with elastic stains.

**Reactive Perforating Collagenosis**
See Figs. VF5.d–f.

**Perforating Folliculitis**
See Fig. VF5.g.

**Conditions to consider in the differential diagnosis:**
-elastosis perforans serpiginosum
-Kyrle’s disease
-perforating folliculitis
-reactive perforating collagenosis
-perforating disorder of renal failure and diabetes
-perforating calcific elastosis
-perforating granuloma annulare

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**Clin. Fig. VF5.** *Elastosis perforans serpiginosa.* Papules in an annular and serpiginous configuration appeared on the volar forearms in a healthy adult female.

**Fig. VF5.a.** *Elastosis perforans serpiginosa, low power.* There is a narrow, curved channel extending through an acanthotic epidermis. The upper portion of the channel contains basophilic degenerate material. The lower portion of the channel contains elastic fibers, in addition to the degenerate material. (E. Heilman & R. Friedman).

**Fig. VF5.b.** *Elastosis perforans serpiginosa, high power.* There are thickened degenerated elastic fibers at the origin of the epidermal channel. (E. Heilman & R. Friedman).

**Fig. VF5.c.** *Elastosis perforans serpiginosum, high power, Verhoff Van Giezen stain.* Black elastic fibers are seen perforating through the epidermis.
The dermis serves as a reaction site for a variety of inflammatory, infiltrative, and desmoplastic processes, which may include accumulations of matrix molecules that may either be indigenous to the normal dermis, or foreign to it.

1. Increased Normal Nonfibrous Matrix Constituents
2. Increased Material Not Normally Present in the Dermis
3. Parasitic Infestations of the Dermis and/or Subcutis

**DEPOSITION OF MATERIAL IN THE DERMIS**

**Fig. VF5.d.** Reactive perforating collag enosis, low power. A cup-shaped channel containing degenerated collagen bundles and basophilic material.

**Fig. VF5.e.** Reactive perforating collag enosis, trichrome stain, medium power. Blue stained collagen fibers perforating the channel and extending to the surface.

**Fig. VF5.f.** Reactive perforating collag enosis, trichrome stain, medium power. Blue stained collagen fibers perforating the channel and extending to the surface.

**Fig. VF5.g.** Perforating folliculitis, medium power. A dilated follicular unit contains a keratotic plug with an admixture of basophilic debris. The follicular epithelium is perforated, and there are degenerated collagen fibers in the adjacent dermis. (E. Heilman & R. Friedman).
lymphocytes, plasma cells, and eosinophils. Digital mucous cysts and focal mucinosis (86) are common examples.

**Digital Mucous Cysts and Focal Mucinosis**

**CLINICAL SUMMARY.** Two types of digital mucous cysts exist. One type presents as a pale papule, analogous to focal mucinosis. It differs from focal mucinosis only by its location near the proximal nail fold and by its greater tendency to fluctuate (87). The other type is located on the dorsum of a finger near the distal interphalangeal joint and is due to a herniation of the joint lining, thus representing a ganglion (88). Digital mucous cysts commonly cause a longitudinal indentation in the nail plate.

**HISTOPATHOLOGY.** The myxomatous type of digital mucous cyst in its early stage has the same histologic appearance as that seen in focal mucinosis, namely, an ill-defined area of mucinous material. Subsequently, multiple clefts form and then coalesce into one large cystic space containing mucin composed largely of hyaluronic acid, which stains with alcian blue and colloidal iron. The cystic space in early lesions is separated from the epidermis by mucinous stroma but in older lesions is found in a subepidermal location with thinning of the overlying epidermis. The collagen at the periphery of the cyst appears compressed. No lining of the cyst wall is apparent. In the ganglion type of digital mucous cyst, on surgical exploration the cyst shows a flattened lining and evidence of a pedicle leading to the joint spaces.
**Mucinosis in Lupus Erythematosus**

See Fig. VG1.d.

**Mucinoses**

Six types of primary cutaneous mucinosis include: (1) generalized myxedema; (2) pretibial myxedema; (3) lichen myxodematosus or papular mucinosis; (4) reticular erythematous mucinosis or plaquelike mucinosis; (5) self-healing juvenile cutaneous mucinosis; and (6) scleremia. Regular demonstration of the presence of mucin in the dermis is possible only in pretibial myxedema, in self-healing juvenile cutaneous mucinosis, and in lichen myxematosus. In reticular erythematous mucinosis, it is possible in most cases. In generalized myxedema, the amount of mucin usually is too small to be demonstrable, and in scleremia, mucin may be present only in the early stage.

**Pretibial Myxedema**

**CLINICAL FEATURES.** In pretibial myxedema, the lesions are limited to the anterior aspects of the legs, but they may extend to the dorsa of the feet and rarely the forearms. They consist of raised, nodular, yellow, waxy plaques with prominent follicular openings that give a peau d’orange appearance.

Pretibial myxedema usually occurs in association with thyrotoxicosis and not infrequently becomes more pronounced after treatment of the thyrotoxicosis. Rarely, it occurs in nonthyrotoxic thyroid disease such as chronic lymphocytic thyroiditis.

**HISTOPATHOLOGY.** The epidermis and papillary dermis are usually normal. Mucin in large amounts is present in the dermis, particularly in the upper half. As a result, the dermis is greatly thickened. The mucin occurs not only as individual threads and granules but also as extensive deposits resulting in the splitting up of collagen bundles into fibers and wide separation of the fibers. As a result of shrinkage of the mucin during the process of fixation and dehydration, there are empty spaces within the mucin deposits. The number of fibroblasts is not increased as a rule, but in areas in which there is much mucin, some fibroblasts have a stellate shape and are then referred to as mucoblasts. A perivascular infiltrate of lymphocytes may be seen in some cases and mast cells are moderately increased in number.

**Myxedema**

See Figs. VG1.e, f.

**Scleremia**

See Figs. VG1.g–i.

**Lichen Myxematosus and Scleromyxedema**

According to a modern classification, two main clinicopathologic subsets of lichen myxematosus (papular mucinosis) should be distinguished: a generalized papular and scleroderoid form, also called scleromyxedema, and a localized papular form (89). Diagnosis of scleromyxedema should fulfill the following criteria: (1) generalized...
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

papular and sclerodermoid eruption; (2) mucin deposition, fibroblast proliferation, and fibrosis; (3) monoclonal gammopathy; and (4) the absence of thyroid disease. The criteria for localized lichen myxedematosus are as follows: (1) papular or nodular/plaque eruption; (2) mucin deposition with variable fibroblast proliferation; and (3) the absence of both monoclonal gammopathy and thyroid disease.

Histologically, in the diffusely thickened skin of scleromyxedema, there is extensive proliferation of fibroblasts throughout the dermis, associated with irregularly arranged bundles of collagen. In many areas, the collagen bundles are split into individual fibers by mucin. As a rule, the amount of mucin is greater in the upper half than in the lower half of the dermis. A paraprotein, usually IgG, is present in the sera of most patients with scleromyxedema, and is often associated with hyperplasia of bone marrow plasma cells, which synthesize the monoclonal IgG. In some cases, these cells may be atypical, however frank multiple myeloma is uncommon.

In localized lichen myxedematosus (papular mucinosis), clinically the patients exhibit small, firm, waxy papules, which may become confluent, confined to only a few sites, usually upper and lower limbs and trunk. Histopathologic examination reveals mucin deposition with variable fibroblast proliferation without sclerotic features, paraproteinemia, systemic involvement, or thyroid disease. Clinicopathological correlation may be required to establish a definitive diagnosis.

**Conditions to consider in the differential diagnosis:**
- granuloma annulare
- pretibial myxedema
- generalized myxedema
- juvenile cutaneous mucinosis
- papular mucinosis (lichen myxedematosus)
- scleromyxedema
- reticulated erythematous mucinosis (REM)
- scleredema
- focal dermal mucinosis
- digital mucous cyst/myxoid cyst
- cutaneous myxoma
- mucocoele, mucinous mucosal cyst
- lupus erythematosus
- hereditary progressive mucinous histiocytosis

**Fig. VG1.g.** *Scleredema, low power.* The dermis is greatly thickened. The collagen bundles are thickened and separated by clear spaces, causing “fenestration” of the collagen.

**Fig. VG1.h.** *Scleredema, medium power, colloidal iron.* The separation of collagen bundles is not accompanied by an increase in cellularity.

**Fig. VG1.i.** *Scleredema, high power, colloidal iron.* In this and the previous figure, the separation is seen to be due to interstitial mucin, which is highlighted by the colloidal iron reaction.
Deposition of Material in the Dermis

Perivascul lar, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Fig. VG1.j. Scleromyxedema, low power. The skin is diffusely thickened, and there is an appearance of increased cellularity.

Fig. VG1.k. Scleromyxedema, medium power. The increased cellularity is due to extensive proliferation of fibroblasts throughout the dermis, associated with irregularly arranged bundles of collagen.

Fig. VG1.l. Scleromyxedema, high power. The collagen bundles tend to be split into individual fibers by mucin. As a rule, the amount of mucin is greater in the upper half than in the lower half of the dermis.

Increased Material Not Normally Present in the Dermis

Materials not present in substantial amounts in the normal dermis are deposited, as crystals (gout), amorphous deposits (calcinosis), hyaline material (colloid milium, amyloidosis, porphyria), or as pigments. Gout is prototypic (90).

Gout

CLINICAL SUMMARY. In the early stage of gout, there usually are irregularly recurring attacks of acute arthritis. In the late stage, deposits of monosodium urate form within and around various joints, leading to chronic arthritis with destruction in the joints and the adjoining bone. During this late stage, urate deposits, called tophi, may occur in the dermis and subcutaneous tissue. Tophi are observed most commonly on the helix of the ears, over the bursae of the elbows, and on the fingers and toes. They may attain a diameter of several centimeters; and when large, may discharge a chalky material. In rare instances, gout may present as tophi on the fingertips or as panniculitis on the legs without the coexistence of a gouty arthritis.

HISTOPATHOLOGY. For the histologic examination of tophi, fixation in absolute ethanol or an ethanol-based fixative, such as Carnoy's fluid, is preferable to fixation in formalin; aqueous fixatives such as formalin dissolve the characteristic urate crystals, leaving only amorphous material which, however, can usually be recognized as the residue of a tophus because of the characteristic rim of foreign-body giant cells and macrophages which surrounds the aggregates of amorphous material. Anhydrous tissue processing is also important to preserve the urate crystals. On fixation in alcohol, tophi can be seen to consist of variously sized, sharply demarcated aggregates of needle-shaped urate crystals lying closely packed in the form of bundles or sheaves. The crystals often have a brownish color and are doubly refractile on polariscopic examination.

Oxalosis

CLINICAL SUMMARY. Deposition of oxalate crystals within the skin is seen with hyperoxaluria (91). Hyperoxaluria may be primary (familial) or secondary (acquired from exogenous sources or underlying disease). There are three types of primary hyperoxaluria: type I is a deficiency...
This elderly female had a 17 year history of large, globular tophi which become tender and required drainage.

**Fig. VG2.a.** *Gout.* Irregular masses of pale material are present in the dermis.

**Fig. VG2.b.** *Gout, medium power.* Granulomatous inflammation surrounds the amorphous material.

**Fig. VG2.c, d.** *Gout, high power.* The material consists of narrow elongated crystals, best seen post fixation in alcohol. After aqueous fixation, as here, a negative impression of the dissolved crystals can usually be discerned. There is a surrounding foreign-body giant cell reaction.
Fig. VG2.e. *Oxalosis, low power.* The epidermis is ulcerated and there is superficial dermal necrosis. Beneath the ulceration, there is a medium size blood vessel with a thickened wall.

Fig. VG2.f. *Oxalosis, medium power.* At the base of the tissue of the same specimen, there is a detached piece of connective tissue which contains a medium sized vessel that shows marked thickening of the vascular wall with a very small lumen. Within the wall of the vessel are large aggregates of crystalline material.

Fig. VG2.g. *Oxalosis, medium power.* The blood vessel seen in figure 2f visualized with polarized lights reveals refractile crystalline material in the vessel wall.

Fig. VG2.h. *Oxalosis, high power.* Upon close inspection, some of the crystals show a radial arrangement.

in the enzyme alanine glyoxalate aminotransferase; type II is a deficiency in D-glycerate dehydrogenase; type III is secondary to increased oxalate absorption without any known intestinal pathology. Secondary hyperoxaluria can be secondary to increased absorption of oxalates, secondary to small bowel resection or inflammatory bowel disease, end-stage renal disease, pyridoxine deficiency and excess intake of oxalate or oxalate precursors. This latter category includes ethylene glycol poisoning, methoxyflurane anesthesia, or large doses of ascorbic acid.

With hyperoxaluria, oxalate will precipitate as calcium oxalate in virtually all tissues of the body. There are some preferential sites including the bones which have metabolic activity, and tissues where calcium modulates electric current, such as myocardium and smooth muscle of blood vessels. Patients with primary hyperoxaluria generally develop renal failure, cardiac disease, severe peripheral vascular ischemia, retinal deposits, and liver failure. Without a liver–kidney transplant, many patients die in the third to fourth decades.
Skin manifestations generally are secondary to calcium oxalate deposition in blood vessels resulting in livedo reticularis, ulcerations, skin infarctions, acrocyanosis, or gangrene (92,93). Calcified nodules may also be seen.

**HISTOPATHOLOGY.** Yellow-brown calcium oxalate deposits are most commonly seen within the walls of both small and large blood vessels. Crystals may also be seen deposited as nodular aggregates in the subcutaneous tissue. The crystals characteristically show a radial array or rosette-like appearance. The birefringent crystalline material is highlighted with polaroscopy. Frequently there is an associated sparse mononuclear cell infiltrate as well as multinucleated giant cells. The overlying epidermis and superficial dermis may show secondary necrosis and/or ulceration (94).

**Colloid Milium**

See Clin. Fig. VG2.b and Figs. VG2.i, j.

**Idiopathic Calcinosis Cutis**

**CLINICAL SUMMARY.** Calcinosis cutis is often associated with a connective tissue disease such as scleroderma. In some instances of this *dystrophic calcinosis cutis*, the underlying disease may be mild and can be overlooked unless specifically searched for. There remain cases of idiopathic calcinosis cutis that resemble dystrophic calcinosis cutis but there is no underlying disease. Tumoral calcinosis is regarded as a special manifestation of idiopathic calcinosis cutis (95). It consists of numerous large, subcutaneous, calcified masses that may be associated with papular and nodular skin lesions of calcinosis. The disease usually is familial and is associated with hyperphosphatemia. Otherwise, the resemblance of tumoral calcinosis to the dystrophic calcinosis universalis observed with dermatomyositis is great.

**HISTOPATHOLOGY.** Tumoral calcinosis shows in the subcutaneous tissue large masses of calcium surrounded by a foreign-body reaction. Intradermal aggregates are present in some cases. Discharge of calcium may take place through areas of ulceration or by means of transepidermal elimination.

**Cryoglobulinemia**

See Fig. VG2.n.
Clin. Fig. VG2.c. Calcinosis cutis. Firm, grouped whitish papules on the trunk of an individual without obvious predisposing factors for calcification.

Fig. VG2.k. Idiopathic calcinosis cutis, low power. A tumoral mass of calcium is present in the dermis. There are no obvious changes of associated connective tissue disease, or other predisposing condition for dystrophic calcification.

Fig. VG2.l. Idiopathic calcinosis cutis, medium power. An amorphous mass of calcium in the dermis, with an adjacent reaction.

Fig. VG2.m. Idiopathic calcinosis cutis, high power. There are irregular aggregates of purple material without nuclei.

Keratin Granuloma
See Figs. VG2.o–q.

Suture Granuloma
See Figs. VG2.r–t.

Minocycline Pigmentation

CLINICAL SUMMARY. Presenting as macular blue-black pigmentation of the skin, the pigmentation is often seen in a perifollicular location or at the sites of prior inflammation such as old acne scars. The pigmentation is most prominent in sun exposed sites, such as the face. Diffuse pigmentation is another clinical variation exhibiting a “slate-grey” hue most commonly on the extremities, with the legs exhibiting the most striking change, or the pigmentation may be generalized over the body. This latter presentation also occurs with medications other than minocycline (96,97). Other parts of the body affected by minocycline pigmentation include the nail beds, sclera, teeth, thyroid, and bone (98).

HISTOPATHOLOGY. The epidermis may show an increase in basilar pigment; this can be seen in all clinical types but is most striking in the diffuse type. In the dermis, there are...
aggregates of brown-black granules, in macrophages and in a perivascular and peri-eccrine locations. Pigment granules may be found only in the subcutis. The granules stain with silver (Fontana-Masson) and Iron (Perls') stains. The differential diagnosis includes post-inflammatory hyperpigmentation and other drug causes of dermal pigmentation include amiodarone, anti-malarials, cyclophosphamide, phenytoin, chlorpromazine, gold, silver, and clofazimine (99).

Conditions to consider in the differential diagnosis:

- Gout
- Osteomalacia
- Colloid milium
- Calcinosis cutis
- Calcinosis universalis, circumspecta (scleroderma)
- Tumoral calcinosus
- Idiopathic calcification of the scrotum
- Subepidermal calcified nodule
- Calciphylaxis
- Monckeberg's calcification
- Polyarteritis nodosa
- Amyloidosis
- Dermal pigments
- Minocycline
- Argyria
- Chrysiasis
mercury pigmentation
hemochromatosis
alkaptonuric ochronosis
calcaneal pettechiae (hemoglobin)
lipoid proteinosis (hyalinosis cutis et mucosae, Urbach–Wiethe)
cryoglobulinemia
porphyria cutanea tarda

foreign material—dirt, glass, paraffin, grease, etc
tattoo reactions
silicone, talc, starch
cactus, sea-urchin, hair granulomas
intrallesional steroids
vaccines
Hunter’s syndrome (lysosomal storage granules)
V. Perivascular, Diffuse and Granulomatous Infiltrates of the Reticular Dermis

Clin. Fig. VG2.d. *Minocycline pigmentation.* Note grayish-blue discoloration resulting from pigmentation of ear cartilage.

Fig. VG2.u. *Minocycline pigmentation.* Pigment granules in a perivascular location in the dermis.

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**VG3 Parasitic Infestations of the Dermis and/or Subcutis**

Macroskopically visible parasitic agents may infest the dermis and subcutis. Creeping eruption (larva migrans) is a good example (100).

**Larva Migrans Eruption**

Larva migrans eruption, commonly known as creeping eruption, is caused by filariform larvae of the dog and cat hookworms *Ancylostoma braziliensis* and *A. caninum*. Migration is manifested by an irregularly linear, thin, raised burrow, 2 to 3 mm wide. The larva moves a few millimeters per day. The eruption is self-limited because humans are abnormal hosts. The feet and buttocks are the areas most commonly involved. Most cases in developed countries are seen in travelers. The organism is transmitted when bare skin comes in contact with contaminated soil (101).

**HISTOPATHOLOGY.** The larva is found in a specimen taken from just beyond the leading edge of the track. It is located in a burrow in the superficial epidermis. The lesion, aside from the larva which is often not observed in the biopsies, shows spongiosis and intraepidermal vesicles containing necrotic keratinocytes. The epidermis and the upper dermis contain a chronic inflammatory infiltrate with many eosinophils.

**Conditions to consider in the differential diagnosis:**

- *larva migrans* (*Ancylostoma*)
- subcutaneous dirofilariasis
- onchocerciasis
- strongyloidiasis
- *schistosomiasis*
- subcutaneous cysticercosis
- myiasis
Clin. Fig. VG3. *Larva migrans.* Shortly after vacationing in Jamaica, a patient noticed a pruritic creeping movement which manifested as a serpiginous plaque. Aggressive cryotherapy resulted in resolution.


References


Tumors and Cysts of the Dermis and Subcutis

Neoplasms in the reticular dermis may arise from any of the tissues included in the dermis—lymphoreticular tissue, connective tissue, and epithelial tissue of the skin appendages. In addition, metastases commonly present in the dermis and subcutis. A neoplastic nodule is a circumscribed collection of neoplastic cells in the dermis. Abscesses, granulomas, and cysts may also present as nodules. Cysts are considered separately. In general, neoplastic nodules can be differentiated from reactive and inflammatory nodules by the presence of a monotonous population of cells consistent with a clonal proliferation, while inflammatory nodules are composed of inflammatory cell types (lymphocytes, neutrophils, histiocytes, etc.), generally in a heterogeneous mixture.

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The cells of this group of tumors range in size from that of a small lymphocyte to approximately that of a histiocyte. These tumors in general are characterized by having very scant cytoplasm, so that the nuclei are closely apposed to one another and may even mold on one another as is characteristic in small cell carcinomas of the lung. The nuclei, while larger than those of lymphocytes (except in the case of a well-differentiated small cell lymphoma) are relatively small by virtue of having compact hyperchromatic chromatin and, usually, absent or inconspicuous nucleoli.

1. Tumors of Lymphocytes or Hemopoietic Cells
2. Tumors of Lymphocytes and Mixed Cell Types
3. Tumors of Plasma Cells
4. Small Round Cell Tumors

**VIA1 Tumors of Lymphocytes or Hemopoietic Cells**

Nodular infiltrates or extensive diffuse infiltrates of normal and/or atypical lymphocytes are found in the dermis. In a single center follow-up study of 299 patients with primary cutaneous lymphomas, 63% expressed a T-cell phenotype; and 37%, a B-cell phenotype (1). The most common primary cutaneous T-cell entities were mycosis fungoides (31%, with an overall disease-specific 5-year survival of 80%), lymphomatoid papulosis (LyP) (16%, with a 100% survival), and anaplastic large cell lymphoma (9%, 92% survival). The most common primary cutaneous B-cell entities were follicular center cell lymphoma (17%, with a 98% survival), marginal zone B-cell lymphoma (10%, 100% survival), and diffuse large B-cell lymphoma, leg type (9%, 63% survival). Primary cutaneous mantle cell lymphoma, with a very poor prognosis, is very rare (2). Cutaneous follicular center cell lymphoma (FL) is prototypic (3).

**Cutaneous B-Cell Lymphoma**

**CLINICAL SUMMARY.** The clinical presentation of primary cutaneous FL stereotypically comprises one or several nodules situated in a single area, most often the skin of the scalp or forehead. The lesions are red to purple and can have intact or ulcerated surfaces. In general, the prognosis of cutaneous B-cell lymphomas is favorable if the disease is primary and unfavorable if the skin is secondarily involved from a nodal or systemic lymphoma. Spread to the skin is observed in about 4% of the cases of nodal FL.

**HISTOPATHOLOGY.** The infiltrates of cutaneous B-cell lymphomas are most easily diagnosed when they are “bottom-heavy” (the larger proportion of the tumor is in the lower dermis or subcutaneous fat), but top-heavy...
VI. Tumors and Cysts of the Dermis and Subcutis

patterns also occur. In cutaneous FL, the neoplastic follicles can be of uniform size, with mantles that are thin or absent, resulting in coalescence of follicles. Tingible body macrophages, which represent cells engulfing the remnants of apoptotic lymphocytes, are rare. In contrast, a heterogeneous composition of follicles, with many tingible body macrophages and well-formed mantles of small lymphocytes around them, would favor a benign interpretation. The mitotic rate is low in cases in which small cleaved cells (centrocytes) predominate, and higher as the proportion of large noncleaved cells or centroblasts increases. Most of the many variations of FL that occur in lymph nodes, such as irregularly shaped follicles, follicles with serrated outlines, follicles with thick mantles, conspicuous follicular dendritic cells, many tingible body macrophages, and follicles with extracellular amorphous material, can also occur in cutaneous lesions. In lesions with an immunophenotype resembling MALToma (marginal zone lymphoma), the cells can resemble centrocytes, which are small lymphocytes with indented nuclei and varying amounts of pale cytoplasm, and/or may be plasmacytoid.

By immunohistochemistry, the B cells of cutaneous FL may express monotypic cell surface immunoglobulin (more commonly in frozen sections or by flow cytometry), or may fail to express immunoglobulin at all (so-called “immunoglobulin-negative” FL). Light chain restriction can be used to demonstrate clonality. Genotypic studies can detect clonal rearrangement of the immunoglobulin heavy or light chain genes, or both. Cutaneous FL express the B-cell markers CD19+, CD20+, CD22+, and are bcl-2+/–, bcl-6+, and CD10+/–. The immunophenotype of marginal zone lymphoma is positive for the B-cell markers CD19+, CD20+, CD22+, CD79a+, and is bcl-2+, CD5–, CD10–, bcl-6–, CD23–. In contrast, reactive germinal centers are bcl-6+, bcl-2–. Large cell lymphomas that occur most commonly on the leg of women, but also on other sites, and are therefore classified as DLBCL, leg type, have the immunphenotype CD20+, CD70a+, CD10–, CD138–, bcl-6+/–, bcl2+, MUM-1/RF-4+. Mantle cell lymphomas are typically CD20+, CD10–, CD23–, cyclin D+, bcl-6–, and characteristically but not always CD5+. The vast majority of mantle cell lymphomas have a translocation involving the cyclin D locus with subsequent overexpression of this gene (4–7).

Cutaneous Diffuse B-Cell Lymphoma

See Figs. VIA1.c–f.
**Fig. VIA1.c.** *Cutaneous diffuse B-cell lymphoma, low power.* There is a dense dermal infiltrate of basophilic cells which does not involve the overlying epidermis. Typically, in cutaneous B-cell lymphoma, the infiltrate is “bottom-heavy,” meaning that a significant portion of the infiltrate involves the lower dermis.

**Fig. VIA1.d.** *Cutaneous diffuse B-cell lymphoma, medium power.* The dermal infiltrate may be nodular in appearance, however, as seen here the cells frequently permeate between bundles of reticular dermal collagen.

**Fig. VIA1.e.** *Cutaneous diffuse B-cell lymphoma, high power.* High power reveals cytologically atypical lymphoid cells admixed with nuclear fragments. With little pressure from a punch biopsy, these cells frequently show crush artifact.

**Fig. VIA1.f.** *Cutaneous diffuse B-cell lymphoma, high power.* Not all cells in cutaneous B-cell lymphoma are large and atypical. In this example, the cells are small, hyperchromatic, and monotonous in appearance.
Primary Cutaneous Marginal Zone Lymphoma

See Figs. VIA1.g–i.

A dense tumor with a "bottom heavy" configuration in the dermis and subcutis.

The tumor comprises sheets of monotonous small cells.

The cells have a plasmacytoid configuration, with eccentric purple cytoplasm.

Cutaneous T-Cell Lymphoma, Tumor Stage

Mycosis fungoides is the prototype of cutaneous T-cell lymphomas (CTCL). From an initial patch and plaque stage (illustrated in IID1, IIF1, and IIF5), the lesions may progress to a tumor stage in which the dermal infiltrates
become diffuse, epidermotropism may be lost, and the cells are larger. The immunophenotype is typically CDE2+, CD3+, CD4+, CD5+, CD45RO+, CD8−, CD30−. During progression of the disease, loss of CD2, CD5, and CD7 can occur, and CD30 expression may be acquired. The CD4+ cells may have a cytotoxic phenotype of TIA-1+, granzyme+. Occasionally the phenotype is CD8+ CD4− (8).

**Conditions to consider in the differential diagnosis:**
cutaneous B-cell lymphoma
lymphoblastic lymphoma, B-cell type
small lymphocytic lymphoma
immunocytoma (lymphoplasmacytoid lymphoma)
primary cutaneous follicular lymphoma
diffuse large B-cell lymphoma (centroblastic/immunoblastic)
drug-induced pseudolymphoma
aluminum granuloma
pseudolymphomatous tattoo reaction
leukemia cutis
VI. Tumors and Cysts of the Dermis and Subcutis

VIa2 Tumors of Lymphocytes and Mixed Cell Types

Nodular infiltrates or extensive diffuse infiltrates of normal lymphocytes are found in the dermis. Other reactive cell types (plasma cells, histiocytes) are admixed. B-Cell cutaneous lymphoid hyperplasia is prototypic (9).

B-Cell Cutaneous Lymphoid Hyperplasia (B-CLH, Pseudolymphoma, Lymphocytoma Cutis)

CLINICAL SUMMARY. The term “pseudolymphoma” loosely refers to a group of conditions in which the microscopic appearance of lymphocytic infiltrates in the skin resembles that of one of the cutaneous lymphomas. There are many cutaneous pseudolymphomas, including lymphoid proliferations of B-cell or T-cell composition. B-CLH is often referred simply to as pseudolymphoma, because it was the first simulant of cutaneous lymphoma to be studied comprehensively. In B-CLH, nodules or plaques result from the recapitulation in the skin of the elements found in the cortices of reactive lymph nodes. Clinically, B-CLH generally presents with red to purple nodules or plaques, usually on the face or scalp. Lesions are usually solitary but may be multiple. Patients with multiple lesions often have only a few lesions affecting a circumscribed area (most often the skin of the head or the neck), but rare patients have generalized lesions. Most lesions persist for months or years, sometimes to resolve spontaneously.

HISTOPATHOLOGY. The infiltrates of B-CLH are nodular or diffuse, and involve the dermis and/or the subcutis. A “top-heavy” pattern is often observed at scanning magnification—that is, the infiltrate is denser in the dermis than in the subcutis. Follicles may be distinct or inconspicuous. In the follicular pattern, distinct germinal centers are present, identical in composition to secondary follicles in reactive lymph nodes. These consist of follicular center cells which include small cleaved and large lymphocytes, and tingible body macrophages surrounded by a mantle of small lymphocytes. Mitotic figures are commonly found in these reactive follicles. The polarization seen in reactive lymph nodes is usually not evident. The mantle zone is composed of small lymphocytes. Peripheral to the follicles and their mantles is an admixture of cells. These may include T cells with small but irregularly shaped nuclei, immunoblasts (large cells with large vesicular nuclei and prominent,
central nucleoli), histiocytes and rarely histiocytic giant cells, eosinophils, polyclonal plasma cells, and plasmacytoid monocytes. The venules found in these interfollicular areas resemble the "high endothelial venules" of lymph nodes in that their endothelial cells have protuberant nuclei.

The nonfollicular pattern of B-CLH can present as a nodular or diffuse infiltrate with a mixture of cell types. A *sine qua non* is the presence of follicular center cells, but there are often eosinophils, macrophages, and plasma cells. Hints of follicles are sometimes apparent at scanning magnification as zones of pale-staining cells; the presence of follicular elements in such areas can be confirmed by immunostaining for antigens such as CD35 that recognize follicular dendritic cells, whose processes form a meshwork in lymphoid follicles.

In a study of 24 cases, the lesions were classified according to characteristic histologic features and immunophenotypic staining patterns as follows: 10 cases with presence of germinal center (GC) cell clusters forming well-defined lymphoid follicles; 6 with clusters of GC cells not forming well-defined lymphoid follicles; 1 case of persistent arthropod assault type CLH; 4 cases of CLH with a prominent histiocytic component; and 3 of CLH without specific histologic and immunophenotypic features, that is, nonspecific mixed T-cell and B-cell CLH. Most of the CLH cases did not demonstrate clonal T-cell receptor and/or immunoglobulin heavy chain gene rearrangements except for 3 cases in which long-term follow-up was uneventful (10).

**Conditions to consider in the differential diagnosis:**

*cutaneous lymphoid hyperplasia/lymphocytoma cutis*

Lennert’s (lymphoepithelial) lymphoma

*angioimmunoblastic lymphadenopathy*

*Borrelial lymphocytoma cutis*

*chronic myelogenous leukemia*

**VIA3 Tumors of Plasma Cells**

Nodular plasma cell infiltrates, with scattered lymphocytes. Cutaneous plasmacytoma (11) and multiple myeloma (12) exemplify this reaction pattern.

**Cutaneous Plasmacytoma and Multiple Myeloma**

**CLINICAL SUMMARY.** Cutaneous lesions of multiple myeloma (MM) or plasmacytoma are usually circumscribed, violaceous papules or nodules. Diffusely infiltrated plaques are occasionally observed. Cutaneous deposits of myeloma are rare, occurring in only about 2% of myeloma patients. Patients with myeloma can also develop a variety of nonspecific cutaneous complications (13), including deposits of light-chain derived amyloid (primary systemic amyloidosis), purpuric lesions resulting from monoclonal cryoglobulinemia, diffuse normolipemic plane xanthoma, pyoderma gangrenosum, Sweet’s syndrome, leukocytoclastic vasculitis, and erythema elevatum diutinum.

Monoclonal gammopathies can complicate a variety of other cutaneous diseases, such as scleromyxedema, necrobiotic xanthogranuloma with paraproteinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin lesions), and scleredema. Myeloma supervenes in a small minority of patients with any of these disorders.

**HISTOPATHOLOGY.** In cutaneous lesions of MM and in plasmacytomas, there are monomorphous infiltrates of plasma cells, arrayed as densely cellular nodules or interstitially between collagen bundles. In the nodular...
pattern, clusters of macrophages are sometimes present. Multinucleate plasma cells, plasmacytes with large atypical nuclei, and mitotic figures can be observed. Plasma cell bodies, round eosinophilic fragments of plasma cell cytoplasm, can be present in the background between intact cells, but are not specific for MM. Intranuclear inclusions of immunoglobulin, known as Dutcher bodies, are rare in MM. Infiltrates that are composed of nuclei with a "clock-face" clumping of chromatin typical of mature, or Marshalko-type, plasma cells have been referred to as the plasmacytic variant. Infiltrates that are composed of cells with nuclei that resemble those of immunoblasts are sometimes referred to as plasmablastic plasmacytoma, whereas an even greater degree of nuclear atypia is observed in the anaplastic variant.

**Conditions to consider in the differential diagnosis:**
- cutaneous plasmacytoma
- multiple myeloma

**Cutaneous Small Cell Undifferentiated Carcinoma (Merkel Cell Tumor)**

**CLINICAL SUMMARY.** Cutaneous small cell undifferentiated carcinoma (CSCUC) (Merkel cell, neuroendocrine, or trabecular carcinoma), an uncommon tumor, mostly occurs as a solitary nodule, usually on the head or on the extremities, often in an immunosuppressed or elderly patient. The tumors are usually few in number but occasionally are multiple. The lesions of Merkel cell tumors are firm, nodular, and red-pink. They usually are nonulcerated and range in size from 0.8 to 4.0 cm. The prognosis is quite poor with an overall disease-specific survival of 64%; however, when lymph nodes are pathologically negative, the prognosis improves dramatically to 97% (16).

**HISTOPATHOLOGY.** Tumor cells with scant cytoplasm and plump, round or irregular nuclei are closely spaced in sheets and trabecular patterns, and less commonly in ribbons and festoons. Pseudorosettes are an occasional feature. The nuclear chromatin often is dense and uniformly distributed. In some examples, nuclei focally or uniformly show margination of chromatin. Nucleoli generally are inconspicuous or absent. Nuclear molding may be a feature. Mitoses and nuclear fragments are regular features. In some tumors, the nests of cells are supported by scant, delicate, and paucicellular stroma. Lymphoid infiltrates are common at the margin and focally in the stroma. Contact with the epidermis is rare, but if a lesion invades the epidermis, the patterns may include rounded "pagetoid" defects in which tumor cells

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- **Fig. VIA3.b.** Plasmacytoma, low power. The tumor cells do not involve the epidermis.
- **Fig. VIA3.c.** Plasmacytoma, high power. The infiltrate consists of a monotonous population of histologically typical plasma cells. These appearances, taken in isolation, are suspicious but not diagnostic of an evolving myeloma. Demonstration of clonality would confirm the impression of a neoplastic rather than reactive infiltrate. Myeloma would need to be ruled out clinically.
are collected. Keratinocytic dysplasia or carcinoma in situ in the overlying epidermis is not uncommon, and islands of squamous cell differentiation in the dermal nests occur uncommonly. Lymphatic invasion is commonly present.

The immunohistochemical profile is positive for NSE, chromogranin, Ber-EP4, and CD57. A single punctate zone of cytoplasmic immunoreactivity for cytokeratins, especially CK20, or neurofilaments is most characteristic.

EMA is expressed in 75% to 80% of CSCUC. A reaction for CK20 is evidence against the diagnosis of metastatic small-cell carcinoma of the lung. Ultrastructurally, cytoplasmic, membrane-bound, round, dense-core granules of neuroendocrine type measure 100 to 200 nm in diameter. Perinuclear bundles or whorls of intermediate filaments 7 to 10 nm wide and small desmosomes are regularly present. Tonofilaments attached to the desmosomes have been found in only a few cases.

Clin. Fig. VIA4. Merkel cell tumor. A smooth-topped erythematous nodule appeared suddenly and grew on the cheek of an elderly woman.

Fig. VIA4.a. Merkel cell tumor, low power. Scanning magnification reveals a dense dermal infiltrate of small basophilic cells. At this magnification the differential diagnosis includes cutaneous lymphoma and metastatic small cell carcinoma.

Fig. VIA4.b. Merkel cell tumor, high power. The individual cells are small, compared to most carcinoma cells, although larger than small lymphocytes. They are round and have scant cytoplasm. The nuclei show a characteristic stippled appearance. Mitoses and apoptotic cells are frequently seen.

Fig. VIA4.c. Merkel cell carcinoma, high power, CK20 immunoperoxidase stain. Stains for cytokeratin 20 reveal a characteristic perinuclear dot staining pattern, helping to differentiate the lesion from a metastatic small cell carcinoma of the lung.
Metastatic Small Cell Carcinoma

See Figs. VIA4.d–f.

Conditions to consider in the differential diagnosis:
- primitive neuroepithelial tumors (PNET)
- peripheral neuroblastoma/neuroepithelioma
- Ewing’s sarcoma
- cutaneous small cell undifferentiated carcinoma (CSCUC/Merkel cell tumor)
- melanotic neuroepithelial tumor of infancy
- lymphoma/leukemia
- rhabdomyosarcoma
- metastatic neuroendocrine carcinoma
- small cell melanoma
- small cell carcinoma (squamous or adenocarcinoma)
- eccrine spiradenoma

Fig. VIA4.d. Metastatic small cell carcinoma. There is an asymmetrical nodular and diffuse collection of cells in the reticular dermis.

Fig. VIA4.e. Metastatic small cell carcinoma. The tumor consists of a monotonous population of small blue cells, infiltrating and disrupting the dermal architecture.

Fig. VIA4.f. Metastatic small cell carcinoma. The small cells have scant cytoplasm, resulting in molding of nuclei against one another. The nuclei are small, but larger than those of a lymphocyte. They have homogeneous chromatin and lack nucleoli. Crush artifact is common. Immunohistochemistry may be needed to rule out a lymphoma in a case like this. CK20 staining is typically negative.
**LARGE POLYGONAL & ROUND CELL TUMORS**

Large polygonal and round cell tumors have large round to oval nuclei that often exhibit relatively open chromatin. Especially in adenocarcinomas and in melanomas, there may be prominent nucleoli. The cytoplasm is abundant, and often amphophilic because of an abundant content of ribosomes.

1. Squamous Cell Tumors
2. Adenocarcinomas
3. Melanocytic Tumors
4. Eccrine Tumors
5. Apocrine Tumors
6. Pilar Tumors
7. Sebaceous Tumors
8. “Histiocytoid” and Miscellaneous Clear Cell Tumors
9. Tumors of Large Hemato-Lymphoid Cells
10. Mast Cell Tumors
11. Tumors With Prominent Necrosis
12. Miscellaneous & Undifferentiated Epithelial Tumors

**VIB1 Squamous Cell Tumors**

Proliferations of large cells with more or less abundant cytoplasm, and with evidence of desmosome formation and/or keratin production occupy the dermis as nodular masses. Primary tumors may show evidence of origin from the epidermis in the form of a contiguous precursor (actinic keratosis) or, less specifically, of blending between the tumor cells and the epidermal cells. The possibility of metastatic squamous cell carcinoma must be considered and differentiated from the possibility of a primary cutaneous squamous cell carcinoma.

**Squamous Cell Carcinoma**

**CLINICAL SUMMARY.** Squamous cell carcinoma may occur anywhere on the skin and on mucous membranes with squamous epithelium. Clinically, squamous cell carcinoma of the skin most commonly consists of a shallow ulcer surrounded by a wide, elevated, indurated border and often covered by a crust that conceals a red, granular base. Occasionally, raised, fungoid, verrucous lesions without ulceration occur. Most commonly, it arises in sun-damaged skin, either as such or from an actinic keratosis. Next to sun-damaged skin, squamous cell carcinomas arise most commonly in scars from burns and in stasis ulcers, termed Marjolin’s ulcers. Carcinomas arising in sun-damaged skin in general have a very low propensity to metastasize, except for carcinomas of the lower lip, even though in most cases, these are also induced by exposure to the sun (17).

**HISTOPATHOLOGY.** The tumors consist of irregular masses of epidermal cells that proliferate downward into the dermis. The invading tumor masses are composed in varying proportions of more or less mature squamous cells and of atypical (anaplastic) squamous cells. The latter are characterized by such changes as great variation in the size and shape of the cells, hyperplasia and hyperchromasia of the nuclei, absence of intercellular bridges, keratinization of individual cells, and the presence of atypical mitotic figures. Differentiation in squamous cell carcinoma is in the direction of keratinization, which often takes place in the form of horn pearls. These are very characteristic structures composed of concentric layers of squamous cells showing gradually increasing usually incomplete keratinization toward the center. Keratohyaline granules within the horn pearls are sparse or absent.

**Keratoacanthoma**

Solitary keratoacanthoma, a common lesion, occurs in elderly persons usually as a single lesion, and consists of a firm, dome-shaped nodule 1.0 to 2.5 cm in diameter with a horn-filled crater in its center. The lesions may occur on any hairy cutaneous site, with a predilection for exposed areas. They usually reach their full size within 6 to 8 weeks and involute spontaneously leaving a slightly depressed scar, generally in less than 6 months. Healing takes place. An increased incidence of keratoacanthoma is observed in immunosuppressed patients, and in the Muir–Torre syndrome of sebaceous neoplasms and keratoacanthomas associated with visceral carcinomas. “Giant” and locally destructive forms of keratoacanthoma exist.

**HISTOPATHOLOGY.** The architecture of the lesion is as important to the diagnosis as the cellular characteristics. Therefore, if the lesion cannot be excised in its entirety, it is advisable that a fusiform specimen be excised for biopsy from the center of the lesion and that this specimen includes the edge at least of one side and preferably of both sides of the lesion. A shave biopsy is inadvisable, since the histologic changes at the base of the lesion are often of great importance in the differentiation from squamous cell carcinoma.

In the early proliferative stage, there is a horn-filled cup-shaped invagination of the epidermis from which strands of epidermis protrude into the dermis. These strands are poorly demarcated from the surrounding stroma in many areas and may contain cells showing nuclear atypia as well as many mitotic figures including occasionally atypical mitoses. Perineural invasion is occasionally seen. A fully developed lesion shows in its center a large, irregularly shaped crater filled with keratin. The nondysplastic adjacent epidermis extends like a lip or a buttress over the sides of the crater. At the base of the crater, irregular epidermal proliferations extend downward. There are only one or two layers of basophilic, nonkeratinized cells at the periphery of the proliferations, whereas the cells within this shell
VI. Tumors and Cysts of the Dermis and Subcutis

appear eosinophilic and glassy as a result of keratinization. There are many horn pearls, most of which show complete keratinization in their center. The base appears regular and well demarcated and usually does not extend below the level of the sweat glands. In the involuting stage, proliferation has ceased, and most cells at the base of the crater have undergone keratinization. The distinction between keratoacanthoma and well-differentiated squamous cell carcinoma is often difficult and a descriptive diagnosis expressing uncertainty is then appropriate (18).

Inverted Follicular Keratosis

Inverted follicular keratosis (IFK) may be regarded as an endophytic form of the irritated, or activated, type of seborrheic keratosis, in which the characteristic feature is the presence of numerous whorls or eddies composed of eosinophilic flattened squamous cells arranged in an onion-peel fashion, somewhat resembling poorly differentiated keratin pearls (19). These “squamous eddies” can be differentiated from the horn pearls of squamous cell carcinoma by their large number, small size, and circumscribed configuration. Frequently, some of these proliferations are seen to originate from the walls of keratin-filled invaginations. The combination of an inverted or invaginated architectural pattern and the squamous eddies can falsely suggest the possibility of squamous cell carcinoma. IFK can be seen in association with trichoblastoma, supporting its follicular derivation (20).
**Clin. Fig. VIB1.a.** Keratoacanthoma. A symmetrical tumor with a keratin-filled cup-shaped center developed suddenly in chronically sun-damaged skin of an elderly man.

**Fig. VIB1.d.** Keratoacanthoma, low power. The epidermis is invaginated forming a cup-like crater, which is filled with masses of keratin. At the dermal-epidermal junction, there is an infiltrate of mononuclear cells.

**Fig. VIB1.e.** Keratoacanthoma, medium power. The epidermis shows an abrupt transition from relatively normal to a proliferation of eosinophilic hyalinized ground-glass-appearing atypical keratinocytes. At the dermal-epidermal junction, there is a brisk infiltrate of lymphocytes that are exocytotic to this proliferative atypical epithelium.

**Fig. VIB1.f.** Keratoacanthoma, high power. The dermal-tumor junction shows a dense infiltrate of mononuclear cells that are exocytotic to this proliferative, eosinophilic, hyalinized ground-glass-appearing tumor.

**Fig. VIB1.g.** Keratoacanthoma, medium power. Within the proliferative epithelium of a cup-shaped tumor, there are intra-epidermal collections of polymorphonuclear leukocytes (which may be considerable more numerous than in this example).
Pseudoepitheliomatous Hyperplasia

Pseudoepitheliomatous hyperplasia (PEH) is a reaction pattern of squamous epithelium that usually occurs in association with certain neoplasms or over a chronic inflammatory process and may be regarded as reparative in nature (21). Conditions that may be associated with PEH are listed below in the differential diagnosis section. The reactive epithelium may extend into the superficial reticular dermis, simulating a carcinoma. However, the epithelium is typically very bland, with a single layer of basal cells maturing continuously to the surface. Although mitoses may be present, they are not abnormal. There may be evidence of the underlying stimulus in the dermis. Without such a finding, the distinction between PEH and well-differentiated invasive squamous cell carcinoma may be almost impossible to make on histologic grounds alone.

Proliferating Trichilemmal Cyst (Pilar Tumor)

**CLINICAL SUMMARY.** The proliferating trichilemmal cyst (22) is nearly always a single lesion, usually located on the scalp or on the back, most commonly in an elderly woman. Starting as a subcutaneous nodule suggestive of a wen, the tumor may grow into a large, elevated, lobulated mass that may undergo ulceration and thus greatly resemble a squamous cell carcinoma. The lesions may recur after simple local excision, and malignant transformation may occur (23).

**HISTOPATHOLOGY.** The lesion usually is well demarcated from the surrounding tissue, and is composed of variably sized lobules of squamous epithelium. Some of the lobules are surrounded by a vitreous layer and show palisading of their peripheral cell layer. Characteristically, the epithelium in the center of the lobules abruptly changes into eosinophilic amorphous keratin of the same type as that seen in the cavity of ordinary trichilemmal cysts. In addition to this trichilemmal pattern of keratinization, some proliferating trichilemmal cysts exhibit epidermoid changes resembling that of the follicular infundibulum. This may result in horn pearls, some of which resemble “squamous eddies.” The tumor cells in many areas show some degree of nuclear atypia, as well as individual cell keratinization, which at first glance may suggest a squamous cell carcinoma. The tumor differs from a squamous...

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**Fig. VIB1.h.** *Inverted follicular keratosis, low power.* This epithelial neoplasm arises from the epidermis and shows an endophytic architecture which vaguely resembles that of a hair follicle.

**Fig. VIB1.i.** *Inverted follicular keratosis, medium power.* This epithelial proliferation is embedded in a fibrotic stroma and it is sharply separated from the adjacent reticular dermal collagen. Keratin-filled cystic structures are seen within it.

**Fig. VIB1.j.** *Inverted follicular keratosis, high power.* Numerous squamous eddies as depicted here are a characteristic feature of an inverted follicular keratosis.
Clin. Fig. VIB1.b. Pseudoepitheliomatous hyperplasia. An elderly woman had an ulcer of 10 years duration characterized by granulation tissue and a hypertrophic, irregular border. Multiple biopsies ruled out squamous cell carcinoma.

Fig. VIB1.k. Pseudoepitheliomatous hyperplasia, low power. This reactive epithelial hyperplasia is present adjacent to a healing biopsy site. Squamous cell carcinoma should always be considered in the differential diagnosis of this process and a careful search for cytologic atypia and/or adjacent actinic keratosis or carcinoma in situ should be undertaken. The epidermis reveals marked irregular acanthosis with endophytic tongues extending into the superficial dermis. There is associated hyperkeratosis.

Fig. VIB1.l. Pseudoepitheliomatous hyperplasia, medium power. PEH can be difficult to differentiate from invasive squamous cell carcinoma. The presence of dermal fibrosis as seen in this example suggests a reactive process such as previous procedure at this site, or a healing ulceration.

Fig. VIB1.m. Pseudoepitheliomatous hyperplasia, high power. Despite the irregular architecture and infiltrative pattern of the epithelial tongues, there is no high-grade atypia and the lesional cells appear to mature smoothly from a basal layer. (continues)
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**Intraepidermal abscesses**

Fig. VIB1.n. *Pseudoepitheliomatous hyperplasia in North American blastomycosis, low power.* There is florid irregular epidermal hyperplasia extending deeply into the reticular dermis, associated with a mixed-cell inflammatory infiltrate and with multiple intraepithelial abscesses, a clue to the diagnosis of a deep fungal infection. This should be demonstrated with special stains and if possible with culture.

**Trichilemmal keratinization**

Fig. VIB1.o. *Proliferating trichilemmal cyst, low power.* There is a neoplasm in the dermis comprises multiple lobules of interconnecting epithelium with multiple associated cystic spaces.

Fig. VIB1.p. *Proliferating trichilemmal cyst, medium power.* There are large bands of connected epithelial tissue with zones of trichilemmal keratinization, that is keratinization without formation of a granular cell layer.

Fig. VIB1.q. *Proliferating trichilemmal cyst, high power.* The epithelial cells may be large with an abundance of cytoplasm and may appear infiltrative into the tumor stroma at the periphery of the nodule, but they fail to reveal high-grade cytologic atypia, and the tumor does not infiltrate into the surrounding native tissue.
cell carcinoma by its rather sharp demarcation from the surrounding stroma as well as by its abrupt mode of keratinization. Malignant proliferating trichilemmal tumors may arise focally within a benign lesion and are characterized by increased cytologic atypia and an infiltrative growth pattern (23).

**Prurigo Nodularis**

**CLINICAL SUMMARY.** This is a chronic dermatitis characterized by discrete, raised, firm hyperkeratotic papulonodules, usually from 5 to 12 mm in diameter but occasionally larger (24). They occur chiefly on the extensor surfaces of the extremities and are intensely pruritic. The disease usually begins in middle age and women are more frequently affected than men. The condition may coexist with lesions of lichen simplex chronicus and there may be transitional lesions. The cause remains unknown but local trauma, insect bites, atopic background, and metabolic or systemic diseases have been implicated as predisposing factors in some cases.

**HISTOPATHOLOGY.** There is pronounced hyperkeratosis and irregular acanthosis. In addition, there may be papillomatosis and irregular downward proliferation of the epidermis and adnexal epithelium approaching pseudoepitheliomatous hyperplasia. The papillary dermis shows a predominantly lymphocytic inflammatory infiltrate and vertically oriented collagen bundles. Occasionally, prominent neural hyperplasia may be observed; however, this is an uncommon finding and is not considered to be an essential feature for the diagnosis of prurigo nodularis. In some cases, silver stains or cholinesterase stains demonstrate the increased number of cutaneous nerves. Eosinophils and marked eosinophil degranulation may be seen more frequently in patients with an atopic background. Dermal Langerhans cells are increased, and there may be enlarged dendritic mast cells in the dermis.

**PATHOGENESIS.** It is generally assumed that the neural proliferation in prurigo nodularis is a secondary phenomenon due to chronic trauma by scratching. Still, it may be that the extreme pruritus is related to the increased number of dermal nerves. It has been shown that nerve growth factor (NGF) and its receptors are over-expressed in lesional skin of prurigo nodularis, compared to normal controls, with the inflammatory cell infiltrate being the source of NGF with resulting neural hyperplasia (25).

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**Fig. VIB1.r**  
Prurigo nodularis, low power. There is hyperkeratosis and the epidermis is hyperplastic and highly irregular, with protrusion of tongues of cells well into the reticular dermis. The appearances, caused by chronic irritation, are reminiscent of pseudoepitheliomatous hyperplasia.

**Fig. VIB1.s**  
Prurigo nodularis, medium power. The hyperplastic epithelium is well differentiated, without substantial cytologic atypia. As in lichen simplex chronicus, there may be vertically oriented thick collagen fibers in the elongated dermal papillae.
Conditions to consider in the differential diagnosis:
- primary squamous cell carcinoma
- metastatic squamous cell carcinoma
- proliferating trichilemmal cyst
- inverted follicular keratosis
- keratoacanthoma
- inverted follicular keratosis
- prurigo nodularis

**VIB2 Adenocarcinomas**

Proliferations of atypical cells with more or less abundant cytoplasm, and with evidence of gland formation and/or mucin production occupy the dermis as nodular masses.

The possibility of metastatic adenocarcinoma must be considered and differentiated from the possibility of a primary cutaneous adenocarcinoma of skin appendages (refer to eccrine, apocrine, pilar, sebaceous tumor sections below).

**Metastatic Adenocarcinoma**

**CLINICAL SUMMARY.** In women, the majority of all cutaneous metastases are mammary or pulmonary adenocarcinomas. The latter are the most common in men. Colon in both sexes and ovaries in women account for most of the rest. Cutaneous metastatic disease as the first sign of internal cancer is most commonly seen with adenocarcinomas of the lung, kidney, and ovary. Inflammatory mammary carcinoma is a distinctive disorder that is

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**Fig. VIB2.a.** Metastatic adenocarcinoma, low power. There is a tumor which forms glands and extends from the dermis into the subcutis.

**Fig. VIB2.b.** Metastatic adenocarcinoma, medium power. There is a patchy lymphocytic infiltrate.

**Fig. VIB2.c.** Metastatic adenocarcinoma, medium power. The cribriform architecture of this lesion would be fairly characteristic but not diagnostic of a metastasis from a mammary carcinoma.
characterized by an erythematous patch or plaque with an active spreading border that resembles erysipelas and usually affects the breast and nearby skin. The inflammatory appearance and warmth are attributed to capillary congestion. En cuirasse or scirrhous metastatic mammary carcinoma is characterized by a diffuse morphea-like induration of the skin and rarely occurs in association with other primary carcinomas. It usually begins as scattered papular lesions coalescing into a sclerodermoid plaque without inflammatory changes.

**HISTOPATHOLOGY.** In scirrhous mammary carcinoma, the indurated areas are fibrotic and may contain only a few tumor cells. The tumor cells may be confused with fibroblasts. They have elongated nuclei similar to those of fibroblasts, but larger, more angular, and more deeply basophilic. The tumor cells often lie singly, but in some areas they may form small groups or single rows between fibrotic and thickened collagen bundles. This latter feature of “single filing” is of diagnostic importance. In inflammatory carcinoma, there is extensive invasion of the dermal and often

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**Fig. VIB2.d.** Metastatic mammary carcinoma, infiltrating ductal type, low power. The entire dermis is expanded and replaced by an infiltrative tumor. The tumor has replaced the adnexal structures.

**Fig. VIB2.e.** Metastatic mammary carcinoma, infiltrating ductal type, medium power. Throughout the dermis, there are multiple small tumor aggregates permeating between bundles of reticular dermal collagen. Many of the tumor aggregates form small ducts. There is an area of confluent necrosis, characterized by eosinophilia with loss of nuclear and cytoplasmic cellular detail.

**Fig. VIB2.f.** Metastatic mammary carcinoma, infiltrating ductal type, high power. Infiltrating cords of cells are characteristic of this subtype, which is also known as “scirrhous carcinoma” because of its tendency to have a dense collagenous stroma. The tumor cells show enlarged hyperchromatic nuclei and eosinophilic cytoplasm. The cytoplasm may show small clear vacuoles.
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Dilated lymphatics with tumor

Fig. VIB2.g

Fig. VIB2.h

**Fig. VIB2.g.** Inflammatory carcinoma, low power. In this example of breast carcinoma, there are dilated lymphatics containing clusters of tumor cells. The appearances are consistent with "inflammatory carcinoma," a condition in which there is extensive lymphatic involvement with slight if any inflammation.

**Fig. VIB2.h.** Inflammatory carcinoma, high power. Solid collections of malignant cells are seen within dilated lymphatics. They have irregular, hyperchromatic nuclei and high nuclear to cytoplasmic ratios.

the subcutaneous lymphatics by groups and cords of tumor cells. These cells are similar to those in the primary growth and atypical in character with large, pleomorphic, hyperchromatic nuclei. Adenocarcinomas metastatic to skin from lung are often moderately differentiated, but some show well-formed, mucin-secreting, glandular structures. Individual tumor cells sometimes contain abundant cytoplasmic mucin, but usually lack large pools of mucin, which is more characteristically seen from gastrointestinal metastatic adenocarcinomas.

**Metastatic Mammary Ductal Carcinoma**

See Figs. VIB2.d–f.

**Mammary Carcinoma, “Inflammatory” Type**

See Figs. VIB2.g, h.

**Conditions to consider in the differential diagnosis:**

- primary adenocarcinoma of skin adnexal origin (see below)
- mucin-producing squamous cell carcinoma (mucoepidermoid, adenosquamous carcinoma)
- metastatic adenocarcinoma

**Melanocytic Tumors**

The proliferations in the dermis are melanocyte derived, pigmented or amelanotic, benign, atypical, or malignant. Superficial lesions may involve the epidermis (junctional component). There may be a fibrous and inflammatory host response. S100, Melan-A, HMB-45, tyrosinase and MITF stains may be of value in recognizing melanocytic differentiation in amelanotic tumors (26). Intradermal melanocytic nevi, halo nevi, cellular blue nevi, Spitz nevi, and primary melanomas of the “nodular” type, and metastatic melanomas will be discussed here as examples of dermal melanocytic tumors (27,28), even though many of these have an epidermal as well as a dermal component. Non-tumorigenic primary melanomas have been discussed elsewhere (IIB1, IID2).

**Melanocytic Lesions With Little or No Cytologic Atypia**

With rare exceptions, such as perhaps a few nevoid melanomas (at least at first glance), malignant melanocytic tumors are characterized by cytologic atypia and usually also by mitotic activity in the dermis. Benign melanocytic nevi, in contrast, tend to lack these features. If atypia is present at all, it tends to be “random” (confined to a minority of the lesional cells) rather than “diffuse” as in most melanomas.

**Melanocytic Nevi, Acquired and Congenital Types**

**CLINICAL SUMMARY.** Five types of melanocytic nevi can be distinguished, namely (1) flat lesions which for the most part are histologically junctional nevi, and compound nevi which include (2) slightly elevated lesions often with raised centers and flat peripheries many of which are histologically dysplastic nevi, (3) papillomatous lesions,
(4) dome-shaped lesions, and (5) pedunculated lesions (see IIA.2). Most non-pigmented papillomatous, dome-shaped, and pedunculated nevi are intradermal nevi. Strictly defined congenital melanocytic nevi are by definition present at birth. They may be "small" (<1.5 cm and especially when <1 cm generally indistinguishable from acquired nevi), “intermediate” (amenable to excision with primary closure) or “large” (not amenable to excision except with extraordinary measures). Pigment is variable in nevi, and often absent in dermal nevi.

**HISTOPATHOLOGY.** The lesional cells of nevi (“nevus cells”) tend to be arranged in more-or-less well-defined nests and to contain variable pigment, especially superficially within the lesion. In non-pigmented lesions, the tendency to nesting is often the key feature in recognizing that a lesion is melanocytic. The most important architectural features that distinguish a dermal nevus from a melanoma are their overall smaller size and greater symmetry, and the decrease in size of lesional cells from superficial to deep within the dermis which is often referred to as “maturation.” If dermal nevus cells are confined to the papillary dermis, they often retain a discrete, or “pushing” border with the stroma. However, nevus cells that enter the reticular dermis tend to disperse among collagen fiber bundles as single cells or attenuated single files of cells, differing from melanomas, where groups rather than single cells tend to dissect and displace the collagen. Nevus cells entering the reticular dermis are seen in many congenital nevi, but also in acquired nevi, which may be termed "congenital pattern nevi." Relatively more specific indicators of congenital nevus include size greater than 1.5 cm, and nevus cells within skin appendages, especially sebaceous units. Cytologically, nevus cells differ from melanoma cells by lacking high-grade and uniform cytological atypia, and mitoses are totally absent in the vast majority of benign nevi.

Lesions where nevus cells extend into the lower reticular dermis and the subcutaneous fat, or are located within nerves, hair follicles, sweat ducts, and sebaceous glands, are termed “congenital pattern nevi” because these patterns may be seen, though not exclusively, in nevi that have been present since birth.

**Acquired Nevi, Compound and Dermal**

See Clin Fig. VIB3.a.a and Figs. VIB3.a.a–a.f.

**Congenital Nevus**

See Clin. Fig. VIB3a.b and Figs. VIB3a.g, a.h.

**Acral Nevus**

See Figs. VIB3a.i, a.j.

**Balloon Cell Nevus**

See Figs. VIB3a.k–a.m.

**Halo Nevus**

**CLINICAL SUMMARY.** A halo nevus, also known as Sut- ton’s nevus, nevus depigmentosa centrifugum, or leu- koderma acquisitum centrifugum (29), represents a pigmented nevus surrounded by a depigmented zone. A similar halo reaction may be seen in relation to a primary or metastatic melanoma. In the common type of halo nevus, the central

![Clin. Fig. VIB3a.a](image-url)
**Fig. VIB3a.b.** *Compound nevus, medium power.* As in the junctional component of a nevus, the dermal nevus cells are recognized at this power chiefly by their tendency to be arranged in nests.

**Fig. VIB3a.c.** *Compound nevus, high power.* The nests of nevus cells in the epidermis overly a dermal component of orderly nevus cells, which extend into the reticular dermis in a “congenital pattern.”

**Fig. VIB3a.d.** *Predominantly dermal nevus with neurotization ("neurotized nevus" or "neuronevus"), low power.* A moderately symmetrical proliferation of cells with an ill-defined nested arrangement.

**Fig. VIB3a.e.** *Predominantly dermal nevus, medium power.* Cells at the top of the dermal component are arranged in a nevoid nested pattern and they blend with a different pattern at the base of the image.
Fig. VIB3a.f. *Predominantly dermal nevus, high power.* The cells at the base tend to be more spindled and they are arranged in leaf-like structures that recapitulate sensory nerve appendages such as Wagner-Meissner corpuscles, constituting “maturation”.

Clin. Fig. VIB3a.b. *Congenital nevus.* This giant, hairy nevus was present at birth and covers a “garment-like” or “bathing-trunk” distribution.

Fig. VIB3a.g. *Congenital pattern nevus, low power.* This relatively large nevus is compound but is predominantly in the dermis. The lesion extends to the mid and deep reticular dermis.

Clin. Fig. VIB3a.h. *Congenital pattern nevus, medium power.* The dermal component is composed of bland, uniform ovoid melanocytic cells. These cells extend into the reticular dermis and also around eccrine ducts and a hair follicle. This pattern may be seen in truly congenital nevi but may also be seen in some acquired nevi.
VI. Tumors and Cysts of the Dermis and Subcutis

Fig. VIB3a.i. Compound nevus, acral type, low power. One can identify that this biopsy is from an acral site because of the thick, compact stratum corneum. The nevus is small and symmetrical and shows both a junctional and superficial dermal component.

Fig. VIB3a.j. Compound nevus, acral type, medium power. The nests in the papillary dermis are small, orderly, and lack atypia. Slight or even marked upward pagetoid scatter of cells as seen here is acceptable in the absence of other indicators of melanoma. The nest at the top left is an example of “transepidermal elimination,” a phenomenon often seen in benign acral nevi (and also Spitz nevi).

Fig. VIB3a.k. Balloon cell nevus, low power. This shave biopsy shows a compound nevus with a slightly papillomatous architecture. In the upper/mid dermis, there is a collection of clear cells.

Fig. VIB3a.l. Balloon cell nevus, medium power. At the dermal-epidermal junction and within the superficial dermis, there are nests of orderly pigmented melanocytic cells. These cells blend with larger melanocytic cells which show an abundance of clear cytoplasm.

Fig. VIB3a.m. Balloon cell nevus, high power. Upon close inspection, the clear cells all show small, uniform, centrally placed nuclei. The lack of cytologic atypia and mitotic activity help differentiate this lesion from a balloon cell melanoma.
nevus gradually involutes over a period of several months. The area of depigmentation shows no clinical signs of inflammation and ultimately disappears in most cases often after many months or even years. Most persons with halo nevi are children or young adults, and the back is the most common site. Not infrequently, halo nevi are multiple, occurring either simultaneously or successively.

**HISTOPATHOLOGY.** In the early stage, there are nests of nevus cells embedded in a dense inflammatory infiltrate, in the upper dermis and at the epidermal-dermal junction. Later, more scattered nevus cells than nests are observed. Even when melanin is still present in the nevus cells, these cells often show evidence of damage to their nuclei and cytoplasm, and some frankly apoptotic nevus cells are commonly observed. Some cells, especially superficially, may have enlarged ovoid nucleoli, changes that may be regarded as a form of “reactive atypia,” but high-grade and uniform nuclear atypia is not observed, and lesional cell mitoses are usually absent. Importantly, the lesional cells tend to show evidence of “maturation,” becoming smaller with descent from superficial to deep within the lesion. Most of the cells in the dense inflammatory infiltrate are lymphocytes. However, some of them are macrophages containing various amounts of melanin. As the infiltrate invades the nevus cell nests, it often is difficult to distinguish between the lymphoid cells of the infiltrate and the type B nevus cells in the mid-dermis, because they, too, have the appearance of lymphoid cells. At a later stage, only a few and finally no distinct nevus cells can be identified. Gradually, after all nevus cells have disappeared, the inflammatory infiltrate subsides. The epidermis of the halo, lateral to the dermal nevus cells, may show subtle lymphocytic inflammation with damage to melanocytes followed by their disappearance, and a progressive absence of melanin.

**Blue Nevus**

Blue nevi differ from most acquired nevi in that they are present in the reticular dermis, yet contain abundant pigment, and comprise spindle cells.

**Cellular Blue Nevus**

**CLINICAL SUMMARY.** A cellular blue nevus (30) presents as a blue nodule that is usually larger than the common blue nevus. It generally measures 1 to 3 cm in diameter, but it may be larger. It shows either a smooth or an irregular surface. About half of all cellular blue nevi

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**Clin. Fig. VIB3a.c**

**Fig. VIB3a.n**

**Clin. Fig. VIB3a.c.** Halo nevus. A small compound nevus in a teenager was found to have a clear halo after the development of a tan in late spring.

**Fig. VIB3a.n.** Halo nevus. The nevus architecture is obscured by a dense lymphocytic infiltrate.

**Fig. VIB3a.o.** Halo nevus. Lymphocytes infiltrate among the dermal nevus cells, which eventually degenerate and disappear.
have been located over the buttocks or in the sacrococcygeal region. Although rare, malignant degeneration of cellular blue nevi can occur (malignant blue nevus).

**HISTOPATHOLOGY.** In the most common “mixed-biphasic” pattern, areas of deeply pigmented dendritic melanocytes, as observed also in common blue nevi, are admixed with cellular islands composed of closely aggregated, rather large spindle-shaped cells with ovoid nuclei and abundant pale cytoplasm often containing little or no melanin. Not infrequently, the cellular islands penetrate into the subcutaneous fat, often forming a bulbous expansion there that is highly characteristic of cellular blue nevi. In some of the intersecting bundles, the cells appear rounded, perhaps as a result of cross sectioning. Melanophages with abundant melanin may be present between the islands. The diagnosis of cellular blue nevus is generally easy in these “biphasic” lesions with both dendritic and spindle-shaped cells and with areas that resemble common blue nevi, but it can be difficult in occasional lesions without dendritic cells and in a few lesions that lack readily appreciable melanin. Larger islands composed of spindle-shaped cells may consist of many intersecting bundles of cells extending in various directions and resembling the storiform pattern observed in a neurofibroma. Some lesions consist entirely of pigmented spindle cells extending into the dermis. These lesions, referred to as the “monophasic spindle cell type” of cellular blue nevus, overlap histologically with Spitz nevi, deep penetrating nevi, and spindle cell melanomas. They tend to differ from the latter by overall architectural symmetry, by their monotony of cell type, and by lacking necrosis or frequent mitoses. Although frank anaplastic high-grade nuclear atypia is generally absent in cellular blue nevi, the nuclei may be large with prominent nucleoli. Although most of these lesions have a benign course, a few have been locally aggressive or have metastasized at least to regional lymph nodes, and a guarded prognosis is appropriate in the presence of more than a few mitoses (melanocytic tumor of uncertain malignant potential). The absence or scarcity of

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![Fig. VIB3a.p](image1)

**Fig. VIB3a.p.** *Blue nevus, low power.* Within the dermis, there is a poorly defined but symmetrical spindle cell proliferation which is dark brown in color. There is no significant change in the overlying epidermis.

![Fig. VIB3a.q](image2)

**Fig. VIB3a.q.** *Blue nevus, medium power.* The spindled, heavily pigmented cells encircle collagen bundles in the reticular dermis, a pattern which is also seen in dermatofibromas.

![Fig. VIB3a.r](image3)

**Fig. VIB3a.r.** *Blue nevus, high power.* The lesion is composed of elongate cells which are heavily pigmented and show prominent pigmented dendrites. The nuclei are small. The cells may be arranged in wavy fiber bundles consistent with schwannian differentiation.
Clin. Fig. VIB3a.d. *Blue nodule in the scalp.* This blue nodule on clinical grounds could represent a cellular blue nevus, a malignant blue nevus, or malignant melanoma (primary or metastatic). Despite the symmetry of the lesion and its relatively small size, a malignant diagnosis is favored clinically by the presence of focal ulceration.

Fig. VIB3a.s. *Cellular blue nevus, low power.* Cellular blue nevi are frequently relatively large, involving a good portion of the reticular dermis and extending deeply as tongue-like aggregates of tumor cells at the base of the lesion. The dendritic melanocytic component that resembles a common blue nevus can be seen at the periphery of the lesion.

Fig. VIB3a.t. *Cellular blue nevus, medium power.* Involvement of the subcutaneous fat is common and does not imply a malignant diagnosis.

Fig. VIB3a.u. *Cellular blue nevus, high power.* The cellular areas are composed of uniform spindled melanocytic cells with more cytoplasm and larger nuclei than what is seen in common blue nevus. There are irregularly distributed collections of coarse melanin pigment within the cells.
mitotic figures and the absence of areas of necrosis are evidence against a diagnosis of malignant blue nevus, and the presence of areas of dendritic cells elsewhere in the tumor, as well as the lack of a characteristic intra-epidermal component, argue against a diagnosis of melanoma.

**VI.B3b Melanocytic Lesions With Cytologic Atypia**

Although some benign lesions may exhibit “significant” cytologic atypia, in most such cases, such as deep penetrating nevi, the atypia is “random,” or confined to a minority population of scattered lesional cells. Spitz nevi are an exception; in these lesions there is a characteristic nuclear morphology of large nuclei with open chromatin, regular nuclear membranes, and large nucleoli. This nuclear morphology is uniform across the lesion, and needs to be distinguished from the more hyperchromatic nuclei with irregular nuclear membranes and clumped chromatin seen in most melanomas.

**Deep Penetrating Nevus**

This is a distinctive entity that has some features of combined nevus, blue nevus, and Spitz nevus (31). In the first report of 70 cases from a referral center, many cases had previously been mis-diagnosed histologically as melanomas. Similar lesions have also been described as plexiform spindle cell nevi. The lesions occur in children as well as adults, and the head, neck and shoulder are the most frequent sites of involvement. The lesions range in size up to about 10 mm, and are darkly pigmented papules and nodules, often diagnosed clinically as blue nevi or cellular blue nevi. Occasional recurrences have been described, and there are anecdotal examples of metastasis from lesions with many if not all features of deep penetrating nevi (32,33). On cross section, the lesions extended at least half-way into the dermis, with a smooth, dome-shaped elevation of the epidermis. Lesions termed “nevus with focal atypical epithelioid component” or “clonal” or “combined” nevi may represent a superficial variant. These distinctions are of little or no importance; the key distinction is from melanoma.

**HISTOPATHOLOGY.** At scanning magnification, the lesions are circumscribed and pyramidal in shape, with a broad base abutting the epidermis, and an apex extending into or towards the fat. Nests of nevus cells at the dermal-epidermal junction are usually present. The dermal component is composed of loosely arranged nests or plexiform fascicles of large pigmented spindle and epithelioid cells interspersed with melanophages. There is a tendency to formation of narrow spindle cells at the periphery of the nests, reminiscent of sustentacular cell differentiation. In many cases there is an admixture of smaller, more conventional nevus cells. The lesional cell nests tend to surround skin appendages, and to infiltrate the collagen at the periphery of the lesion. The cells do not tend to “mature” with descent into the dermis. Some lesions have a patchy mild lymphocytic infiltrate.

At higher magnification, nuclear pleomorphism may be striking in some lesions, with variation in size and shape, hyperchromasia, and nuclear pseudo-inclusions. The atypia tends to be confined to randomly scattered cells rather than being “uniform,” or present in a majority of the cells. Nucleoli are usually inconspicuous but a few large eosinophilic nucleoli may be observed. Importantly, mitoses are absent or very rare, with no more than one or two in multiple sections of any given lesion. The cytoplasm is abundant, and contains finely divided brown melanin pigment. The lesional cells react positively for S-100 protein and HMB-45 antigen, and other melanocytic markers.

**Spitz Tumor/Nevus**

**CLINICAL SUMMARY.** The importance of recognizing Spitz tumors is that the histology often resembles a nodular melanoma because of the large size of the lesional cells, often with considerable nuclear and cytoplasmic pleomorphism and an inflammatory infiltrate (34). This lesion, described by Sophie Spitz in 1948 as “juvenile melanoma,” is known also as spindle and epithelioid cell nevus or as “nevus of large spindle and/or epithelioid cells.” It occurs in children, and in young to early middle-aged (and occasionally older) adults. Typically, it consists of a dome-shaped, hairless pink nodule, usually smaller than 6 mm to 1 cm, and encountered most commonly on the lower extremities and face. The color is usually pink, and the lesion is then often diagnosed clinically as granuloma pyogenicum, angioma, or dermal nevus. However, it may be tan, brown, or even black. After an initial period of growth, most Spitz nevi are stable. In rare instances, there are multiple tumors, either agminated (grouped) in one area or widely disseminated. Some lesions exhibit atypical features histologically and there is overlap with nevusoid or “Spitzoid” melanomas, so that the term “tumor” (or “melanocytoma”) is currently preferred to that of a “nevus” with its implication of an invariably benign neoplasm (35). Nevertheless, the vast majority of Spitz tumors, especially in children, will have a benign course. Even after the discovery of lymph node metastases in a Spitzoid lesion, long survivals have been reported (36). Atypical Spitz nevi have recently been found to lack the BRAF mutations that characterize most common nevi, and some atypical lesions have been found to have an activating mutation of H-RAS, which is rare in other nevi and in melanomas (37). These genetic findings may have some utility in diagnosis (38).

**HISTOPATHOLOGY.** In their overall architectural pattern, Spitz nevi resemble junctional, compound or junctional nevi. They are small, symmetrical, and well circumscribed. The epidermis is often hyperplastic with elongated rete ridges. The epidermal component is arranged in nests that tend to be oriented vertically and,
although large, do not vary a great deal in size and shape or tend to become confluent. In Spitz nevi with junctional activity, there are often artifactual clefts between the nests of nevus cells and the surrounding keratinocytes, a feature that is less often seen in melanoma. Pagetoid permeation of the epidermis by tumor cells is usually slight, except occasionally and especially in young children.

Important cytologic features of Spitz nevi include especially the “large spindle and/or epithelioid cells,” which define the lesion histologically. Apart from the shape of their cell bodies, the spindle cells and epithelioid cells in any given Spitz nevus resemble one another in nuclear and cytoplasmic consistency, suggesting that they may represent dimorphic expression of a single cell type. They have abundant amphophilic cytoplasm and prominent eosinophilic nucleoli. A useful although not pathognomonic cytologic criterion for Spitz nevi is the presence within the epidermis of coalescent pink globular “Kamino bodies.” Of special importance is maturation of the cells with increasing depth, so that they become smaller and look more like the cells of a common nevus. Also important is the uniformity of the lesional cells from one side of the lesion to the other: at any given level of the lesion from the epidermis to its base, the lesional cells look the same. The small lesional cells at the base of most Spitz nevi tend to disperse as single cells or files of single cells among reticular dermis collagen bundles. Mitoses are found in about half of the cases, usually in small numbers (<3/sq. mm). Atypical mitoses are rare or absent. The complete absence of mitoses in at least 50% of Spitz nevi is very helpful in ruling out melanoma in these cases.

Bulky tumors with spitzoid cytology occur and cause difficulty in diagnosis. A series of such cases was recently reported as “epithelioid melanocytomas of uncertain malignant potential” (39). Features in these lesions that were associated with more aggressive behavior (which was usually but not always limited to bulky regional nodal metastases) included mitoses in the lower third of the lesion, and the presence of a lymphocytic infiltrate. These authors concluded that “The major outcome of this study of a series of “MELTUMPs” suggests as a preliminary observation that these lesions as a group exist and that they may be biologically different from conventional melanoma and benign melanocytic nevi. The terminology remains highly controversial, reflecting the uncertainty in classification and interpretation of these atypical melanocytic tumors.” Genomic studies including comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) may...
be helpful in decision making in these difficult cases, but are not at present likely to be independently diagnostic (40).

**Nodular Melanoma**

**CLINICAL SUMMARY.** Nodular melanoma, by definition, contains only tumorigenic vertical growth (29). The lesion starts as an elevated, variably pigmented papule that increases in size quite rapidly to become a nodule and often ulcerates. The ABCD criteria reviewed earlier do not apply to nodular melanomas, which are often quite small, symmetrical, and well-circumscribed. They may be conspicuously pigmented, oligomelanotic, or amelanotic.

**Clin. Fig. VIB3b.a.** *Spitz nevus.* A symmetrical pink nodule which appeared suddenly in a child but then remained stable for several weeks before excision was arranged.

**Fig. VIB3b.d.** *Spitz nevus/tumor, low power.* At scanning magnification, there is a symmetrical zone of epithelial hyperplasia, with an underlying cellular plaque/nodule.

**Fig. VIB3b.e.** *Spitz nevus/tumor, medium power.* Lesional cells show a characteristic pattern of maturation and dispersion as single cells into the reticular dermis at the base of the tumor.

**Fig. VIB3b.f.** *Spitz nevus/tumor, medium power.* Nests of spindled melanocytes in the epidermis demonstrate clefting artifact, a common finding in Spitz tumors.
When other risk factors such as thickness are controlled, the prognosis of nodular melanoma is not worse than that of other forms of melanoma.

HISTOPATHOLOGY. There is contiguous growth of uniformly atypical melanocytes in the dermis, forming an often asymmetrical tumor mass. Asymmetry is often apparent at the cytologic level as variation in cell size, shape, and pigmentation, and in the distribution of the host response, such that one half of the lesion is not a mirror image of the other half. However, the silhouette of the entire lesion may be quite symmetrical in a nodular melanoma because of the lack of an adjacent component. There is a variable lymphocytic infiltrate around the base or within the tumor. The epidermis is frequently ulcerated, or there is an adherent scale-crust. In a nodular melanoma, “pagetoid” permeation of the epidermis with tumor cells is limited to that portion overlying the dermal tumor, and in some cases, the epidermal involvement may be quite limited in degree. For this reason, nodular melanoma may be difficult or impossible to distinguish from a metastatic melanoma in the skin, and when the tumor is amelanotic, the distinction from other malignancies may require immunohistochemistry.

Cytologically, the tumor cells in the dermis tend to vary greatly in size and shape. Nevertheless, two major types of cells—epithelioid and spindle-shaped—can be recognized. Usually one type predominates. The epithelioid cells tend to lie in nested or alveolar formations surrounded by delicate collagen fibers, and the spindle-shaped cells in irregularly branching formations. Tumors in which spindle cells predominate may resemble sarcomas but in most cases differ from them by the presence of junctional melanocytic activity. The uniformly atypical nuclei of the melanoma cells are larger than those of melanocytes or nevus cells, with irregular nuclear membranes, hyperchromatic chromatin, and often prominent nucleoli that tend to be irregular in size, shape, and number. There is also a diagnostically important failure of the melanocytes in the deeper layers of the dermis to decrease in size (“absence of maturation”). Mitotic Figures are usually present and often numerous in the lesional cells of the dermal and epidermal compartments of tumorigenic melanomas.

**Superficial Spreading Melanoma**

CLINICAL SUMMARY. Unlike nodular melanoma, most melanomas evolve through a clinically evident stage of tumor progression termed the radial growth phase (RGP) in which they enlarge as they were along the radii of
Clin. Fig. VIB3b.b. Malignant melanoma, tumorigenic. An elderly man presented with an asymmetrical black tumor and cervical adenopathy.

Fig. VIB3b.i. Nodular melanoma, low power. This subtype of malignant melanoma frequently shows a dome-shaped or polypoid architecture, which may seem deceptively symmetrical at scanning magnification. S100 staining (inset) demonstrates asymmetrical arrangements of the cells in the dermis. There is no radial growth phase to this lesion, the feature which distinguishes it from other forms of melanoma.

Fig. VIB3b.j. Nodular melanoma, medium power. The tumor shows its origination from the overlying epidermis which shows single and nested atypical melanocytes at the dermal-epidermal interface. In nodular melanoma, pagetoid spread may not be prominent.

Fig. VIB3b.k. Nodular melanoma, high power. Mitotic figures are generally identified and occasional cells show brown pigment within the cytoplasm. Necrosis “en masse” and/or ulceration are commonly seen in bulky vertical growth phase tumors.

Fig. VIB3b.l. Nodular melanoma, high power. The tumor cells infiltrate the reticular dermis as pushing fascicles rather than as single cells as is the rule in Spitz and congenital pattern nevi, benign lesions that also involve the reticular dermis.
an imperfect circle in the skin. Subsequently a tumorigenic phase may ensue, in which a vertical growth phase nodule appears within the pre-existing radial growth phase plaque. The ABCD criteria reviewed earlier apply mostly to the radial growth phase component. Histologic criteria, reviewed below, also apply mainly to the radial growth phase. The tumorigenic vertical growth phase differs not at all from that in most “nodular melanomas” (which by definition lack an RGP), and prognosis is the same when all of the microstaging attributes are taken into consideration.

**Histopathology.** Key features that define a superficial spreading melanoma, compared to the other most common radial growth phase subtype, lentigo maligna melanoma, include the following. The lesions tend to be characterized by a hyperplastic epidermal contour rather than the atrophic pattern seen in lentigo-maligna melanoma. Pagetoid scatter of lesional cells into the epidermis is a striking feature even at scanning magnification. Lesional cells tend to be arranged in a prominent nested pattern, with nests varying in size, shape, orientation, and distribution within the epidermis. The cells tend to be large epithelioid cells, and pigment is more abundant in superficial spreading than in lentigo maligna melanoma. Superficial spreading melanoma is also more likely than lentigo maligna melanoma to be associated with a nevus, and less likely to be associated with severe chronic solar damage. In recently published genotype-phenotype correlation studies which have helped to refine the criteria for the subtypes of melanoma, these features of superficial spreading melanoma correlate generally with mutations of the oncogene BRAF (41,42).

**Nevoid Melanoma**

Nevoid melanomas are defined as lesions that, to a considerable extent, mimic a benign nevus histologically, especially in terms of lesional architecture (43,44). Usually, the resemblance is most apparent at scanning magnification, where lesions may appear symmetrical, nested, and devoid of radial growth. These features can lead to a missed diagnosis if sufficient attention is not paid to cytologic and subtle architectural features including the presence of multiple mitoses. In a seminal study by Schmoeckel, useful discriminating attributes included cellular atypia, mitoses, infiltration of adnexa, infiltrative growth in the deeper dermis, and absence of maturation. Tumor thickness was the most important prognostic criterion (44). Nevoid melanomas are generally considered to have the same biologic potential as other melanomas with similar microstaging attributes. Key to the recognition of a nevoid melanoma is a high index of suspicion, and the identification of high cellularity, mitotic activity and cytologic atypia in the dermal component of the lesion.

**Metastatic Malignant Melanoma**

**Clinical Summary.** Metastatic malignant melanoma most commonly presents as a firm, red-purple to blue-black subcutaneous mass. Epidermotropic metastatic

### TABLE VI.1. Spitz Tumor versus Atypical Spitz Tumor versus Nodular Melanoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Spitz Tumor</th>
<th>Atypical Spitz Tumor/MELTUMPP</th>
<th>Nodular Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Smaller</td>
<td>Larger</td>
<td>Larger</td>
</tr>
<tr>
<td>Symmetry</td>
<td>Good</td>
<td>Fair</td>
<td>May be good but often imperfect</td>
</tr>
<tr>
<td>Cytology</td>
<td>Uniform large spindle and/or epithelioid cells</td>
<td>May be somewhat variable from side to side</td>
<td>More variable—large and small, pigmented and non-pigmented etc.</td>
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<tr>
<td>Ulceration and necrosis</td>
<td>Rare</td>
<td>Occasionally</td>
<td>Often</td>
</tr>
<tr>
<td>Consumption of epidermis</td>
<td>Epidermis thickened</td>
<td>Usually thickened</td>
<td>Often thinned</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Very few if any</td>
<td>More readily detectable</td>
<td>Often frequent</td>
</tr>
<tr>
<td>Kamino bodies</td>
<td>Usually</td>
<td>Usually</td>
<td>Hardly ever</td>
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<tr>
<td>Maturation</td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
</tr>
<tr>
<td>Dispersion into reticular dermis</td>
<td>Single cells at base</td>
<td>May be clusters/nests</td>
<td>Clusters at base</td>
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<tr>
<td>Lymphocytic infiltrate</td>
<td>Often absent</td>
<td>Often present</td>
<td>Often present</td>
</tr>
</tbody>
</table>
melanoma presents as small symmetrical papules that may simulate a benign nevus (45).

**HISTOPATHOLOGY.** The histologic appearance usually differs from that of a primary melanoma by the absence of an inflammatory infiltrate and of junctional activity. However, primary melanomas may occasionally fail to involve the epidermis, and may also not show an inflammatory infiltrate, particularly when they are deeply invasive. Furthermore, some metastases exhibit a prominent lymphocytic infiltrate, and can contact the overlying epidermis in a way that is suggestive of junctional activity. *Epidermotropic metastatic melanoma* refers to a metastatic deposit that is initially localized in the papillary dermis and involves the overlying epidermis. Most of these lesions occur in an extremity regional to a distal primary melanoma. Epidermotropic metastasis is characterized by (1) thinning of the epidermis by aggregates of atypical melanocytes within the dermis, (2) inward turning of the rete ridges at the periphery of the lesion, and (3) usually no lateral extension of atypical melanocytes within the epidermis beyond the concentration of the metastasis in the dermis. However, this distinction can be very difficult in a few lesions where extension beyond the dermal component occurs. In some of these cases, the metastatic cells are small and nevoid, with few if any mitoses, and in these instances of *differentiated epidermotropic metastatic melanoma* the lesions can be mistaken for compound nevi.

**Fig. VIB3b.c.** Malignant melanoma, superficial spreading type, tumorigenic. This lesion has a prominent blue-black tumorigenic vertical growth phase nodule, and an adjacent tan plaque component which represents an associated radial growth phase.

**Fig. VIB3b.m.** Superficial spreading melanoma, with bulky tumorigenic vertical growth phase, low power. An asymmetric tumor nodule is the prominent feature at scanning magnification.

**Fig. VIB3b.n.** Superficial spreading melanoma, with bulky tumorigenic vertical growth phase, medium power. Adjacent to the nodule, there is pagetoid scatter of uniformly atypical epithelioid cells arranged singly and in ill-defined nests. The presence and pagetoid/nested morphology of this adjacent radial growth phase component define this lesion as a superficial spreading melanoma.
Metastatic Malignant Melanoma, Satellite Lesion

See Figs. VIB3b.v, w.

Epidermotropic Metastatic Melanoma

This term refers to a metastatic deposit that is initially localized to the papillary dermis and involves the overlying epidermis. Most of these lesions occur in an extremity regional to a distal primary melanoma. Epidermotropic metastasis is characterized by thinning of the epidermis by aggregates of atypical melanocytes within the dermis, inward turning of the rete ridges at the periphery of the lesion, and usually no lateral extension of atypical melanocytes within the epidermis beyond the concentration of the metastasis in the dermis. However, this distinction can be very difficult at times, and cases have been reported in which there was such lateral extension. In some other cases, the metastatic cells are small and nevoid, with few if any mitoses, and in these instances of differentiated or nevoid epidermotropic metastatic melanoma or “epidermotropic metastatic melanomas with maturation” the lesions can be mistaken for compound nevi. A molecular study of 21 lesions suggested that epidermotropic metastatic melanomas are clonally related to their primary lesion in many cases. Interestingly, the data also indicated that some cases so diagnosed might be divergent clones or even new primaries rather than metastases (46).

Pigmented Epithelioid Melanocytoma/Epithelioid Blue Nevus

CLINICAL SUMMARY. This is a recently described melanocytic tumor that closely resembles epithelioid blue nevi as seen in Carney’s complex, and also some cellular blue nevi (47,48). This lesion appears to represent a distinctive tumor that affects males and females equally with a median age of occurrence of 27 years (range 0.6–78 years). Multiple body sites may be affected, with extremities being the most common. Loss of expression of a presumptive suppressor gene has been described in these lesions (49).

HISTOPATHOLOGY. Histologically there is a deep dermal nodule of heavily pigmented epithelioid and/or spindled melanocytes. Some lesions occur as a component of a combined nevus. Ulceration may be present in occasional lesions, a finding generally not present in epithelioid blue nevi. Although tumor cells may be bland and mitoses and necrosis inconspicuous or absent, regional lymph node involvement has been seen in 46% of cases studied. Nonetheless, extranodal spread is rare, and even
VI. Tumors and Cysts of the Dermis and Subcutis

with involvement of draining lymph nodes, the clinical course may be remarkably indolent. Similar or identical lesions associated with the Carney complex appear to be benign.

**Melanocytic Tumor of Uncertain Malignant Potential**

Some lesions present conflicting histologic criteria, making it impossible to clearly distinguish between a benign nevus (or tumor) and a tumorigenic melanoma which could have metastasizing as well as locally recurring potential. A recent study described the difficulties and lack of agreement in the histopathologic diagnosis of particular melanocytic tumors, such as atypical Spitz tumors (AST), atypical blue nevi, and deep penetrating nevi (39). These lesions are often referred to as “melanocytic tumors of uncertain malignant potential” (MELT-UMP). This of course is a descriptive term and not a definitive diagnosis or a homogeneous category. Principles of classification of these lesions have been discussed above. The term “melanocytoma” has been proposed as a designation that is noncommittal as to the predicted behavior of some of these difficult and controversial lesions (39). Even when these lesions are found to have metastasized to regional nodes in a sentinel node staging procedure, the subsequent course is usually benign, based on multiple follow-up studies reviewed in a recent report (50).

**Conditions to consider in the differential diagnosis:**

**Superficial Melanocytic Nevi**
- compound melanocytic nevus
- dermal melanocytic nevus, acquired type
- dermal recurrent melanocytic nevus
- dysplastic nevi, compound
- nevus of genital skin
- nevus of acral skin
- halo nevus
- combined nevus

**Fig. VIB3b.q.** *Nevoid melanoma, low power.* Although there is an impression of a nevoid configuration at first glance, the cellularity of this lesion is high, with extensive confluent sheetlike growth of the small nevoid lesional cells in the dermis.

**Fig. VIB3b.r.** *Nevoid melanoma, high power.* At high magnification, the cells demonstrate uniform albeit mild to moderate atypia, and dermal mitotic figures are present although not frequent.

**Fig. VIB3b.s.** *Nevoid melanoma, medium power.* A Ki-67 study demonstrates more than a sprinkling of cycling cells. Although not diagnostic in and of itself, this finding supports the diagnosis of nevoid melanoma when taken in conjunction with the high cellularity, confluent growth, failure of maturation, and mitotic activity seen in this lesion.
Clin. Fig. VIB3b.d. Metastatic malignant melanoma. A 69-year-old man presented with translucent erythematous and black nodules and papules surrounding the skin graft at the site of a previous melanoma of the foot.

Fig. VIB3b.t. Metastatic malignant melanoma, low power. In this example of metastatic melanoma, there is a nodular tumor within the subcutaneous fat and lower dermis. There is no overlying tumor in the dermis or epidermis.

Fig. VIB3b.u. Metastatic malignant melanoma, high power. The tumor is composed of large atypical cells with an abundance of cytoplasm, large nuclei and prominent nucleoli. Brown melanin pigment is seen within the cytoplasm of these cells. Mitotic figures, which may be few or numerous, can generally be identified in metastatic lesions. This tumor has a brisk lymphocytic infiltrate and appears to be undergoing partial regression. Melan-A (upper panel) and S100 stains are positive in scattered residual melanoma cells.

Clin. Fig. VIB3b.v. Metastatic malignant melanoma, satellite lesion, low power. This small black papule was present adjacent to a malignant melanoma. Within the upper dermis, there are collections of heavily pigmented melanocytic cells without an overlying epidermal component.

Fig. VIB3b.w. Malignant melanoma, satellite lesion, high power. Small satellite lesions histologically may look nevic. However, the aggregates are of various sizes and the individual cells are large with hyperchromatic nuclei. Atypia is not always severe in these lesions, as in this example. The presence of mitotic figures, although not always numerous, is helpful in differentiating these lesions from nevi.
Fig. VIB3b.x. Epidermotropic metastatic malignant melanoma, medium power. In this example of epidermotropic metastatic melanoma, the cells lack melanin pigment and they show pagetoid scatter of atypical cells into the epidermis, a pattern which mimics a primary malignant melanoma.

Fig. VIB3b.y. Epidermotropic metastatic malignant melanoma, medium power. Pagetoid scatter is typically confined to the epidermis above the dermal component in these lesions. Readily detectable lymphatic invasion (not shown) may be a clue to the diagnosis but is often absent.

Fig. VIB3b.z. Pigmented Epithelioid Melanocytoma (PEM), low power. A heavily pigmented nodule spanning the dermis. There is a bulbous expansion into the subcutis similar to what is often seen in cellular blue nevi.
**Fig. VIB3b.za.** PEM. The lesion comprises heavily pigmented cells which are melanophages and more lightly pigmented cells which are the lesional cells. There is often as here a prominent junctional component with marked keratinocytic hyperplasia.

**Fig. VIB3b.zb.** PEM, high power. The lesional cells (inset) are epithelioid or sometimes spindled in configuration, and have prominent nucleoli with open chromatin and regular nuclear membranes. Mitoses are usually present but not numerous.

**Fig. VIB3b.zc.** PEM, medium power. A melanin bleach stain reveals the nuclear detail of the characteristic lesional cells (smooth contour, pale chromatin, prominent nucleolus, see also inset in previous image), and the infiltrating melanophages.

**Fig. VIB3b.zd.** Melanocytic Tumor of Uncertain Malignant Potential (MELTUMP). At scanning magnification, this lesion from the back of a teenager is quite large and very cellular, but relatively symmetrical.

**Fig. VIB3b.zc.** MELTUMP/AST/Spitzoid melanoma. Large epithelioid cells are uniform from side to side. Mitoses were present. There is only slight evidence of maturation to the base. (continues)
VI. Tumors and Cysts of the Dermis and Subcutis

VIB4 Eccrine Tumors

Proliferations of eccrine ductal (small dark cells usually forming tubules at least focally) or glandular tissue or both in a hyalinized or sclerotic dermis. The inflammatory infiltrate is mainly lymphocytic. Malignant examples of most of the tumor categories exist. These are rare, and are characterized in general by infiltration of the native dermis and other adjacent structures beyond the stroma of the tumor itself, by severe uniform cytologic atypia, increased mitotic activity, and necrosis or ulceration. Immunohistochemical studies have been proposed to help distinguish between primary adnexal carcinomas and metastatic adenocarcinomas; p63 and D2-40 expression appear to be especially useful as markers of adnexal origin (51). Eccrine spiradenoma and nodular hidradenoma are the prototypic examples of the benign tumors.

VIB4a Circumscribed, Symmetrical Eccrine Tumors

Eccrine Spiradenoma

CLINICAL SUMMARY. As a rule, eccrine spiradenoma (52) occurs as a solitary intradermal nodule measuring 1 to 2 cm in diameter. Occasionally, there are several nodules, and rarely, there are numerous small nodules in a zosteriform pattern or large nodules in a linear arrangement. The nodules are often tender and occasionally painful.
Clin. Fig. VIB4a.a. *Eccrine spiradenoma.* A 55-year-old man had a 30-year history of a bluish nodulo-cystic lesion of the wrist, with a history of recent enlargement and tenderness.

Fig. VIB4a.a. *Eccrine spiradenoma, low power.* This adnexal neoplasm is a basaloid nodular tumor within the dermis. The lesion is sharply circumscribed and separated from the adjacent dermal collagen.

Fig. VIB4a.b. *Eccrine spiradenoma, medium power.* This tumor may be separated from the surrounding dermis by a thin fibrous capsule. At this power, the tumor cells form an interlocking pattern. “Satellite” tumors are common as seen here and are not indicators of malignancy.

Fig. VIB4a.c. *Eccrine spiradenoma, high power.* The tumor is composed of small basaloid cells with small nuclei and scant cytoplasm. A second population of cells is also present with slightly larger, vesicular nuclei, and more cytoplasm.
HISTOPATHOLOGY. The tumor may consist of one large, sharply demarcated lobule, or of several such lobules located in the dermis without connections to the epidermis. There may be a fibrous capsule. The tumor lobules often appear deeply basophilic because of the close aggregation of the nuclei. The epithelial cells within the tumor lobules are arranged in intertwining cords, which may enclose small, irregularly shaped islands of edematous connective tissue. Two types of epithelial cells are present in the cords, both with only scant cytoplasm. The cells of the first type have small, dark nuclei; they are generally located at the periphery of the cellular aggregates. The cells of the second type have large, pale nuclei; they are located in the center of the aggregates and may be arranged partially around small lumina observed in about half of the tumors, or in a rosette arrangement. The lumina frequently contain small amounts of a PAS-positive granular, eosinophilic material. In some cases, hyaline material is focally present in the stroma that surrounds the cords of tumor cells. A heavy diffuse lymphocytic infiltrate may be present.

Cylindroma

CLINICAL SUMMARY. Cylindromas present as slow-growing, soft or firm dermal pink to reddish nodules, usually as solitary lesions on the head, neck and scalp. They arise predominantly in elderly and middle-aged females, with a female-to-male ratio of reportedly 9:1. Cylindroma can undergo malignant transformation, with potential for metastatic disease. These usually benign tumors may occur in the Brooke-Spiegler syndrome, an autosomal dominantly inherited disease in which multiple cylindromas develop. Mutations in the CYLD tumor suppressor gene have been associated with this syndrome. Cutaneous cylindromas are benign and should not be confused with adenoid cystic carcinomas which may occur in the skin as in other sites such as salivary glands.

HISTOPATHOLOGY. Cylindromas most frequently occur in the dermis of scalp and facial skin, and comprise irregularly shaped islands of basaloid cells surrounded by an eosinophilic hyaline sheath. The tumor islands typically consist of
two types of cells: a peripheral palisade of cells with small dark nuclei, representing relatively undifferentiated basaloid tumor cells; and more centrally located, more differentiated cells with large, pale nuclei that resemble ductal or secretory cells. The thickened basement membrane zone of cylindromas is abnormal in terms of laminin, integrin and collagen expression, and in lack of hemidesmosomes (53).

Poroma

See Clin. Fig. VIB4a.b and Figs. VIB4a.g–a.i.

Syringoma

See Figs. VIB4a.j, a.k.

Nodular Hidradenoma

CLINICAL SUMMARY. Nodular hidradenoma (54) is presently also called clear cell hidradenoma and eccrine acrospiroma, although apocrine features are seen in many of these neoplasms (55). It is a fairly common tumor without a preferred site. The tumors present as intradermal nodules in most instances between 0.5 and 2.0 cm in diameter, although they may be larger. They are usually covered by intact skin, but some tumors show superficial ulceration and discharge serous material. Although clinically the tumor only rarely gives the impression of being cystic, gross examination of the specimen often reveals cysts.

Clin. Fig. VIB4a.b. Eccrine poroma. A firm slightly erythematous papule on the volar aspect of the wrist.

Fig. VIB4a.g. Eccrine poroma, low power. A circumscribed proliferation of cells extending from the epidermis into the dermis.

Fig. VIB4a.h. Eccrine poroma, medium power. The epithelial cells form monotonous sheets.

Fig. VIB4a.i. Eccrine poroma, high power. A structure within the tumor is consistent with an abortive duct.

In other examples, ducts may be lined by an eosinophilic cuticle similar to that of an eccrine duct.
Fig. VIB4a.j. *Syringoma, low power.* Within the upper half of the dermis, there is a well-circumscribed adnexal tumor which is embedded in an eosinophilic stroma. Although this lesion has no capsule, the edge of the lesion is defined by the edge of the stroma.

**Fig. VIB4a.k.** *Syringoma, medium power.* The tumor is composed of multiple small islands of bland-appearing epithelial cells. Many of the islands form small ducts lined by an eosinophilic cuticle. The islands may show a “tad-pole” or “comma-like” appearance.

**HISTOPATHOLOGY.** The tumor is well circumscribed and may appear encapsulated. It is composed of lobulated masses located in the dermis and often extending into the subcutaneous fat, usually with no connection to the surface epidermis. The tumor nodules are frequently separated by a characteristic eosinophilic hyalinized stroma. Within the lobulated masses, tubular lumina of various sizes are often present. However, these may be absent or few in number. The tubular lumina may be branched or straight, and are lined by cuboidal ductal cells or by columnar secretory cells, which may show evidence of decapitation secretion (i.e., apocrine differentiation). There are often cystic spaces, which may be of considerable size and contain a faintly eosinophilic, homogeneous material. In solid portions of the tumor, two types of cells can be recognized in varying proportions, and with transitional forms. One type of cell is usually polyhedral or fusiform with a rounded nucleus and slightly basophilic cytoplasm. The second type of cell is usually round with very clear cytoplasm, so that the cell membrane is distinctly visible. Its nucleus appears small and dark. In some tumors, epidermoid differentiation is seen, with the cells appearing large and polyhedral and showing eosinophilic cytoplasm. There even may be keratinizing cells with formation of horn pearls or structures reminiscent of the follicular infundibulum, and there may also be sebaceous differentiation. In other tumors, groups of squamous cells are arranged around small lumina that are lined with a well-defined eosinophilic cuticle and thus resemble the intra-epidermal portion of the eccrine duct.

**Clear Cell Syringoma**

See Figs. VIB4a.p, a.q.

**Chondroid Syringoma**

See Figs. VIB4a.r, a.s.

**Conditions to consider in the differential diagnosis:**
- eccrine nevus
- papillary eccrine adenoma
- *clear cell (nodular) hidradenoma* (eccrine acrospiroma)
- syringoma
- chondroid syringoma
- eccrine spiradenoma
- cylindroma (some consider apocrine)
- eccrine syringofibroadenoma
- mucinous syringometaplasia
**Clin. Fig. VIB4a.c.** Nodular hidradenoma. A 55-year-old man presented with an asymptomatic 1 cm pink, telangiectatic slightly scaly nodule on the lateral forearm. The lower pole was pigmented.

**Fig. VIB4a.l.** Nodular hidradenoma, low power. Within the dermis, this neoplasm is composed of several well-circumscribed tumor lobules.

**Fig. VIB4a.m.** Nodular hidradenoma, medium power. These tumor aggregates are well circumscribed from the surrounding normal dermis and subcutaneous fat. The tumor islands may be surrounded by a thin fibrous capsule.

**Fig. VIB4a.n.** Nodular hidradenoma, medium power. Within the tumor islands, there may be small or large, cystic spaces containing amorphous fluid. The spaces are lined by two rows of flattened epithelial cells.

**Fig. VIB4a.o.** Nodular hidradenoma, high power. The epithelial cells frequently show clear cell change with the small basophilic nucleus pushed to the side of the cell. The clear cell change is secondary to glycogen deposition and stains positively with PAS.
Infiltrative, asymmetrical eccrine Tumors

Microcystic Adnexal Carcinoma

CLINICAL SUMMARY. Microcystic adnexal carcinoma (56), or sclerosing sweat duct carcinoma, may best be considered as a sclerosing variant of ductal eccrine carcinoma. This tumor, which is most commonly seen on the skin of the upper lip, but occasionally also on the chin, nasolabial fold, or cheek, is an aggressive neoplasm that invades deeply. Local recurrence is common; however, metastases have not been reported.

HISTOPATHOLOGY. Microcystic adnexal carcinoma is a poorly circumscribed dermal tumor that may extend into the subcutis and skeletal muscle. Continuity with the...
epidermis or follicular epithelium may be seen. Two components within a desmoplastic stroma may be evident. In some areas, basoloid keratinocytes are seen, some of which contain horn cysts and abortive hair follicles; in other areas, ducts and gland-like structures lined by a two-cell layer predominate. The tumor islands typically reduce in size as the tumor extends deeper into the dermis. Cells with clear cytoplasm may be present, and sebaceous differentiation has been reported. Cytologically, the cells are bland without significant atypia; mitoses are rare or absent. Perineural invasion may be seen, a feature that may account for the high recurrence rate. Lack of circumscription, deep dermal involvement, and perineural involvement all aid in diagnosis, since the cytology mimics benign adnexal neoplasms.

**Mucinous Eccrine Carcinoma**

See Figs. VIB4b.e–b.f.

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Clin. Fig. VIB4b.a. *Microcystic adnexal carcinoma.* A middle-aged woman developed a visually inconspicuous indurated swelling on the ala of the nose.

Clin. Fig. VIB4b.b. *Microcystic adnexal carcinoma.* Moh’s micrographic surgery was used to delineate the extent and to excise the tumor, resulting in the large defect seen here.

Fig. VIB4b.a. *Microcystic adnexal carcinoma, low power.* In another case treated by surgical excision, a poorly circumscribed dermal tumor extends through the dermis to the base of the biopsy.

Fig. VIB4b.b. *Microcystic adnexal carcinoma, medium power.* Ducts and solid cords of cells are present in a desmoplastic stroma. (continues)
Subtle tumor cells near base

Microcystic adnexal carcinoma, medium power. Some of the ducts are lined by a single layer of cells; others may appear to have two layers.

Subtle lesional cells infiltrating to near the base of the tumor. Perineural invasion was not seen in this example.

Clusters of cells in pools of mucin

Mucinous eccrine carcinoma, low power. Within the deep dermis and subcutaneous fat there are basophilic islands of tumor cells embedded in a mucinous matrix. The islands are of various sizes. The overlying epidermis and superficial dermis are generally uninvolved.

Mucinous eccrine carcinoma, medium power. These basaloid islands appear to be floating in the abundant hypocellular mucinous matrix.
**Digital Papillary Adenocarcinoma**

**CLINICAL SUMMARY.** This is an uncommon tumor that arises from the sweat glands, and presents as cutaneous nodules, usually on the hands (85%) and feet (15%) (57,58). These tumors are more common in men in the 5th decade with an age range of 17 to 85 years. The clinical differential diagnosis includes glomus tumor, pyogenic granuloma, foreign body granuloma and other tumors or tumor-like lesions. The diagnosis is based on the histologic findings.

**HISTOPATHOLOGY.** The epidermis may have tumor connections but is usually effaced and unaffected. In the dermal is a multilobular tumor composed of tubuloalveolar and ductal structures, cystic areas are also seen. Papillary projections can be seen in the cystic portions of the tumors. Cysts are thought to be formed secondary to tumor necrosis. The tumors may be poorly circumscribed and have a cribriform pattern. p63 may be a useful marker.
for distinguishing primary from metastatic adenocarcinomas, and in addition, the proliferation marker Ki67 may be a indicator of aggressive behavior and thus be helpful in therapeutic decision-making (59).

The tumors are thought to be of eccrine origin although they may exhibit apocrine characteristics. Cytologic atypia is variable. Mitoses are present in most all tumors with an averages range of 0 to 50 per high power field. The tumors stain positively with Cytokeratin, S100, CEA and EMA. The differential diagnosis includes digital papillary adenoma, metastatic carcinoma, and apocrine carcinoma.

**Conditions to consider in the differential diagnosis:**
- sclerosing sweat duct carcinoma
- microcystic adnexal carcinoma
- malignant chondroid syringoma
- malignant clear cell (nodular) hidradenoma
- malignant eccrine spiradenoma
- malignant eccrine poroma (porocarcinoma)
- eccrine adenocarcinoma
- mucinous eccrine carcinoma
- adenoid cystic eccrine carcinoma
- aggressive digital papillary adenoma/adenocarcinoma
- syringoid eccrine carcinoma

**VIB5 Apocrine Tumors**

Tumors in the dermis are composed of proliferations of apocrine ductal and glandular epithelium (large pink cells with decapitation secretion). The stroma is sclerotic, well vascularized and the inflammatory cells are mainly lymphocytes.

**Tubular Apocrine Adenoma**

**CLINICAL SUMMARY.** This tumor (60) consists of a well-defined nodule that is commonly located on the scalp. Most tumors have a smooth surface and are under 2 cm in diameter.

**HISTOPATHOLOGY.** The characteristic feature of this tumor is the presence of numerous irregularly shaped tubular structures that are usually lined by two layers of epithelial cells. The peripheral layer consists of cuboidal or flattened cells, and the luminal layer is composed of columnar cells. Some of the tubules have a dilated lumen with papillary projections extending into it. Decapitation secretion of the luminal cells is seen in many areas, and cellular fragments are seen in some lumina.

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**Fig. VIB5.a**  
*Tubular apocrine adenoma, low power.* Irregularly shaped tubules lined by two layers of cells extend through the reticular dermis.

**Fig. VIB5.b**  
*Tubular apocrine adenoma, medium power.* The double layer of cells and the presence of decapitation secretion differentiate this lesion from a microcystic adnexal carcinoma. The absence of high-grade atypia helps to eliminate a metastatic adenocarcinoma.
Syringocystadenoma Papilliferum

CLINICAL SUMMARY. Syringocystadenoma papilliferum (61) occurs most commonly on the scalp or the face. It is usually first noted at birth or in early childhood and consists of either one papule or several papules in a linear arrangement, or of a solitary plaque. The lesion increases in size at puberty, becoming papillomatous and often crusted. On the scalp, syringocystadenoma papilliferum frequently arises around puberty within a nevus sebaceous that has been present since birth.

HISTOPATHOLOGY. The epidermis shows varying degrees of papillomatosis. One or several cystic invaginations extend downward from the epidermis, lined in their upper portions by squamous, keratinizing cells similar to those of the surface epidermis. In the lower portion of the cystic invaginations, numerous papillary projections extend into the lumina, lined by glandular epithelium often with two rows of cells. The luminal row of cells consists of high columnar cells with oval nuclei, faintly eosinophilic cytoplasm and, occasionally, active decapitation secretion. The outer row consists of small cuboidal cells with round nuclei and scanty cytoplasm. Beneath the cystic invaginations, deep in the dermis, one can often find groups of tubular glands with large lumina, lined by apocrine cells with evidence of active decapitation secretion. A helpful diagnostic feature is the almost invariable presence of a fairly dense cellular infiltrate composed nearly entirely of lymphocytes and plasma cells.
of plasma cells in the stroma of this tumor, especially in the papillary projections. In about one third of the cases, syringocystadenoma papilliferum is associated with a nevus sebaceous.

Syringocystadenocarcinoma papilliferum is extremely rare and may present within a pre-existing lesion as in situ and/or invasive adenocarcinoma, or rarely squamous cell carcinoma. Ductal changes analogous to those in mammary carcinoma are often present and have suggested a transformation that may involve a pathway from usual ductal hyperplasia to atypical ductal hyperplasia to in situ to invasive adenocarcinoma (62).

**Conditions to consider in the differential diagnosis:**

**Circumscribed, Symmetrical Apocrine Tumors**
- apocrine nevus
- tubular apocrine adenoma (“tubulopapillary hidradenoma”)
- cylindroma (some consider eccrine)
- hidradenoma papilliferum
- syringocystadenoma papilliferum
- apocrine hidrocystoma

**Infiltrative, Asymmetrical Apocrine Tumors**
- apocrine adenocarcinoma
- malignant cylindroma
- erosive adenomatosis (florid papillomatosis of the nipple)

### Pilar Tumors

The dermal infiltrating tumor is composed of epithelium that differentiates toward hair, or is a proliferation of portions of the follicular structure and its stroma. The inflammatory cell infiltrate is mainly lymphocytic, and the dermis is fibrocellular. Trichoepithelioma is prototypic (63).

#### Trichoepithelioma

**CLINICAL SUMMARY.** The differentiation in this tumor is directed toward hair structures. It occurs either in multiple lesions or as a solitary lesion. Multiple trichoepitheliomas are transmitted as an autosomal dominant and may occur in association with the Brooke-Speigler syndrome and a CYLD mutation (53). Typically, the first lesions appear in childhood and gradually increase in number. There are numerous rounded, skin-colored, firm papules and nodules located mainly in the nasolabial folds but also elsewhere on the face, and occasionally also the scalp, neck, and upper trunk. Solitary trichoepithelioma is not inherited and consists of a firm, elevated, flesh-colored nodule usually less than 2 cm in diameter. Its onset usually is in childhood or early adult life, and it is commonly located in the anterior facial triangle.

**HISTOPATHOLOGY.** As a rule, the lesions of multiple trichoepithelioma are superficial, well circumscribed, small, and symmetrical. Horn cysts are the most characteristic histologic feature, present in most lesions. They consist of a fully keratinized center surrounded by basophilic cells that lack high-grade atypia and mitoses. The keratinization is abrupt and complete, in the manner of so-called “trichilemmal” keratinization, not gradual and incomplete as in the horn pearls of squamous cell carcinoma. As a second major component, tumor islands composed of basophilic cells are arranged in a lacelike or adenoid network and occasionally also as solid aggregates. These tumor islands show peripheral palisading of their cells and are surrounded by a fibroblastic stroma. This stroma lacks the retraction artifact typical of basal cell carcinoma, and frequently contains foci of granulomatous inflammation about fragments of keratin. The epithelial aggregates form invaginations, which contain numerous fibroblasts and thus resemble follicular papillae. Solitary trichoepithelioma is used as a histologic designation only for highly differentiated lesions. Solitary lesions with relatively little differentiation toward hair structures are best classified as keratotic basal cell carcinoma. If a lesion is to qualify for the diagnosis of solitary trichoepithelioma, it should contain numerous horn cysts and abortive hair papillae. Mitotic figures should be very rare or absent, and the lesion should not be unduly large, asymmetrical, or infiltrative.

#### Desmoplastic Trichoepithelioma

**CLINICAL SUMMARY.** This tumor occurs most commonly as a morpheaform plaque, having slightly raised borders and a central depression (64). The tumors are typically located on the face, mainly on the cheeks, and rarely occur on other areas of the head and neck. It is seen most frequently in the second decade usually in women. The history is of slow progressive growth of many years duration.

**HISTOPATHOLOGY.** A dermal tumor composed of streams and cords of basoloid cells immersed in a dense fibrocellular stroma that compresses the tumor islands into thin delicate strands (65). Calcification and cystic keratinization occur on or within the basoloid tumor. Mitoses and cytologic atypia are uncommon. An inflammatory response is variable and is usually lymphatic. Tumors do not usually extend into the subcutis. Differential diagnoses include sclerosing basal cell carcinoma, microcystic adnexal carcinoma, trichoepithelioma, poroma, tumor of the follicular infundibulum, and syringomas (66).

#### Dilated Pore of Winer

See Figs. VIB6.e, f.

#### Pilar Sheath Acanthoma

See Figs. VIB6.g, h.
Clin. Fig. VIB6. *Trichoepithelioma*. Since early childhood, a 22-year-old woman had developed firm flesh-colored discrete papules and nodules over the face around the nose and mouth.

**Fig. VIB6.a. Trichoepithelioma, low power.** At scanning magnification, there is a dome-shaped epithelial neoplasm within the dermis. The epithelial islands do not connect to the overlying epidermis.

**Fig. VIB6.b. Trichoepithelioma, medium power.** These basaloid epithelial islands are associated with small cystic structures filled with laminated keratin.

**Fig. VIB6.c. Trichoepithelioma, medium power.** The epithelial islands show follicular differentiation mimicking the follicular bulb. The stroma is fibrotic and closely associated with these epithelial islands. Retraction artifact as one sees in basal cell carcinoma is absent in these lesions.
Fig. VIB6.d.  *Desmoplastic trichoepithelioma*. Low, medium and high powers. Basaloid cells in a dense fibrocellular stroma, with cystic structures.

Fig. VIB6.e.  *Dilated pore of Winer, low power*. There is a sinus-like structure which originates from the surface epidermis. The center of the lesion may contain laminated keratin and there is a proliferative epithelial wall.

Fig. VIB6.f.  *Dilated pore of Winer, medium power*. The epithelial wall shows a verrucous inner surface with elongation of rete ridges. There is infundibular keratinization with formation of a granular cell layer.
**Trichilemmoma**
See Figs. VIB6.i–k.

**Trichofofliculoma**
See Figs. VIB6.l–n.

**Fibrofolliculoma/Trichodiscoma**
Fibrofolliculoma, and also trichodiscoma and possibly acrochordon may occur in association with the Birt Hogg Dubé syndrome which is a rare autosomal dominant genodermatosis that is caused by germline mutations in the folliculin (FLCN) gene, encoding the folliculin tumor-suppressor protein. Phenotypic manifestations related to this disease include lung cysts, leading to pneumothorax, and a markedly increased risk for renal neoplasia. Other neoplastic manifestations have been described including correlations between FLCN mutations and risk of colon or breast cancer (67).

**Trichoadenoma**
See Figs. VIB6.r, s.

**Pilomatricoma**
See Figs. VIB6t–w.

**Trichoblastoma**

**CLINICAL SUMMARY.** Trichoblastoma presents as a solitary nodule, rarely multiple, most commonly on the scalp and is often associated with nevus sebaceus of Jadassohn (68). The tumor does not have a distinctive enough clinical appearance that would allow for diagnosis without biopsy. Trichoblastomas occur on most body surfaces but not on non hair-bearing sites such as the mucosa, palms and soles.

**HISTOPATHOLOGY.** A dermal tumor without epidermal connection composed of collections of basaloid cells that may nest (69). The tumor may extend into the subcutaneous tissue. When there is a mixture of fibrocellular stroma and epithelial islands, the tumors have been designated “trichoblastic fibromas.” When the epithelial component predominates, tumors are designated “trichoblastomas.” This is an arbitrary distinction and probably not warranted in practice. In some tumors, immature follicular structures are seen and these have been called the trichogenic...
Trichilemmoma is a benign epithelial neoplasm that is well circumscribed and shows both an endophytic architecture as well as a verrucous and hyperkeratotic surface. Histologically, it is characterized by bland-appearing epithelial cells which may show clear cell change. At the periphery, the basal cells show a palisaded architecture and there may be a thickened basement membrane. These lesions do not have a mucinous stroma, a feature which helps differentiate them from basal cell carcinomas.

Histologic variants include the so-called “rippled” pattern, in which there are basaloid cells in linear rows parallel to each other giving a rippled appearance, and the adamantoid, pigmented and clear cell patterns. Immunohistochemically, the tumors express cytokeratins 5/6, 14, 7 and focally CK17 and CK19. The stromal cells are positive for vimentin and CD34. The differential diagnosis includes basal cell carcinoma, trichoepithelioma, poroma, acrospiroma, spiradenoma and melanoacanthoma (70).

Conditions to consider in the differential diagnosis:
- Follicular infundibular neoplasms
  - Dilated pore of Wine
  - Pilar sheath acanthoma
  - Trichilemmoma
  - Tumor of the follicular infundibulum
Fig. VIB6.l. *Trichofolliculoma, low power.* A central cystic structure is filled with keratin and is associated with a hyperplastic wall, from which secondary hairs extend into the stroma.

Fig. VIB6.m. *Trichofolliculoma, medium power.* The secondary hair follicles arise from the central cystic structure. Tertiary follicles may also be present, branching from the secondary follicles.

Fig. VIB6.n. *Trichofolliculoma, medium power.* The secondary follicles produce hair shafts seen within the cystic canal.

Fig. VIB6.o. *Fibrofolliculoma/trichodiscoma, low power.* Note the fibrous stroma enveloping the epithelial proliferation which may include a cystic space and/or epithelial strands as here. (continues)
**Fig. VIB6.p.** Fibrofolliculoma/trichodiscoma, medium power. The thin, delicate strands of epithelium show follicular differentiation, which may in some cases include formation of sebaceous lobules.

**Fig. VIB6.q.** Fibrofolliculoma/trichodiscoma, medium power. The characteristic thin strands of epithelium ramifying in a fibrous stroma.

**Fig. VIB6.r.** Trichoadenoma, low power. Within the upper two thirds of the dermis is a well-circumscribed lesion composed of multiple cystic structures embedded in a fibrotic stroma.

**Fig. VIB6.s.** Trichoadenoma, medium power. The cystic structures are formed by mature squamous epithelium which shows infundibular differentiation. They contain laminated keratin. Although not shown here, they may be associated with a granulomatous infiltrate secondary to rupture of these cysts.
Fig. VIB6.t. *Pilomatricoma, low power.* This well-circumscribed tumor shows both basophilic and eosinophilic elements.

Fig. VIB6.u. *Pilomatricoma, medium power.* The basophilic areas are composed of crowded areas of small basaloid cells which are in contiguity with the eosinophilic areas.

Fig. VIB6.v. *Pilomatricoma, high power.* The basaloid cells are small and crowded; however, they lack significant atypia. These cells blend with the eosinophilic shadow cells which show the ghost of an epithelial cell without viable basophilic staining.

Fig. VIB6.w. *Pilomatricoma, high power.* Adjacent to the shadow cells seen here are foreign body-type giant cells, a frequent finding in these lesions.
branching and lobular pilosebaceous neoplasms
- trichofolliculoma
- trichoepithelioma
tumor of follicular infundibulum
top of nevus sebaceous
	nodular pilosebaceous neoplasms
- hair follicle nevus
- keratoacanthoma
- trichoepithelioma
desmoplastic trichoepithelioma
immature trichoepithelioma
- hair follicle hamartoma
- pilomatricoma
- trichoblastoma
- trichoblastic fibroma
- trichoadenoma
- proliferating trichilemmal cyst (pilar tumor)
inverted follicular keratosis

tumors of pilosebaceous mesenchyme
- trichodiscoma
- fibrofolliculoma
tumors of the erector pilae muscle
infiltrative, asymmetrical
- pilomatrix carcinoma (malignant pilomatricoma)
- trichilemmal carcinoma
- basal cell carcinoma with follicular differentiation

VIB7 Sebaceous Tumors

The dermal masses are proliferations of the germinative epithelium and of mature sebocytes. The admixture of these cells varies from one tumor to the other. The dermis is fibrocellular. Sebaceous adenomas, epitheliomas, and carcinomas are the prototypes (71). These tumors are often seen in association with the Muir–Torre syndrome, which is a subset of the hereditary non-polyposis colorectal
carcinoma (HNPCC) syndrome, that is, an autosomal dominant cancer predisposition syndrome due to inheritance of a defective gene encoding a DNA mismatch repair protein. These proteins function to detect and repair errors in base pairing occurring during DNA replication, leading to genomic instability (72).

**Sebaceous Adenoma and Sebaceous Epithelioma (Sebaceoma)**

**CLINICAL SUMMARY.** Sebaceous adenoma presents as a yellow, circumscribed nodule located on either the face or the scalp. Sebaceous epithelioma, or sebaceoma, varies from a circumscribed nodule to that of an ill-defined plaque. Some of the lesions are yellow. Sebaceous epithelioma occasionally arises within a nevus sebaceus. Sebaceous epitheliomas and adenomas may also be found among the multiple sebaceous neoplasms that occur in association with multiple visceral carcinomas in the Muir–Torre syndrome.

**HISTOPATHOLOGY.** On histologic examination, sebaceous adenoma is sharply demarcated from the surrounding tissue. It is composed of incompletely differentiated sebaceous lobules that are irregular in size and shape. Two types of cells are present in the lobules. The first are undifferentiated basaloid cells identical to the cells at the periphery of normal sebaceous glands. The second are mature sebaceous cells. In most lobules, the two types of cells occur in approximately equal proportions, often arranged in such a way that groups of sebaceous cells are surrounded by basaloid cells. There may be foci of squamous epithelium with keratinization.

![Clin. Fig. VIB7.a](image1)

**Clin. Fig. VIB7.a.** Sebaceous adenoma. A 67-year-old woman with bladder cancer and colon cancer and a history of keratoacanthoma and sebaceous adenoma (Muir–Torre syndrome) presented with an ill-defined flesh-colored yellowish papule on the upper lip.

**Fig. VIB7.a.** Sebaceous adenoma, low power. Arising from the surface epidermis is a multilobated epithelial neoplasm with clear cell change.

**Fig. VIB7.b.** Sebaceous adenoma, medium power. The clear cell change represents sebaceous differentiation manifested by vacuolated cytoplasm which indents the central nucleus. These cells compose at least 50% of the lesion. The second population of cells is composed of an increased number of basaloid cells at the periphery of the lobules.
The histologic spectrum of sebaceous epithelioma (sebaceoma) extends from that in sebaceous adenoma to lesions that may be difficult to distinguish from sebaceous carcinoma. Generally, a sebaceoma shows irregularly shaped cell masses in which more than half of the cells are undifferentiated basaloid cells but in which there are significant aggregates of sebaceous cells and of transitional cells. Lesions verging on a sebaceous carcinoma show some degree of irregularity in the arrangement of the cell masses, and, although the majority of cells are basaloid cells, many cells show differentiation toward sebaceous cells. Sebaceous adenoma and sebaceous epithelioma lack nuclear atypia and invasive, asymmetric growth patterns, which are hallmarks of sebaceous carcinoma. Considerable mitotic activity in the basaloid regions may be present in either, however.

**Sebaceous Hyperplasia**

See Clin. Fig. VIB7.b and Figs. VIB7.c, d.

**Nevus Sebaceus of Jadassohn**

See Clin. Fig. VIB7.c and Figs. VIB7.e, f.

**Sebaceous Epithelioma**

See Figs. VIB7.g, h.

**Sebaceous Carcinoma**

**CLINICAL SUMMARY.** Carcinomas of the sebaceous glands occur most frequently on the eyelids, but they may also occur elsewhere on the skin. The tumors usually manifests as a nodule that may or may not be ulcerated.
Sebaceous carcinomas of the eyelids quite frequently cause death resulting from visceral metastases. Sebaceous carcinomas arising on the skin away from the eyelids may cause regional metastases, but visceral metastases resulting in death is very rare. The histopathology of sebaceous tumors and their association with the Muir–Torre syndrome have been recently reviewed (72).

**HISTOPATHOLOGY.** The tumors are characterized at scanning magnification by asymmetry and an infiltrative border formed by irregular lobular formations that vary greatly in size and shape. Although many cells are undifferentiated, distinct sebaceous cells showing a foamy cytoplasm are present in the center of most lobules. Many cells are atypical, showing considerable variation in the shape and size of their nuclei. Some of the large lobules contain areas composed of atypical keratinizing cells, as seen in squamous cell carcinoma. Sebaceous carcinomas of the eyelids often show pagetoid spread of malignant cells in the conjunctival or adjacent epithelium, a change that is seen very rarely in extraocular sebaceous carcinoma.

**Conditions to consider in the differential diagnosis:**

**Symmetrical, Circumscribed Sebaceous Neoplasms**

sebaceous hyperplasia

![Fig. VIB7.c](image)

Nevus sebaceus of Jadassohn. A well-defined, yellow-brown verrucous plaque on the scalp that was present at birth.

![Fig. VIB7.e](image)

Nevus sebaceus of Jadassohn, prepubertal, low power. At scanning magnification there is an area in the center of this specimen which shows a decreased number of terminal hairs in the subcutaneous fat. This corresponds with the alopecia noted clinically.

![Fig. VIB7.f](image)

Nevus sebaceus of Jadassohn, prepubertal, medium power. In this area there are several abortive follicular structures in the superficial dermis which fail to produce a hair shaft. This nevus sebaceus is from a 1-year-old child. In this age group, the lesions do not show the characteristic verrucous epidermal hyperplasia and large mature sebaceous lobules which show direct association with the overlying epidermis.
VI. Tumors and Cysts of the Dermis and Subcutis

Fig. VIB7.g. Sebaceous epithelioma/sebaceoma, low power. There is a well-circumscribed neoplasm with a surface crust. At scanning magnification it resembles a basal cell carcinoma but lacks the typical mucinous stroma with retraction artifact.

Fig. VIB7.h. Sebaceous epithelioma/sebaceoma, medium power. This lesion is composed of greater than 50% basaloid cells with a smaller population of mature sebaceous cells.

Fig. VIB7.i. Sebaceous carcinoma, low power. This lesion shows focal ulceration, an infiltrative growth pattern, and an associated inflammatory reaction. At this magnification it has many features which resemble an invasive squamous cell carcinoma.

Fig. VIB7.j. Sebaceous carcinoma, medium power. Although in some areas the lesion may resemble squamous cell carcinoma, the characteristic feature is focal sebaceous differentiation characterized by vacuolated cytoplasm which indents the central nucleus.
Fordyce’s condition (ectopic sebaceous glands in mucosae)  rhinophyma  nevus sebaceous  sebaceous adenoma  sebaceous epithelioma  sebaceous trichofolliculoma

**Infiltrative, Asymmetrical Sebaceous Neoplasms**
- sebaceous carcinoma
- basal cell carcinoma with sebaceous differentiation

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**“Histiocytoid” and Miscellaneous Clear Cell Tumors**

“Histiocytes” may have foamy cytoplasm reflecting the accumulation of lipids, or may have eosinophilic or amphophilic cytoplasm surrounding an ovoid nucleus with open chromatin. Some non-histiocytic lesions whose cells may simulate histiocytes are also included here. There is a great diversity of primary histiocytic dermatoses (73). The conditions may be divided into Langerhans histiocytosis, and non-Langerhans histiocytosis. The latter have been recently reviewed and include juvenile xanthogranuloma, multicentric reticulohistiocytosis, sea-blue histiocyte syndrome, sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman syndrome, necrobiotic xanthogranuloma, xanthoma disseminatum (XD), and hemophagocytic lymphohistiocytosis, which although not formally malignant can all show aggressive behavior to a greater or lesser extent (74). Xanthelasma and juvenile xanthogranuloma are prototypic. Reticulohistiocytoma is an important differential (75).

**Xanthomas and Xanthelasma**

Tuberos and tuberoueruptive xanthomas are found predominantly in patients with an increase in chylomicron and VLDL remnants. They are large nodes or plaques located most commonly on the elbows, knees, fingers, and buttocks. Most of the lipid in these xanthomas is in the form of cholesterol. Xanthelas mata consist of slightly raised, yellow, soft plaques on the eyelids. Although xanthelasma are the commonest of the cutaneous xanthomas, they are also the least specific because they occur frequently in persons with normal lipoprotein levels. Plane xanthomas typically develop in skin folds and especially in the palmar creases. Diffuse plane xanthomas are typically seen as multiple grouped papules and poorly defined yellowish plaques in normolipemic patients, often with paraproteinemia, lymphoma, or leukemia.

**HISTOPATHOLOGY.** The histologic appearance of xanthomas of the skin and the tendons is characterized by foam cells, which are macrophages that have engulfed lipid droplets. There may be varying degrees of fibrosis, giant cells, and clefts, depending on the type and site of xanthoma sampled, but most are surprisingly similar. Most of these foam cells or “xanthoma cells” are mononuclear, but giant cells, especially of the Touton type with a wreath of nuclei, may be found. Larger extracellular deposits of cholesterol and other steroids leave behind clefts. Xanthelasma located on the eyelids are characterized by the fairly superficial location of foam cells and the nearly complete absence of fibrosis. Superficial striated muscles, vellus hairs, small vessels, and a thinned epidermis all suggest location on the eyelid and serve as clues to the histologic diagnosis of xanthelasma.

**Xanthelasma**

See Figs. VIB8.a, b.

**Eruptive Xanthoma**

See Clin. Fig. VIB8.a and Figs. VIB8.c–e.

**Verruciform Xanthoma**

See Figs. VIB8.f, g.

**Juvenile Xanthogranuloma**

**CLINICAL SUMMARY.** Juvenile xanthogranuloma (JXG) (76) is a benign disorder in which one, several, or occasionally numerous red to yellow nodules are present. Despite the name, the lesions are also seen in adults but are most common in young children. In children, the lesions...
may grow rapidly but almost always regress within a year. Lesions in adults are not uncommon but are usually solitary and persistent. JXG has also been identified in many other organ systems, usually in association with macronodular lesions. A number of systemic complications are associated with JXG. Ocular involvement including glaucoma and bleeding into the anterior chamber is the most common, and bone involvement may occur.

**HISTOPATHOLOGY.** The typical JXG contains histiocytes with a variety of cellular features. Early lesions may show large accumulations of histiocytes without any lipid infiltration intermingled with only a few lymphoid cells and eosinophils. When no foam cells or giant cells are seen, the possibility of JXG is often overlooked. Usually some degree of lipidization is present, even in very early lesions, manifested by pale-staining histiocytes. In mature lesions, a granulomatous infiltrate is usually present containing foam cells, foreign-body giant cells, and Touton giant cells as well as histiocytes, lymphocytes, and eosinophils. Older, regressing lesions show proliferation of fibroblasts and fibrosis replacing part of the infiltrate. The oncocytic or reticulohistiocytic type of histiocyte with an eosinophilic cytoplasm is uncommon in childhood lesions but may be seen in adult lesions. The spindle cell variant is also more common in adults. Here one sees predominantly a spindle cell proliferation, similar to blue nevus or dermatofibroma, with few foamy or giant cells.

**Fig. VIB8.a.** Xanthelasma, low power. Throughout the dermis there are poorly defined aggregates of pale staining cells.

**Fig. VIB8.b.** Xanthelasma, high power. These foam cells are seen throughout the dermis without an organized pattern. They have small nuclei and prominent vacuolated cytoplasm.

**Clin. Fig. VIB8.a.** Eruptive xanthomas. Multiple yellow-red papules-nodules developed suddenly on the buttock skin of a 35-year-old woman. Testing revealed markedly elevated triglycerides.

**Fig. VIB8.c.** Eruptive xanthoma, low power. Within the mid dermis there is an inflammatory infiltrate associated with clear spaces forming clefts.
**Fig. VIB8.d.** Eruptive xanthoma, medium power. These variably sized clefts represent the lipid deposition. In the lower half of this photomicrograph are foam cells (macrophages).

**Fig. VIB8.e.** Eruptive xanthoma, high power. Multiple foamy histiocytes are found throughout the dermis. In eruptive xanthomas, neutrophils are often admixed with these histiocytes.

**Fig. VIB8.f.** Verruciform xanthoma, low power. The epidermis shows prominent hyperplasia as well as hyperkeratosis. There is a mixed infiltrate in the papillary and superficial reticular dermis.

**Fig. VIB8.g.** Verruciform xanthoma, high power. Within the tips of the dermal papillae there are large histiocytes with an abundance of foamy cytoplasm.
VI. Tumors and Cysts of the Dermis and Subcutis

Clin. Fig. VIB8.b. Juvenile xanthogranuloma. A 10-year-old girl developed several discrete red to yellow nodules and papules on the face and trunk, which later resolved spontaneously.

Fig. VIB8.h. Juvenile xanthogranuloma, low power. In a xanthogranuloma there is a dense infiltrate forming a solid mass occupying nearly the entire thickness of the dermis.

Fig. VIB8.i. Juvenile xanthogranuloma, medium power. There is a dense mixed infiltrate composed predominantly of histiocytes. There may be few or multiple multinucleated giant cells. Eosinophils and neutrophils are frequently seen, especially in early lesions.

Fig. VIB8.j. Juvenile xanthogranuloma, high power. Characteristic Touton giant cells show a wreath of nuclei surrounded by a peripheral rim of cytoplasm which is often vacuolated.

Reticulohistiocytosis

CLINICAL SUMMARY. Two types of reticulohistiocytosis (77) are recognized: giant cell reticulohistiocytoma (GCRH) and multicentric reticulohistiocytosis (MRH). Both types occur almost exclusively in adults. The histologic picture is very similar in the two types. In GCRH, there is usually a single nodule (“solitary reticulohistiocytoma”), but occasionally multiple lesions are seen, most commonly on the head and neck. The nodules are smooth and 0.5 to 2.0 cm in diameter. They may involute spontaneously. Even patients with multiple lesions show no sign of systemic involvement.

In multicentric reticulohistiocytosis, the patients tend to be middle-aged females, with widespread cutaneous involvement and a destructive arthritis. Nodules ranging in size from a few millimeters to several centimeters are most common on the extremities. The polyarthritis may be mild or severe, and may be mutilating, especially on the hands, through destruction of articular cartilage and...
**Fig. VIB8.k.** Reticulohistiocytoma, low power. At this magnification the lesion resembles a xanthogranuloma with a dense nodular infiltrate in the dermis; the overlying epidermis shows an effaced architecture.

**Fig. VIB8.l.** Reticulohistiocytoma, medium power. This dense infiltrate is mixed but there are scattered giant cells whose cytoplasm show an eosinophilic “ground glass” appearance. They may show a ring of nuclei but they lack the foamy cytoplasm typical of a Touton giant cell.

**Fig. VIB8.m.** Reticulohistiocytoma, high power. The infiltrate is mixed with numerous histiocytes as well as lymphocytes and eosinophils. One giant cell seen here shows an eosinophilic cytoplasm without a vacuolated periphery.

**Fig. VIB8.n.** Multicentric reticulohistiocytosis, low power. In the upper third of the reticular dermis there are poorly defined cellular aggregates.

**Fig. VIB8.o.** Multicentric reticulohistiocytosis, high power. This infiltrate is mixed but contains large giant cells with one or more nuclei and eosinophilic “ground glass” cytoplasm.
subarticular bone. The disease tends to wax and wane over many years, with mutilating arthritis and disfigurement real possibilities.

**HISTOPATHOLOGY.** The characteristic histologic feature in both GCRH and MRH is the presence of numerous multinucleate giant cells and oncocytes showing abundant eosinophilic, finely granular cytoplasm, often with a “ground glass” appearance. In older lesions, giant cells and fibrosis are more common. There may be subtle differences between the two lesions. For example, in MRH the giant cells are smaller (50–100 μm), have fewer nuclei (perhaps 10), and are almost always strikingly PAS-positive. However, the two conditions often cannot be separated microscopically. The polyarthritis present in nearly all instances of MRH is caused by the same type of infiltrate as found in the cutaneous lesions, and similar infiltrates of uncertain clinical significance have been described in other organs.

**Metastatic Renal Cell Carcinoma**

Metastatic renal cell carcinoma, which can mimic a histiocytic infiltrate or a sweat gland tumor, should always be considered when there is a proliferation of clear cells in the skin. Cytologic atypia and mitotic activity may be deceptively minimal.

**Conditions to consider in the differential diagnosis:**

**Foamy Histiocytes**

- xanthomas—eruptive, plane, tuberous, tendon
- verruciform xanthoma
- xanthelasma
- cholestanolema, phytosterolema
- xanthoma disseminatum
- diffuse normolipemic plane xanthoma
- papular xanthoma
- eruptive normolipemic xanthoma
- progressive nodular histiocytoma (superficial)
- Langerhans cell histiocytosis (rare xanthomatous type)
- histoid leprosy

**Non-Foamy Histiocytes**

- dermatofibroma/histiocytoma
- Langerhans cell histiocytosis
- congenital self-healing reticulohistiocytosis
- indeterminate cell histiocytosis
- granuloma annulare
eruptive histiocytomas
benign cephalic histiocytosis
sinus histiocytosis with massive lymphadenopathy
juvenile xanthogranuloma

**Giant Cells Prominent**
- juvenile xanthogranuloma
- multicentric reticulohistiocytosis
- solitary reticulohistiocytoma
- giant cell reticulohistiocytoma
- necrobiotic xanthogranuloma with paraproteinemia
- xanthoma disseminatum

**Histiocytic Simulants**
- pleomorphic large cell lymphoma (Ki-1, usually T cells)
- epithelioid sarcoma
- leukemia cutis
- metastatic renal cell carcinoma

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**VIB9**  **Tumors of Large Hemato-Lymphoid Cells**

Large lymphoid cells may be mistaken for carcinoma or melanoma cells, but may be distinguished morphologically by their tendency to less cohesive growth in large sheets, by the absence of epithelial or melanocytic differentiation, and by immunopathology. Anaplastic large-cell lymphoma (ALCL) is prototypic (78). LyP (79) and leukemia cutis are important differentials.

**Cutaneous CD30+ (Ki-1+) Anaplastic Large-Cell Lymphoma**

**CLINICAL SUMMARY.** The entity historically described as “Ki-1+ lymphoma” was first recognized as a neoplasm manifested as cutaneous nodules composed of lymphocytes.

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**Fig. VIB9.a.** Cutaneous anaplastic large cell lymphoma, low power. This relatively large tumor is composed of a dense infiltrate occupying the entire dermis. There is associated ulceration of the overlying epidermis.

**Fig. VIB9.b.** Large cell anaplastic lymphoma, medium power. There are dense sheets of atypical cells admixed with inflammatory cells, frequently eosinophils. A number of the atypical cells show more than one nucleus.

**Fig. VIB9.c.** Large cell anaplastic lymphoma, high power. Many of the cells are large with large hyperchromatic nuclei; bizarre forms and mitotic figures are frequently seen.
with large, strikingly atypical nuclei. The neoplastic cells, usually of T-cell lineage, by definition expressed the Ki-1 (now known as CD30) antigen. The CD30 antigen is an inducible marker of lymphocyte activation that can be identified on either B or T cells. CD30 expression can also be observed in tumor stage MF, some pleomorphic T-cell lymphomas, Hodgkin lymphoma, and some nonneoplastic eruptions including LyP (see below). CD30+ ALCL lesions typically present as a single or a few large nodules or tumors located on the extremities, and ulceration and crusting are common. The lymphoma can present at any age. Patients with cutaneous ALCL do not usually develop systemic symptoms, in contrast to patients with nodal involvement at presentation. CD30+ ALCL appears to be the most common cutaneous lymphoma in patients with HIV. In contrast to immunocompetent individuals, HIV-seropositive patients with CD30+ ALCL have a dismal prognosis.

**HISTOPATHOLOGY.** It is now established that CD30+ lymphoma is not a single entity but comprises a spectrum of disorders linked by the presence of a common

Clin. Fig. VIB9. *Lymphomatoid papulosis.* Indurated erythematous nodules, some with ulcerated centers, developed on a recurrent basis in this elderly man.

Fig. VIB9.d. *Lymphomatoid papulosis, low power.* Scanning magnification reveals a dense cellular infiltrate extending well into the reticular dermis.

Fig. VIB9.e. *Lymphomatoid papulosis, medium power.* There is a mixture of large and small lymphoid cells, and neutrophils.

Fig. VIB9.f. *Lymphomatoid papulosis, high power, CD30 immunoperoxidase stain.* The scattered large atypical cells in lymphomatoid papulosis stain positive with an antibody to CD30. In contrast to anaplastic large cell lymphoma, these cells do not form large sheets or nodular clusters.
neoplastic cell type. The spectrum includes CD30+ ALCL and LyP. CD30+ ALCL is characterized by a nodular dermal and subcutaneous infiltrate of large lymphocytes with abundant, faintly basophilic cytoplasm; large, irregularly shaped vesicular nuclei with coarsely clumped chromatin along nuclear membranes; and large, irregularly shaped nucleoli. Wreath-shaped multinucleated cells are often present, as are “embryo”-shaped nuclei. Sarcomatoid (spindled) cellular morphology is encountered in rare cases. Epidermal hyperplasia or ulceration and an inflammatory infiltrate rich in neutrophils are commonly observed. Because of the abundant cytoplasm and the compact arrangement of the lesional cells, some examples may simulate a carcinoma or a sarcoma. Conversely, CD30 can be expressed by a variety of carcinomas, including embryonal carcinoma. Lesions of LyP are usually separable histologically in that atypical lymphocytes are arrayed in small numbers or in small clusters rather than sheets, within a heterogeneous infiltrate in which neutrophils and/or eosinophils are usually conspicuous.

**Lymphomatoid Papulosis**

**CLINICAL SUMMARY.** The atypical cells of LyP (79) and ALCL share similar cellular morphology, CD30 expression, and clonal rearrangement of the T-cell receptor gene. Thus, a strong case can be made that these conditions comprise a disease spectrum. Within this spectrum, the overall number of clinical lesions is roughly inversely proportional to the durability of the lesions. Thus, lesions of LyP tend to be numerous, short-lived, and recurrent in most instances, whereas ALCL lesions tend to be few in number and persistent.

**HISTOPATHOLOGY.** Lesions of LyP are usually separable histologically from cutaneous anaplastic large cell lymphoma in that atypical lymphocytes are arrayed in small numbers or in small clusters rather than sheets, within a heterogeneous infiltrate in which neutrophils and/or eosinophils are usually conspicuous. The epidermis can show a variety of patterns in LyP biopsies, including infiltration by small to medium-sized convoluted lymphocytes, an interface reaction with necrotic keratinocytes, or necrosis and ulceration.

**Leukemia Cutis**

**CLINICAL SUMMARY.** Leukemias are neoplasms of hematolymphoid cells that usually present with prominent involvement of the peripheral blood. They can be broadly grouped into acute and chronic forms of either lymphoid or myeloid lineage. Cutaneous leukemic infiltrates present as macules, papules, plaques, nodules, and ulcers. Lesions can be erythematous or purpuric. Extramedullary deposits of acute myelogenous leukemia are commonly referred to as granulocytic or myeloid sarcomas or chloromas. In addition to these specific infiltrates of leukemia, there are various inflammatory skin diseases that occur in conjunction with leukemia, sometimes referred to as leukemids. These disorders include leukocytoclastic vasculitis, pyoderma gangrenosum, Sweet’s syndrome, urticaria, erythroderma, erythema nodosum, and erythema multiforme.

**HISTOPATHOLOGY.** The most common pattern of skin involvement consists of an interstitial (reticular) infiltrate marked by diffuse permeation of the reticular dermis by leukemic cells in horizontal strands between collagen bundles. Nodular infiltrates of leukemic cells can also occur. Dense, bandlike infiltrates in the superficial dermis and sparse superficial and deep perivascular infiltrates are occasionally observed.

Acute myelogenous leukemia can assume either an interstitial or a nodular pattern. The epidermis is spared, but the subcutis is often involved. The diagnosis hinges in large part on the recognition of myeloblasts, which have scant cytoplasm, large vesicular nuclei, and nucleoli of variable size. Eosinophilic myelocytes or metamyelocytes are not pathognomonic of AML, but strongly favor that diagnosis in the proper context. These immature cells have the granules of mature eosinophils with monolobed nuclei. Cutaneous infiltrates of chronic myeloid leukemia (CML) are less common than those of AML. Similar diffuse or nodular patterns occur. The infiltrates contain a range of myelocytic differentiation from myeloblasts to segmented neutrophils. Acute lymphocytic (lymphoblastic) leukemia (ALL) shares features with lymphoblastic lymphoma, presenting typically as diffuse or nodular monomorphous infiltrates of lymphoblasts, cells with scant cytoplasm and round nuclei that are slightly to moderately convoluted with thin but well-defined nuclear membranes and finely dispersed chromatin. Histochromatographic and immunophenotypic studies can help in the identification of leukemic infiltrates. As recently summarized, a minimal panel of immunohistochemical markers should include anti-CD43 or anti-lysozyme as sensitive markers of myeloid sarcoma. Use of more specific markers of myeloid disease, such as CD33, myeloperoxidase, CD34, and CD117 is necessary to establish the diagnosis. Other antibodies may be added depending on the differential diagnosis; the choice of these can be guided by flow cytometry if this has been done. Identification of acute myeloid leukemia-associated genetic lesions may also be helpful in arriving at the correct diagnosis (80).

**Conditions to consider in the differential diagnosis:**
- pleomorphic peripheral T-cell lymphoma
- cutaneous anaplastic large cell lymphoma (CD30 (Ki-1) + lymphoma (regressing atypical histiocytosis)
- leukemia cutis
- cutaneous Hodgkin’s disease
**Fig. VIB9.g.** *Leukemia cutis, acute myelogenous leukemia, low power.* There is a dense infiltrate occupying the entire dermis extending into the subcutaneous fat. At this magnification, the predominant differential diagnosis is lymphoma cutis.

**Fig. VIB9.h.** *Leukemia cutis, acute myelogenous leukemia, medium power.* This dense infiltrate is separated from the overlying normal appearing epidermis forming a “grenz zone.” The cells show an infiltrative pattern in between collagen bundles without organization.

**Fig. VIB9.i.** *Leukemia cutis, acute myelogenous leukemia, high power.* The infiltrate is composed entirely of atypical cells with hyperchromatic nuclei and eosinophilic cytoplasm; the cells are monotonous indicating a clonal process.

**Fig. VIB9.j.** *Acute myelogenous leukemia, high power.* Eosinophilic cytoplasm and indented nuclei can be seen in this image.
**Mast Cell Tumors**

Mast cells predominate in a nodular dermal infiltrate, with scattered eosinophils.

**Urticaria Pigmentosa, Nodular Lesions (see also IIIA.2)**

**CLINICAL SUMMARY.** Children or adults with urticaria pigmentosa may present with multiple brown nodules or plaques which, on stroking, show urtication and occasionally blister formation (20). Infants, almost exclusively, may present with a usually solitary, large cutaneous nodule, which on stroking often shows not only urtication but also large bullae. Adults with urticaria pigmentosa have macular lesions with telangiectasia; urtication on stroking is variable. Mast cells are of myeloid lineage and the disease may be associated with mutation of the c-kit oncogene (81). Mast cell tumors (mastocytomas) may occur in a background of urticaria pigmentosa, or de novo.

**HISTOPATHOLOGY.** In these nodular or plaque lesions, the mast cells lie closely packed in tumorlike aggregates.

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**Fig. VIB10.a.** *Mastocytoma, low power.* There is a dense nodular infiltrate involving the upper half of the dermis. The overlying epidermis shows mild hyperplasia.

**Fig. VIB10.b.** *Mastocytoma, medium power.* The infiltrate is composed of uniform ovoid cells which are present densely in the reticular dermis but also fill the papillary dermis. The cells do not involve the overlying epidermis.

**Fig. VIB10.c.** *Mastocytoma, high power.* The individual cells have small uniform ovoid nuclei and an abundance of granular cytoplasm. Scattered eosinophils are frequently seen in all forms of mastocytosis, a clue to the diagnosis.

**Fig. VIB10.d.** *Mastocytoma, Giemsa stain.* The mast cell granules metachromatically stain purple with Giemsa stain.
The infiltrate may extend through the entire dermis and even into the subcutaneous fat. The mast cells’ nuclei in these tumors are cuboidal rather than spindle shaped, and the cells have ample eosinophilic cytoplasm and a well-defined cell border. In adults, the diagnosis can be difficult. An increase in interstitial mast cells is helpful in establishing the diagnosis. Giemsa, toluidine blue and tryptase stains, and also c-kit immunostaining, may be helpful in supporting the diagnosis. In a mastocytoma, the tumor cells present as a dense nodular infiltrate.

**Conditions to consider in the differential diagnosis:**
- mastocytosis (urticaria pigmentosa, nodular lesions)

### Tumors With Prominent Necrosis

Necrosis is a striking feature in epithelioid sarcoma, which may be in consequence be mistaken for a granulomatous process. In addition, many advanced malignancies, often metastatic, have prominent necrosis.

#### Epithelioid Sarcoma

**CLINICAL SUMMARY.** This is a distinctive rare malignant soft tissue neoplasm of uncertain origin, occurring most commonly in the distal extremities of young adult males as a slowly growing dermal or subcutaneous nodule. However, the tumor has been reported in a wide range of anatomic sites. This aggressive neoplasm is characterized by multiple recurrences, often producing ulcerated nodules and plaques in the dermis and subcutis, and by regional and systemic metastases resulting in a poor prognosis (82). An more aggressive subtype has been identified, known as the proximal axial type. Clinically, this differs from the classic type by its multinodular growth pattern, more frequent occurrence in older patients, more proximal/axial distribution (mainly, but not exclusively, involving the pelvic, perineal, and genital areas), more deep-seated location, and more aggressive clinical behavior from the outset. Angiomatoid or angiosarcoma-like and fibrous histiocytoma-like or fibroma-like subtypes have also been described (83).

**HISTOPATHOLOGY.** The tumors are composed of irregular nodules of atypical epithelioid cells with abundant eosinophilic cytoplasm and pleomorphic nuclei, merging with spindle cells. These aggregates are embedded in collagenous fibrous tissue in which there may be focal hemorrhage, hemosiderin, and mucin deposition with a patchy lymphocytic infiltrate. Mitoses are present in varied frequency, vascular invasion is a common feature, and foci of necrosis are present in the centers of tumor nodules. Ulceration follows epidermal involvement by the larger tumor nodules, and invasion extends diffusely into the subcutis and deeper soft tissues. A fibroma-like variant of epithelioid sarcoma has also been reported, in which the spindle cell pattern predominates without the characteristic epithelioid cells and nodularity. At low power, the neoplasm may suggest a granulomatous process such as granuloma annulare, necrobiosis lipoidica, or rheumatoid nodule. The cellular atypia, diffuse stromal invasion, and foci of necrosis involving tumor cells and not only stroma, as in the necrobiotic granulomatous processes, identify the process as malignant. The diagnosis is supported by positive immunostaining for cytokeratin, epithelial membrane antigen and vimentin, and negativity for leukocyte common antigen. Histologically, the proximal subtype differs from the classic type by its larger size and deeper invasion often into muscle, and by larger epithelioid cells, with...
vesicular nuclei, and prominent nucleoli; copious, eccentric cytoplasm; marked cytologic atypia; and frequent rhabdoid features. Tumoral necrosis is also a common finding in the proximal subtype, but usually without the granuloma-like appearance of the classic type.

**Conditions to consider in the differential diagnosis:**
- epithelioid sarcoma
- metastatic carcinomas, sarcomas, melanomas
- occasional advanced primary malignant tumors

### Miscellaneous & Undifferentiated Epithelial Tumors

Proliferations of atypical cells with more or less abundant cytoplasm and contiguous cell borders occupy the dermis as nodular masses.

**Granular Cell Tumor**

See Figs. VIB12.a–c.

### Cellular Neurothekeoma

Cellular neurothekeoma may mimic melanoma, and may express some “melanoma markers” such as MITF and NKI/C3. However, it is negative for S100, Melan-A, HMB-45 and tyrosinase.

### Metastatic Malignant Melanoma

See Figs. VIB12.h, i.

**Conditions to consider in the differential diagnosis:**
- Epithelial Tumors
  - undifferentiated carcinoma (large cell, small cell)
  - neuroendocrine tumor
- Epithelial Simulants
  - anaplastic large cell lymphoma (CD30/Ki-1, usually T cells)
  - epithelioid sarcoma
  - granular cell nerve sheath tumor (granular cell tumor/schwannoma)
  - plexiform granular cell nerve sheath tumor
Fig. VIB12.a. *Granular cell tumor, medium power.* There is a cellular tumor in the dermis. Epidermal hyperplasia overlying a granular cell tumor may be absent or minimal as seen here or there may be striking pseudoepitheliomatous hyperplasia resembling a squamous cell carcinoma.

Fig. VIB12.b. *Granular cell tumor, high power.* The individual cells are large with an abundance of eosinophilic granular cytoplasm. There are small nuclei granules can be highlighted using the PAS stain.

Fig. VIB12.c. *Granular cell tumor with pseudoepitheliomatous hyperplasia, high power.* These granules can be highlighted with a PAS stain, and the tumors are typically S100 positive (not shown).

Fig. VIB12.d. *Cellular neurothekeoma, low power.* There is a relatively well-circumscribed nodule within the dermis.

Fig. VIB12.e. *Cellular neurothekeoma, medium power.* The neoplasm is composed of multiple interlacing clusters of cells which may be reminiscent of a neuroma at this magnification.
**Cellular neurothekeoma, high power.** The cells are spindle and epithelioid in form, some with an abundance of eosinophilic cytoplasm. The nuclei are relatively small and uniform with minimal atypia and minimal mitotic activity.

**Cellular neurothekeoma, high power.** Positive staining for MITF (top) and NKI/C3, while not specific, are characteristic for this tumor. S100 and other melanoma markers were negative.

**Metastatic malignant melanoma, low power.** A pale staining, poorly defined tumor has replaced the reticular dermis.

**Metastatic malignant melanoma, high power.** The tumor is composed of pleomorphic anaplastic cells. Many cells show multiple nuclei as well as atypical nuclei and prominent nucleoli. Because of the presence of melanin pigment, immunoperoxidase stains are not necessary to definitively identify this as metastatic melanoma and not metastatic carcinoma.
malignant granular cell tumor
epithelioid angiosarcoma
cellular neurothekeoma (immature nerve sheath myxoma)
ganglioneuroma
cephalic brain-like hamartoma (nasal glioma)
encephalocele
cutaneous meningiomas

SPINDLE CELL, PLEOMORPHIC & CONNECTIVE TISSUE TUMORS

In the dermis, there is a proliferation of elongated tapered “spindle cells”; these may be of fibrohistiocytic, muscle, neural (Schwannian), melanocytic or unknown origin. Immunohistochemistry may be essential in making these distinctions.

1. Fibrohistiocytic Spindle Cell Tumors
2. Schwannian/Neural Spindle Cell Tumors
3. Spindle Cell Tumors of Muscle
4. Melanocytic Spindle Cell Tumors
5. Tumors and Proliferations of Angiogenic Cells
6. Tumors of Adipose Tissue
7. Tumors of Cartilaginous Tissue
8. Tumors of Osseous Tissue

VIC1 Fibrohistiocytic Spindle Cell Tumors

There is a proliferation of spindle to pleomorphic cells that may synthesize collagen, or be essentially undifferentiated. Because there are no useful specific markers for fibroblasts, immunohistochemistry is of little diagnostic utility except to rule out non-fibrous spindle cell tumors. Morphology is critical for accurate diagnosis.

VIC1a Fibrohistiocytic Tumors With Minimal or No Atypia

In most benign lesions, there is no atypia. Random atypia that may be seen in some dermatofibromas is an exception. Low grade malignancies such as dermatofibrosarcoma protuberans may show little or no atypia.

Dermatofibroma

CLINICAL SUMMARY. Dermatofibromas (84) occur in the skin as firm, indolent red to red-brown or occasionally blue-black single or multiple nodules, usually only a few millimeters in diameter. The cut surface of the lesions varies in color from white to yellowish brown, depending on the proportions of fibrous tissue, lipid, and hemosiderin present. The lesions usually persist indefinitely.

HISTOPATHOLOGY. The epidermis is usually hyperplastic, with hyperpigmentation of the basal layer and elongation of the rete ridges, separated by a clear (Grenz) zone from a spindle cell tumor in the dermis. The highly characteristic hyperplasia of the overlying epidermis in the center of the lesion may mimic basal cell carcinoma and has considerable value in establishing the diagnosis of dermatofibroma. The dermal tumor is composed of fibroblast-like spindle cells, histiocytes, and blood vessels in varying proportions. Foamy histiocytes and multinucleated giant cells containing lipid or hemosiderin may be present, sometimes in large numbers, forming xanthomatosus aggregates. Capillaries may be plentiful in the stroma, giving the lesion an angiomatous component; when associated with a sclerotic stroma, such lesions have been referred to as “sclerosing hemangioma.” In some small lesions, the spindle cells are distributed singly between the collagen bundles, forming a zone of subtly increased cellularity, whereas in larger tumors, there is much denser cellularity and the spindle cells are arranged in sheets or interlocking strands in storiform pattern. The dermal tumor is poorly demarcated on both sides, so that the fibroblasts and the young basophilic collagen extend between the mature, eosinophilic collagen bundles of the dermis and surround them, trapping normal collagen bundles at the periphery of the tumor nodule.

Cellular dermatofibroma is a very dense cellular tumor with fascicular and storiform growth patterns and frequent extension into the subcutis. The neoplasm shares some features, therefore, with dermatofibrosarcoma protuberans (DFSP), from which it is distinguished by the overlying epidermal hyperplasia, polymorphism of the tumor cell population, extension of tumor cells at the edge of the lesion to surround individual hyalinized collagen bundles, and the absence of immunostaining for CD34. The cellular dermatofibroma also extends into the subcutis along the septa or in a bulging, expansile pattern, rather than in the more diffusely infiltrative pattern of DFSP, which produces a typical honeycomb-like pattern and extends far along interlobular septa of the panniculus. Cellular dermatofibromas may recur and rare cases have even been reported to have metastasized to the lung (85). These lesions should therefore be completely excised.

Cellular Dermatofibroma

See Figs. VICa.e, a.f.

Sclerosing/Angiomatoid Spitz Nevus (Desmoplastic Spitz Nevus)

In a few examples of this condition, the Spitz nevus cells may be so inconspicuous that a regressing or desmoplastic melanoma, or a fibrosing disorder or an angiomatous lesion may be simulated (86).

Dermatofibrosarcoma Protuberans

CLINICAL SUMMARY. DFSP (87) is a slowly growing dermal spindle cell neoplasm of intermediate malignancy that
usually forms an indurated plaque on which multiple reddish purple, firm nodules subsequently arise, sometimes with ulceration. A characteristic COL1-PDGF fusion gene is present (see below). The tumors occur most frequently on the trunk or the proximal extremities of young adults and only rarely in the head and neck. A small proportion of cases have been reported in childhood and, rarely, as congenital lesions. Local recurrence is common but metastasis is rare.

**HISTOPATHOLOGY.** DFSP is composed of densely packed, monomorphous, plump spindle cells arranged in a storiform (mat-like) pattern in the central areas of tumor nodules, whereas at the periphery there is diffuse infiltration of the dermal stroma, frequently extending into the subcutis and producing a characteristic honeycomb pattern. Infiltration into the underlying fascia and muscle is a late event. The peripheral elements of the tumor may have a deceptively bland appearance, and may extend far along septa of the panniculus, which can cause difficulties in determining the true extent of the tumor. Myxoid areas, sometimes resembling liposarcoma, include a characteristic vascular component of slitlike anastomosing thin-walled blood vessels presenting a crow’s foot or chicken wire appearance. Melanin-containing cells may be present

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**Clin. Fig. VIC1a.a**

Clin. Fig. VIC1a.a. *Dermatofibroma.* A 47-year-old man presented with a 4 mm deep firm smooth red nodule on the extensor finger.

**Clin. Fig. VIC1a.b**

Clin. Fig. VIC1a.b. *Dermatofibroma.* A sectioned gross specimen demonstrating a circumscribed yellowish nodule in the reticular dermis. The epidermis is hyperplastic and hyperpigmented, and is separated from the epidermis by a clear zone. (P. Heenan).

**Fig. VIC1a.a**

*Dermatofibroma, low power.* There is a symmetrical but non-circumscribed area of hypercellularity in the mid dermis. This proliferation is associated with retraction of the overlying epidermis which produces the “dimple” sign which is seen clinically.

**Fig. VIC1a.b**

*Dermatofibroma, medium power.* Within the mid dermis there is a proliferation of bland-appearing spindled cells. These cells encircle bundles of reticular dermal collagen. *(continues)*
**Fig. VIC1a.c.** *Dermatofibroma, medium power.* The overlying epidermis becomes hyperplastic as well as hyperpigmented.

**Fig. VIC1a.d.** *Dermatofibroma, high power.* There is only slight (or usually no) “honeycombing” of fat at the base.

**Fig. VIC1a.e.** *Cellular dermatofibroma, medium power.* The tumor consists of spindle cells arranged in densely cellular fascicular and storiform patterns.

**Fig. VIC1a.f.** *Cellular dermatofibroma, high power.* There is little or no honeycombing of the fat or extension down septa. Factor XIIIa is positive in the lesional cells. A negative immunohistochemical stain for CD34 (not shown) assists in differentiating a cellular dermatofibroma from a dermatofibrosarcoma protuberans.
Sclerosing/Angiomatoid Spitz nevus. There is an ill-defined area of altered collagen in the dermis.

Fibrovascular lesion

At intermediate magnification prominent vessels are the major feature.

At high power, with searching, one can appreciate the large spindle and/or epithelioid lesional cells among the altered collagen bundles. In case of doubt, an S100 stain will reliably highlight these cells.

Dermatofibrosarcoma protuberans, recurrent. An elderly woman presented with multiple variably shaped flesh-colored nodules and papules in a chest wall excision scar.

Dermatofibrosarcoma protuberans. A sectioned gross specimen reveals an asymmetric tumor spanning the dermis and infiltrating the subcutis. (P. Heenan). (continues)
Fig. VIC1a.j. *Dermatofibrosarcoma protuberans, low power.* There is a tumor which occupies nearly the entire dermis and extends into the underlying subcutaneous fat.

Fig. VIC1a.k. *Dermatofibrosarcoma protuberans, medium power.* The spindle cell proliferation shows a storiform or cartwheel pattern.

Fig. VIC1a.l. *Dermatofibrosarcoma protuberans, high power.* The neoplasm is composed of relatively uniform spindled cells whose nuclei are elongate with tapered ends. Mitoses may be identified but are usually few in numbers.

Fig. VIC1a.m. *Dermatofibrosarcoma protuberans, medium power.* This spindle cell proliferation characteristically infiltrates the subcutaneous fat, producing a “honey-comb” pattern.
in a small proportion of tumors, so-called Bednar tumor (pigmented DFSP, storiform neurofibroma). Giant cells are seen in a small proportion of otherwise typical DFSP; it has been suggested that giant cell fibroblastoma is a juvenile variant of DFSP. Fibrosarcomatous areas are seen in a small proportion of DFSP, characterized by a fascicular or herringbone growth pattern of the spindle cells, usually presenting with larger size, more expansile patterns of invasion of the subcutis and with muscle invasion, p53 expression, and increased proliferative activity. This may have increased propensity for local recurrence and rarely for metastasis. Demonstration of the presence of a COL1A1-PDGFB fusion gene may be a useful tool for diagnosis of DFSP and particularly for the fibrosarcomatous variant (88).

**Fibrous Papule (Angiofibroma)**

See Figs. VIC1a.n–a.p.

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**Recurrent Infantile Digital Fibromatosis**

See Figs. VIC1a.q–a.s.

**Keloid**

See Figs. VIC1a.t, a.u.

**Acquired Digital Fibrokeratoma**

See Figs. VIC1a.v, a.w.

**Giant Cell Tumor of Tendon Sheath**

See Figs. VIC1a.x–a.z.

**Nodular Fasciitis**

See Figs. VIC1a.za–zc.

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**Fig. VIC1a.n.** Fibrous papule (angiofibroma), low power. This dome-shaped neoplasm shows a normal overlying epidermis and a fibrovascular core.

**Fig. VIC1a.o.** Fibrous papule (angiofibroma), medium power. The dermis is fibrotic and one cannot identify a distinction between papillary and reticular dermis. There is an increased number of small, mature vascular channels which contain erythrocytes.

**Fig. VIC1a.p.** Fibrous papule (angiofibroma), high power. The stroma is composed of collagen and stellate fibroblasts around the small vascular channels.
Recurrent infantile digital fibromatosis, low power. The dermis is replaced by a tumor which is relatively uniform and symmetrical.

Recurrent infantile digital fibromatosis, medium power. The tumor is composed of uniform spindled cells embedded in a collagenous stroma. There is no atypia.

Recurrent infantile digital fibromatosis, high power. High magnification reveals elongate nuclei with tapered ends. The collagenous stroma is wavy in appearance. The characteristic finding in these lesions is the eosinophilic cytoplasmic inclusions. These inclusions stain red using the Masson-Trichrome stain.

Keloid, low power. This lesion can be diagnosed at scanning magnification. No adnexal structures are seen within the dermis. Within the dermis, there are multiple bundles of thick eosinophilic collagen.

Keloid, high power. The collagen bundles are markedly thickened and eosinophilic. Scattered small fibroblasts are seen between these hyalinized collagen bundles.
**Fig. VIC1a.v.** Acquired digital fibrokeratoma, low power. This biopsy of acral skin shows a dome-shaped lesion which is hyperkeratotic. There is a fibrovascular core.

**Fig. VIC1a.w.** Acquired digital fibrokeratoma, medium power. The epidermis shows mild, uniform, verrucous hyperplasia. There are no viral cytopathic changes. The core shows fibrosis and a few small vascular channels.

**Fig. VIC1a.x.** Giant cell tumor of tendon sheath, low power. Within the deep tissue there is a large, irregularly shaped nodular fibrohistiocytic proliferation.

**Fig. VIC1a.y.** Giant cell tumor of tendon sheath, medium power. The tumor is composed of plump histiocytes and numerous multinucleated giant cells.

**Fig. VIC1a.z.** Giant cell tumor of tendon sheath, high power. These osteoclast-like giant cells have multiple nuclei. There are also scattered lymphocytes throughout the lesion.
FIBROHISTIOCYTIC TUMORS WITH HIGH-GRADE ATYPIA

High-grade cytologic atypia is often a sign of malignancy. However, atypical fibroxanthoma is a lesion that demonstrates often startling atypia yet usually follows a benign course.

**Atypical Fibroxanthoma**

**CLINICAL SUMMARY.** Atypical fibroxanthoma (89) is a fairly common pleomorphic spindle cell neoplasm of the dermis that, despite apparently malignant histologic features, usually follows an indolent or locally aggressive course. Because a small number of metastases have been reported, atypical fibroxanthoma has become regarded as a neoplasm of low-grade malignancy related to malignant fibrous histiocytoma, from which it may be indistinguishable histologically. According to this view, the more favorable prognosis of atypical fibroxanthoma is related to its small size and superficial location. The disease usually presents as a solitary nodule less than 2 cm in diameter on the exposed skin of the head and neck or dorsum of the hand of elderly patients, often with a short history of rapid growth. The lesions are usually associated with severe actinic damage, and a few have arisen in areas treated by radiation.

**HISTOPATHOLOGY.** Atypical fibroxanthoma is an exophytic, densely cellular neoplasm, unencapsulated but with only limited infiltration of the stroma, frequently with an epidermal collarette. The tumor may extend to the dermo-epidermal junction, but there is no direct continuity with the squamous epithelium, although ulceration is often present. Severe solar elastosis is present in the adjacent dermis. The classical tumor is composed of pleomorphic histiocytelike cells and atypical giant cells, often with bizarre nuclei,
Clin. Fig. VIC1b.a. *Atypical fibroxanthoma.* A symmetrical nodule appeared suddenly and grew rapidly in sun-damaged skin of an elderly man.

**Fig. VIC1b.a.** *Atypical fibroxanthoma, high power.* The ulcerated tumor is composed of elongate spindle cells with a somewhat haphazard arrangement.

**Fig. VIC1b.b.** *Atypical fibroxanthoma, medium power.* There is prominent nuclear pleomorphism, often much more pronounced than in this example.

**Fig. VIC1b.c.** *Atypical fibroxanthoma, high power.* Other spindle cell tumors (melanoma, squamous cell carcinoma, soft tissue tumors) must be excluded with immunostains.

Prominent nucleoli, and numerous mitotic figures, including abnormal forms. The cells are arranged in a compact, disorderly pattern, surrounding but not destroying adnexal structures. Fibroblast-like spindle cells are present in variable numbers; cells of morphology intermediate between these spindle cells and histiocyte-like cells are also present. Scattered inflammatory cells and numerous small blood vessels are present, commonly with focal hemorrhage.

**Malignant Fibrous Histiocytoma**
See Figs. VIC1b.d–g.

**Dermatofibrosarcoma Protuberans With Sarcomatoid Change**
See Figs. VIC1b.h–k.
VI. Tumors and Cysts of the Dermis and Subcutis

Fig. VIC1b.d. Malignant fibrous histiocytoma, low power. Scanning magnification of a large spindle cell tumor shows extensive involvement of the subcutaneous fat and dermis.

Fig. VIC1b.e. Malignant fibrous histiocytoma, low power. The size, location, and depth of involvement distinguish this lesion from atypical fibroxanthoma, a smaller, more superficial lesion.

Fig. VIC1b.f. Malignant fibrous histiocytoma, medium power. This highly cellular tumor may show zones of spindled cells or, as seen here, large epithelioid cells with obvious nuclear atypia and pleomorphism.

Fig. VIC1b.g. Malignant fibrous histiocytoma, high power. The atypical cells may have multiple nucleoli. Mitoses as well as atypical mitoses are easily identified.
Localized myxoid lesions may present clinically as cysts, but they lack an epithelial lining and represent localized lesions of fibroblasts characterized by overproduction of mostly nonfibrillary matrix materials.

**Lesions With Myxoid Changes**

**Mucocele**
See Figs. VIC1c.a, b.

**Digital Mucous Cyst**
See Clin. Fig. VIC1c.a and Figs. c.c, d.

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**Cutaneous Myxoma**
See Figs. VIC1c.e–g.

**Conditions to consider in the differential diagnosis:**

- fibrohistiocytic tumors
  - benign fibrous histiocytoma (dermatofibroma)
  - cellular dermatofibroma
  - aneurysmal fibrous histiocytoma
  - juvenile xanthogranuloma, spindle cell variant
  - progressive nodular histiocytoma (deep fibrous type)
  - plexiform fibrohistiocytic tumor
  - atypical fibroxanthoma

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**Fig. VIC1b.h.** Dermatofibrosarcoma protuberans with Sarcomatoid change, low power. A bulky tumor that extensively involves the subcutaneous fat and the fascia.

**Fig. VIC1b.i.** Dermatofibrosarcoma protuberans with Sarcomatoid change, low power. Extensive honey-combing of the fat.

**Fig. VIC1b.j.** Dermatofibrosarcoma protuberans with Sarcomatoid change, low power. A very cellular and somewhat storiform proliferation.

**Fig. VIC1b.k.** Dermatofibrosarcoma protuberans with Sarcomatoid change, low power. Severe atypia and frequent mitoses.
**Fig. VIC1c.a.** *Mucocele, low power.* Within the submucosa there is a cystic structure filled with amorphous material. Minor salivary glands are seen in the lower portion of this biopsy.

**Fig. VIC1c.b.** *Mucocele, medium power.* This lesion has no true cyst wall but the apparent “wall” is composed of a fibroblastic response. There are also numerous macrophages which have engulfed the mucinous material (muciphages).

**Clin. Fig. VIC1c.a.** Digital mucous cyst. This asymptomatic nodule requires surgical excision for definitive treatment.

**Fig. VIC1c.c.** Digital mucous cyst, low power. This biopsy of acral skin shows a dome-shaped lesion created by an expanded papillary dermis. The overlying stratum corneum shows a focus of crusting.

**Fig. VIC1c.d.** Digital mucous cyst, medium power. The pale staining area is composed of glycosaminoglycans which can be high-lighted using alcian blue or colloidal iron stains. There are scattered small fibroblasts. The adjacent epidermis shows mild hyperplasia.
fibrous tumors
- fibrous papule (angiofibroma)
- hypertrophic scar, keloid
- dermatofibrosarcoma protuberans

sarcomas
- malignant fibrous histiocytoma
- angiomatoid fibrous histiocytoma
- synovial sarcoma

fibromatoses
- desmoid tumor
- recurrent infantile digital fibromatosis
- juvenile hyaline fibromatosis

fibromas
- fibroma of tendon sheath
- follicular fibroma
- acquired digital fibroma
- elastofibroma
- dermatomyofibroma

giant cell tumors
- giant cell fibroblastoma
- giant cell tumor of tendon sheath

proliferative lesions of the fascia
- nodular fasciitis
- cranial fasciitis of childhood

myxoid spindle cell lesions
- cutaneous myxoma
- digital mucous cyst
- mucocele of oral mucosa

VIC2 Schwannian/Neural Spindle Cell Tumors

These tumors are composed of elongated, narrow spindle cells that tend to have serpentine S-shaped nuclei, and to be arranged in “wavy” fiber bundles. Immunohistochemistry for S100 is useful, but not specific.

Neurofibromas

CLINICAL SUMMARY. Extranodal sporadic cutaneous neurofibromas (90) (ESCNs) (the common sporadic neurofibromas) are soft, polypoid, skin-colored or slightly tan,
and small (rarely larger than a centimeter in diameter). They usually arise in adulthood. The presence of more than a few cutaneous neurofibromas raises the possibility of neurofibromatosis, and should prompt an evaluation for other confirmatory stigmata. Diffuse neurofibromas are usually larger and are highly infiltrative, and have a somewhat greater chance of being associated with neurofibromatosis. Plexiform neurofibromas are more likely than not to be associated with NF-1.

**HISTOPATHOLOGY.** Most examples of ESCN are faintly eosinophilic, and are circumscribed but not encapsulated: they are extraneural. Thin spindle cells with elongated, wavy nuclei are regularly spaced among thin, wavy collagenous strands. The strands are either closely spaced (homogeneous pattern) or loosely spaced in a clear matrix (loose pattern). The two patterns are often intermixed in a single lesion. Rarely, ESCNs are composed of widely spaced spindle and stellate cells in a myxoid matrix. The regular spacing of adnexa is preserved in cutaneous neurofibromas. Entrapped small nerves occasionally are enlarged and hypercellular. Tactoid (tactile corpuscle-like) bodies and pigmented dendritic melanocytes are most uncommon. These tumors are essentially the same as those that occur in von Recklinghausen’s neurofibromatosis.

**Neurofibromatosis**

See Clin. Fig. VIC2 and Figs. VIC2.d–g.

**Schwannoma (Neurilemmoma)**

**CLINICAL SUMMARY.** These benign, Schwann cell neoplasms present as solitary, skin-colored tumors along the course of peripheral or cranial nerves (91). Their usual size is between 2 and 4 cm and their usual location is the head or the flexor aspect of the extremities. When small, most schwannomas are asymptomatic, but pain, localized to the tumor or radiating along the nerve of origin, can be a complaint.

**HISTOPATHOLOGY.** Schwannomas are intraneural and symmetrically expansile. They are confined by the perineurium of the nerve of origin and displace and compress the endoneurial matrix. Most of the symmetrically bundled

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**Fig. VIC2.a**  
Neurofibroma, low power. There is a dome-shaped, non-encapsulated neoplasm within the dermis.

**Fig. VIC2.b**  
Neurofibroma, medium power. The lesion is composed of elongate, spindled cells which are embedded in an eosinophilic matrix. In the center of this photomicrograph, there is a structure resembling a small cutaneous nerve.

**Fig. VIC2.c**  
Neurofibroma, high power. The nuclei are elongate and S-shaped or serpentine, with tapered ends, and they are embedded in an eosinophilic matrix made up of “wavy” fibers. Mast cells are frequently seen in neural tumors.
Clin. Fig. VIC2. Neurofibromatosis. A 51-year-old man presented with axillary freckling, café au lait macules and generalized soft pigmented and flesh-colored papules and nodules with “button-hole” compression (soft, compressible centers).

Fig. VIC2.d. Plexiform neurofibroma, low power. This plaque-like lesion shows multiple nodular aggregates embedded in an eosinophilic background.

Fig. VIC2.e. Plexiform neurofibroma, medium power. There are plexiform tangles of neural tissue with slight retraction from the background matrix. The background matrix shows typical changes of a neurofibroma.

Fig. VIC2.f. Plexiform neurofibroma, medium power. The plexiform tangles resemble large nerves. The background shows spindled cells in an eosinophilic matrix.

Fig. VIC2.g. Plexiform neurofibroma, high power. Close inspection of the nodular aggregates reveal wavy spindled cells with small uniform nuclei. There are scattered mast cells.
nerve fibers of the nerve of origin are displaced eccentrically between the tumor and the perineurium. Two variant patterns, namely Antoni A and Antoni B types, have been described. In the Antoni type A tissue, uniform spindle cells are arranged back to back, and each cell is outlined by delicate, rigid reticular fibers (basement membranes). The cells tend to cluster in stacks, and the respective nuclei tend to form palisades. Two neighboring palisades, the intervening cytoplasms of Schwann cells, and associated reticular fibers, all constitute a Verocay body. In Antoni type B tissue, Schwann cells are loosely spaced in a clear, watery matrix.

**Fig. VIC2.h.** Schwannoma (neurilemmoma), low power. Within the dermis there is a relatively well circumscribed, but non-encapsulated cellular neoplasm. The overlying epidermis is unremarkable.

**Fig. VIC2.i.** Schwannoma (neurilemmoma), medium power. In this area of the neurilemmoma the Antoni type A tissue shows Verocay body formation where the nuclei of the spindle cells are aligned in parallel arrays.

**Fig. VIC2.j.** Schwannoma (neurilemmoma), medium power. In the Antoni type B tissue, Schwann cells are loosely spaced in a clear, watery matrix.

**Palisaded Encapsulated Neuroma**

See Figs. VIC2.k–m.

**Accessory Digit**

See Figs. VIC2.n–p.

**Conditions to consider in the differential diagnosis:**

- neurofibromas
  - sporadic cutaneous neurofibroma (common neurofibroma)
  - extraneural (common neurofibroma)
  - intraneural neurofibroma
  - pacinian neurofibroma
- neurofibromatosis
  - plexiform neurofibroma
  - diffuse neurofibroma
nerve sheath tumors
- fibrolamellar nerve sheath tumor
- storiform nerve sheath tumor (perineurioma)
- mature (myxoid) neurothekeoma, nerve sheath myxoma
- granular cell nerve sheath tumor (granular cell tumor/schwannoma)
- plexiform granular cell nerve sheath tumor
- malignant granular cell tumor

intraneural neuromas
- palisaded and encapsulated neuroma (PEN)
- intraneural plexiform neuroma
- mucosal neuroma syndrome
- linear cutaneous neuroma

neurilemmomas (schwannomas)
- typical schwannoma
- cellular schwannoma
- atypical schwannoma
- transformed (borderline) schwannoma
- epithelioid schwannoma

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**Fig. VIC2.k.** Palisaded encapsulated neuroma, low power. Within the superficial dermis there is a well circumscribed nodular tumor.

**Fig. VIC2.l.** Palisaded encapsulated neuroma, medium power. This well circumscribed tumor is surrounded by a thin zone of fibrous connective tissue but despite its name does not always form a true capsule. The tumor is composed of interlacing bundles of neural tissue.

**Fig. VIC2.m.** Palisaded encapsulated neuroma, high power. These bundles are composed of elongate spindled cells which are wavy in appearance. Significant atypia or mitotic activity is not seen. The capsule may stain with epithelial membrane antigen (EMA).
glandular schwannoma
plexiform schwannoma
infiltrating fascicular schwannoma of infancy
malignant schwannomas, intraneural or extraneural
malignant nerve sheath tumor
psammomatous malignant schwannoma
epithelioid malignant schwannoma
miscellaneous
impingement neurofasciitis (Morton's neuroma)
accessory digit
ganglioneuroma

**VIC3 Spindle Cell Tumors of Muscle**

Smooth muscle cells have more abundant cytoplasm than fibroblasts or Schwann cells. The cytoplasm is trichrome positive, and reacts with muscle markers—desmin, muscle-specific actin. The nuclei tend to have blunt ends. In neoplasms, the cells tend to be arranged in whorled bundles.

**Leiomyomas**

**CLINICAL SUMMARY.** Five types of leiomyomas of the skin (92) are: (1) multiple piloleiomyomas and (2) solitary piloleiomyomas, both arising from arrectores pilorum muscles; (3) solitary genital leiomyomas, arising from the dartoic, vulvar, or mammillary muscles; (4) solitary angioleiomyomas, arising from the muscles of veins; and (5) leiomyomas with additional mesenchymal elements.

*Multiple piloleiomyomas*, by far the most common type of leiomyoma, are small, firm, red or brown intradermal nodules arranged in a group or in a linear pattern. Often, two or more areas are affected. Usually, but not always, the lesions are tender and give rise spontaneously to occasional attacks of pain. *Solitary piloleiomyomas* are intradermal nodules that are usually larger than those of multiple piloleiomyomas, measuring up to 2 cm in diameter. Most of them are tender and also occasionally painful. *Solitary genital leiomyomas* are located on the scrotum, the labia...
majora, or, rarely, the nipples. Their location is intradermal. In contrast to the other leiomyomas, most genital leiomyomas are asymptomatic. **Solitary angioleiomyomas** are usually subcutaneous. Pain and tenderness are evoked by most, but not all, angioleiomyomas.

**HISTOPATHOLOGY.** Piloleiomyomas, whether multiple or solitary, and genital leiomyomas are similar in histologic appearance. They are poorly demarcated and are composed of interlacing bundles of smooth muscle fibers with in which varying amounts of collagen bundles are intermingled. The muscle fibers composing the smooth muscle bundles are generally straight, with little or no waviness; they contain centrally located, thin, very long, blunt-edged, “eel-like” nuclei. **Angioleiomyomas** differ from the other types of leiomyomas in that they are encapsulated and contain numerous vessels, with only small amounts of collagen as a rule. The numerous veins that are present vary in size and have muscular walls of varying thickness. On this basis, angioleiomyomas have been subdivided into a capillary or

**Clin. Fig. VIC3.a.** *Multiple scrotal leiomyomas.* A 60-year-old man presented with multiple asymptomatic flesh-colored nodules over the scrotum.

**Fig. VIC3.a.** *Scrotal Leiomyoma, low power.* Within the dermis there is a poorly circumscribed neoplasm which has replaced the pre-existing adnexal structures. The neoplasm is composed of interlacing bundles of eosinophilic material.

**Fig. VIC3.b.** *Scrotal Leiomyoma, medium power.* At this magnification there are interwoven bundles of spindle cells, many perpendicular to one another. The nuclei are small and bland.

**Fig. VIC3.c.** *Scrotal Leiomyoma, high power.* The nuclei of smooth muscle are elongate with blunt ends (cigar-shaped). Perinuclear vacuolization is frequently seen in smooth muscle cells.
solid type, a cavernous type, and a venous type. In the capillary type, the vascular channels are numerous but small.

**Smooth Muscle Hamartoma**

See Clin. Fig. VIC3.b and Figs. VIC.g–i.

**Leiomyosarcoma**

See Figs. VIC3.j–m.

**Conditions to consider in the differential diagnosis:**

- leiomyoma
- angioleiomyoma
- superficial leiomyosarcoma
- infantile myofibromatosis
- solitary myofibroma
dermatomyofibroma
- benign mixed mesodermal proliferations
- malignant mesenchymal tumors of uncertain origin
- smooth muscle hamartoma
- rhabdomyosarcoma

**Fig. VIC3.d.** *Angioleiomyoma, low power.* There is a well-circumscribed nodule within the deep dermis or subcutaneous fat. Unlike piloleiomyoma, the lesion is sharply separated from the surrounding normal tissue.

**Fig. VIC3.e.** *Angioleiomyoma, medium power.* There are only a few dilated vascular channels within this proliferation of smooth muscle.

**Fig. VIC3.f.** *Angioleiomyoma, high power.* The nuclei are elongate with blunt ends and there may be perinuclear vacuolization.

**Clin. Fig. VIC3.b.** Becker’s nevus. This tan patch with feathery borders and terminal hairs became most evident during puberty. Histologically, there is often an associated smooth muscle hamartoma.
**Fig. VIC3.g.** Becker’s nevus/smooth muscle hamartoma, low power. The epidermis is slightly hyperplastic. Within the dermis there is an increased number of smooth muscle bundles. The smooth muscle bundles do not form a solid aggregate as they do in a leiomyoma.

**Fig. VIC3.h.** Becker’s nevus/smooth muscle hamartoma, medium power. The bundles of smooth muscle are separated from one another by intervening normal collagen.

**Fig. VIC3.i.** Becker’s nevus/smooth muscle hamartoma, medium power. The overlying epidermis shows slightly elongate rete ridges and diffuse basal layer hyperpigmentation. There are scattered small melanocytes without formation of nests.

**Fig. VIC3.j.** Leiomyosarcoma, low power. The dermis has been replaced by a highly cellular spindle cell neoplasm. There is no definitive association with the overlying epidermis.

**Fig. VIC3.k.** Leiomyosarcoma, medium power. The tumor has an infiltrative border. (continues)
Melanocytic Spindle Cell Tumors

Melanocytic spindle cell tumors may have many attributes of schwannian tumors described above. S100 is positive, and HMB45 is often negative in the spindle cell melanomas. Diagnosis of melanoma then depends on recognizing melanocytic differentiation—pigment synthesis, or a characteristic intra-epidermal \textit{in situ} or microinvasive component.

Desmoplastic Melanoma

\textbf{Clinical Summary.} Desmoplastic melanoma (93) presents attributes of melanocytic, fibroblastic, and Schwannian differentiation, often mixed within a single lesion. Desmoplasia is most often observed in a spindle cell vertical growth phase of lentigo maligna melanoma or acral lentiginous melanoma. The clinical presentation is therefore that of the \textit{in situ} or microinvasive radial growth phase component. However, desmoplastic changes are occasionally seen in tumors with rounded or undifferentiated melanoma cells. Although the reported survival rate for desmoplastic melanoma is poor, this is because many of the cases reported in the earlier literature had already recurred at the time the diagnoses were made. However, the probability of survival is relatively good for prospectively diagnosed and definitively treated desmoplastic melanoma, because, despite the considerable thickness of many of these lesions, the prognostically important mitotic rate and tumor-infiltrating lymphocyte responses are often favorable. “Mixed” desmoplastic melanomas, which by definition have a $>10\%$ component of epithelial differentiation, have a significantly worse prognosis; in a recent study 5 of 23 mixed but none of 17 pure desmoplastic melanomas had positive sentinel nodes (94).

\textbf{Histopathology.} The collagen in pure desmoplastic melanoma is arranged as delicate fibrils that extend among the tumor cells and separate them from one another. In mixed tumors, there is a component of $>10\%$ of the tumor in which the cells, which may be spindle or epithelioid, are in continuity with each other in nests, fascicles, or sheets. The tumor cells in desmoplastic areas are typically spindle shaped and tend not to exhibit high-grade nuclear atypia. The mitotic rate is often very low or even zero. A characteristic feature is the presence of clusters of tumor-infiltrating lymphocytes within the tumor. The cells tend to be arranged in “wavy” fiber bundles which may recall the “schwannian” patterns of neurofibromas, neurotized nevi, and malignant schwannomas, and may lead to diagnostic error. Because the melanoma cells are usually elongated and amelanotic and are embedded in a markedly fibrotic stroma, the tumors may simulate a fibromatosis or a fibrohistiocytic lesion. Staining with S-100 protein...
**Fig. VIC4.a.** Desmoplastic melanoma, low power. There is a spindle cell proliferation throughout the dermis. It is associated with increased collagen production, a feature which may suggest a diagnosis of a dermatofibroma or a fibromatosis.

**Fig. VIC4.b.** Desmoplastic melanoma, medium power. These lesions are generally not diagnosed early and therefore most lesions are relatively thick extending to the deep reticular dermis or subcutaneous fat.

**Fig. VIC4.c.** Desmoplastic melanoma, high power. The spindle cells are haphazardly arranged and scattered cells show enlarged hyperchromatic nuclei. Nodular clusters of lymphocytes are commonly present.

**Fig. VIC4.d.** Desmoplastic melanoma, high power. Desmoplastic melanoma may mimic a neural tumor and it frequently shows neurotropism with spindle cells extending in and around small cutaneous nerves. The neurotropism is frequently associated with a lymphocytic infiltrate. (continues)
antibody usually marks many of the spindle-shaped cells, indicating that they are not fibroblastic. The HMB-45 and Melan-A antigens are not usually demonstrable in desmoplastic melanomas, although they will often react with the epithelial component of “mixed” desmoplastic melanomas (95). The most convincing evidence that many of the tumors are melanomas may come from examination of the overlying intra-epidermal component, where diagnostic changes of microinvasive or \textit{in situ} melanoma may be seen, usually of the lentigo maligna, acral or mucosal lentiginous types. Electron microscopy may or may not demonstrate melanosomes, often after prolonged searching, and is of little or no diagnostic utility.

Conditions to consider in the differential diagnosis:

- \textit{desmoplastic melanoma}, including amelanotic
- cellular blue nevus, amelanotic
- blue nevus, amelanotic
- desmoplastic Spitz nevus
- spindle cell metastatic melanoma

\section*{Pyogenic Granuloma (Lobular Capillary Hemangioma)}

\textbf{CLINICAL SUMMARY.} Pyogenic granuloma (97) is a common proliferative lesion that often occurs shortly after a minor injury or infection of the skin. Typically the lesion grows rapidly for a few weeks before stabilizing as an elevated, bright red papule, usually not more than 1 to 2 cm in size; it then may persist indefinitely unless destroyed. Recurrence after surgery or cautery is not rare. Pyogenic granuloma most often affects children or young adults of either gender, but the age range is wide; the hands, fingers, and face, especially the lips and gums, are the most common sites. Pyogenic granuloma of the gingiva in pregnancy (epulis of pregnancy) is a special subgroup. A rare and alarming event is the development of multiple satellite angiomatous lesions at and around the site of a previously destroyed pyogenic granuloma.

\textbf{HISTOPATHOLOGY.} The typical lesion presents as a polypoid mass of angiomatous tissue protruding above the surrounding skin, and often constricted at its base by a collarette of acanthotic epidermis. An intact flattened epidermis may cover the entire lesion, but surface erosions are common. In ulcerated lesions, a superficial inflammatory cell reaction can give rise to an appearance suggestive of granulation tissue, but inflammation is usually slight in the deeper part of the lesion and may be absent when the epidermis is intact. The angiomatous tissue tends to occur in discrete masses or lobules, and is composed of a variably dilated network of blood-filled capillary vessels and groups of poorly canalized vascular tufts. Mitotic activity varies and can be prominent. Feeding vessels often extend into the adjacent dermis and rare lesions show a deep component in the reticular dermis.

\section*{Intravascular Papillary Endothelial Hyperplasia (Masson’s Hemangio-Endotheliome Vegetant Intravasculaire)}

\textbf{CLINICAL SUMMARY.} This not uncommon condition is an unusual endothelial proliferation in an organizing thrombus that can be misdiagnosed as angiosarcoma (98). The lesion arises primarily within a venous channel or secondarily within a preceding angioma or some type of vascular anomaly, including hemorrhoids, or extravascularly in association with a hematoma. The lesions are almost always solitary, arising in the skin, subcutaneous tissue, or even muscle with the head and neck region, and the upper extremities, especially the fingers the most common sites. Primary lesions are usually tender nodules less than 2 cm in size, whereas secondary lesions occur because some preceding vascular abnormality increases in size.

\textbf{HISTOPATHOLOGY.} Often, low-power examination allows recognition of the intravascular nature of the process in a single thin-walled vein or as part of a preceding
Clin. Fig. VIC5.a. *Pyogenic granuloma.* A child suddenly developed a single dark red bleeding papule.

**Fig. VIC5.a.** *Pyogenic granuloma, low power.* Pyogenic granulomas show a dome-shaped nodular architecture which sits above the level of the skin surface. The epidermis shows a flattened effaced rete ridge architecture.

**Fig. VIC5.b.** *Pyogenic granuloma, medium power.* At the edge of the neoplasm, the epidermis focally extends underneath the vascular proliferation forming a collarette.

**Fig. VIC5.c.** *Pyogenic granuloma, medium power.* There are lobular aggregates of small mature vascular channels filled with erythrocytes. These aggregates are separated by a fibrous stroma in long standing lesions. This intervening stroma can be very edematous and mucinous in early lesions.

Angiomatous condition. Extravascular lesions fail to reveal a blood vessel wall despite serial sectioning. The main lesion consists of a mass of anastomosing vascular channels with a variable degree of intraluminal papillary projections. The stroma consists of hyalinized eosinophilic material that may merge with uncanalized thrombus remnants. The infiltrating vascular channels show enlarged and prominent endothelial cells that may be “heaped up” to give rise to intraluminal prominences, but atypia and mitotic activity are slight.
VI. Tumors and Cysts of the Dermis and Subcutis

Stasis Dermatitis With Vascular Proliferation (Acroangiodermatitis, Pseudo-Kaposi’s Sarcoma)

**CLINICAL SUMMARY.** Patients with longstanding venous insufficiency and lower extremity edema may develop pruritic, erythematous, scaly papules and plaques on the lower legs, often in association with brown pigmentation and hair loss.

**HISTOPATHOLOGY.** The epidermis is hyperkeratotic with areas of parakeratosis, acanthosis, and focal spongiosis. There is a superficial, perivascular lymphohistiocytic infiltrate that surrounds plump, thickened capillaries and venules. The superficial dermal vessels may be arranged in lobular aggregates. The proliferation may be florid, mimicking Kaposi’s sarcoma [acroangiodermatitis (99)]. The reticular dermis is often fibrotic. Hemosiderin is usually present superficially but may be identified about the deep vascular plexus as well.

Kaposi’s Sarcoma

**CLINICAL SUMMARY.** Kaposi’s sarcoma (100,101) can be classified in four groups. *Classic Kaposi’s sarcoma* is rare, affecting mainly patients of Eastern European and Mediterranean origin, and occurs arises in male patients over the age of 50 with the slow development of angiomatous nodules and plaques on the lower extremities. *Kaposi’s sarcoma in Africa* is very common with a higher proportion of young people affected, and with a more aggressive disease manifested by widespread tumors, deep infiltrative or elevated fungating lesions, and bone involvement. *AIDS-associated Kaposi’s sarcoma* occurs especially in active homosexuals. The clinical features differ from the classic disease in the more rapid evolution of the lesions, their atypical distribution affecting the trunk, and a greater tendency to mucosal involvement. *Kaposi’s sarcoma associated with iatrogenic immunosuppression* occurs in the context of organ transplantation-related immunosuppression, and may regress on discontinuation of the therapy. Kaposi’s sarcoma is associated with immune dysregulation associated with HHV8 infection leading to the production of cytokines that induce activation of endothelial cells leading to spindle cell formation and angiogenesis. The process may spread to multiple sites through spread of virally infected cells. The early lesions appear to be reactive polyclonal proliferations that can progress over time to frankly malignant sarcomatous lesions (101).

The histologic spectrum can be divided into stages roughly corresponding to the clinical type of lesion: early and late macules, plaques, nodules, and aggressive late lesions.

**HISTOPATHOLOGY.** In early macules, there is usually a patchy, sparse, upper dermal perivascular infiltrate consisting of lymphocytes and plasma cells. Narrow cords of cells, with evidence of luminal differentiation, are insinuated between collagen bundles. Usually a few dilated irregular or angulated lymphatic-like spaces lined by delicate endothelial cells are also present. Vessels with “jagged” outlines tending to separate collagen bundles are especially characteristic. Normal adnexal structures and preexisting blood vessels often protrude into newly formed blood vessels, a finding known as the “promontory sign.” In late...
macular lesions, there is a more extensive infiltrate of vessels in the dermis, with “jagged” vessels and with cords of thicker-walled vessels similar to those in granulation tissue. At this stage, red blood cell extravasation and siderophages may be encountered (see IIIA1c).

In the plaque stage, a diffuse infiltrate of small blood vessels extends through most parts of the dermis and tends to displace collagen. The vessels vary in morphology, some occurring as poorly canalized cords, some as blood containing ovoid vessels, and some having lymphatic-like features. Loosely distributed spindle cells, arranged in short fascicles, are also encountered. Intracytoplasmic hyaline globules, seen more often in lesions from patients with AIDS, may be found in areas of denser infiltrate.

In the tumor stage, well-defined nodules composed of vascular spaces and spindle cells replace dermal collagen. These tumor nodules tend to be compartmentalized by dense bands of fibrocollagenous tissue. Dilated lymphatic spaces can also be seen between tumor aggregates. The characteristic feature is a honeycomb-like network of blood-filled spaces or slits, closely associated with interweaving spindle cells. The presence of a closely set honeycomb-like pattern of “back-to-back” vascular spaces is an important diagnostic feature of Kaposi’s sarcoma. In the vascular spaces of pyogenic granuloma and most angiomas, the endothelial cells of the capillary walls are more prominent and the vessels are set farther apart by intervening stroma. Blood pigment-containing macrophages are

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Fig. VIC5.f. *Stasis dermatitis with vascular proliferation, low power.* Within the superficial dermis there is a proliferation of vascular channels associated with dermal pigment deposition.

Fig. VIC5.g. *Stasis dermatitis with vascular proliferation, medium power.* The vascular channels are mature and have thick walls. They form clusters within the superficial dermis. There is prominent pigment surrounding these vascular channels secondary to hemosiderin deposition. The overlying epidermis may or may not show spongiotic changes.

Fig. VIC5.h. *Stasis dermatitis with vascular proliferation, high power.* Surrounding the small vascular channels is extravasation of erythrocytes.
Kaposi’s sarcoma, plaque and early nodule. An HIV positive man developed an elongated erythematous nodule.

Kaposi’s sarcoma, nodular type, low power. In nodular (tumor stage) Kaposi’s sarcoma there is a mass of spindle cells within the dermis. This lesion is ulcerated.

Kaposi’s sarcoma, medium power. The spindle cells fail to reveal an organized pattern. The tumor is highly cellular and occasionally the hemorrhage can be seen at scanning magnification.

Kaposi’s sarcoma, high power. The spindled cells show enlarged nuclei and erythrocytes are seen between tumor cells. Occasionally, one can identify intracytoplasmic pink droplets (not shown).

Kaposi’s sarcoma, high power. An infiltrate of plasma cells is frequently seen in Kaposi’s sarcoma. Red cells are present in slit-like spaces between the tumor cells and interstitially. HHV-8 staining (not shown) is helpful in establishing the diagnosis.
nearly always prominent adjacent to the nodules, especially in lesions at dependent sites. The spindle cells in the nodules are elongated and fusiform with a well-defined cytoplasm. Their nuclei are ovoid and somewhat flattened with finely granular chromatin in the long axis of the cells. Nucleoli are generally inconspicuous and nuclear atypia is absent or slight. Mitosis is infrequent. Prominent and consistent positivity for CD34 is seen in the spindle cell population.

Aggressive late stage “infiltrating” lesions, mostly in African Kaposi’s sarcoma, show a more obviously sarcomatous character with reduction or loss of the vascular component. The spindle cells demonstrate a greater degree of cytologic atypia with regard to size, shape, and nuclear features, with mitosis becoming frequent. In such lesions, phagocytozed erythrocytes and the presence of hyaline globules may provide clues about the tumor’s origin.

**Diffuse Dermal Angiomatosis**

**CLINICAL SUMMARY.** Diffuse dermal angiomatosis is a reactive vascular proliferation under the larger category of reactive angioendotheliomatosis (102). While this latter category generally implies an intraluminal proliferation of endothelial cells, diffuse dermal angiomatosis characteristically is a proliferation of vessels within the dermis. It was initially described in patients with severe atherosclerotic disease (103); however, it is also associated with arteriovenous fistulas of hemodialysis and anticardiolipin antibodies. Patients present with firm violaceous or hyperpigmented plaques. Lesions of the extremities are more common than on axial areas. The lesions may be painful and frequently ulcerate. In patients who have severe atherosclerotic disease, bypass grafting to correct the vascular insufficiency may lead to resolution of the ulcers. The vascular proliferation seen in diffuse dermal angiomatosis is hypothesized to be secondary to ischemia, which may induce vascular endothelial growth factor or endothelial cell hyperplasia produced by small thrombi.

**HISTOPATHOLOGY.** Within the upper and mid–dermis, there is a highly cellular proliferation of small bland–appearing spindle cells which upon close inspection form vascular spaces which contain erythrocytes (104). There may be a sparse mononuclear cell infiltrate. The spindle cells stain positively with endothelial markers CD31 and CD34. Smooth muscle actin is also strongly positive in the associated pericyte layer of spindle cells. Unlike angiosarcoma, the spindle cells are bland and lack cytological atypia. Additionally, the vascular channels are well formed allowing one to eliminate the possibilities of angiosarcoma and Kaposi’s sarcoma. HHV8 staining has been described in lesions not judged to represent Kaposi’s sarcoma. Acroangiodermatitis, which can be associated with venous insufficiency, also shows well-formed channels. However, this entity shows associated dermal fibrosis, mixed inflammation, and extravasation of erythrocytes frequently with hemosiderin deposition.

**Cutaneous Angiosarcoma**

**CLINICAL SUMMARY.** Most angiosarcomas of the skin (105) arise in the following clinical settings: (1) angiosarcoma of the face and scalp in the elderly, (2) angiosarcoma (lymphangiosarcoma) secondary to chronic lymphedema, and (3) angiosarcoma as a complication of chronic radiotherapy or arising from the effects of severe skin trauma or ulceration. In a 2011 study of 98 cases from a single institution, tumors were classified histologically as vasoformative (44%), spindled (21%), epithelioid (16%), and mixed (18%). The median time to death was 2.1 years, with vasoformative tumors having a somewhat less rapid progression of disease (106).

Angiosarcoma of the scalp and face of the elderly is almost invariably a fatal tumor that usually arises as seemingly innocuous erythematous or bruise-like lesions on the scalp or middle and upper face with predilection for men. Subsequent plaques, nodules, or ulcerations develop; metastasis to nodes or internal organs usually arises as a late complication with many patients dying as a result of extensive local disease. Angiosarcoma following lymphedema (postmastectomy lymphangiosarcoma or the Stewart–Treves syndrome) presents in women who have had severe longstanding lymphedema of the arm following breast surgery, but has also been described in men and from causes other than cancer surgery, including congenital lymphedema and tropical lymphedema due to filaria. The prognosis despite radical surgery is extremely poor. Post-irradiation angiosarcoma may arise in the skin after radiotherapy for internal cancer. The most common sites are the breast or chest wall and the lower abdomen after therapy for breast or gynecologic cancer.

**HISTOPATHOLOGY.** Usually the tumor extends well beyond the limits of the apparent clinical lesion. As a rule, the tumor shows varied differentiation in different biopsies, even within different fields in a single biopsy. In well-differentiated areas, irregular anastomosing vascular channels lined by a single layer of somewhat enlarged endothelial cells permeate between collagen bundles. Isolation and enclosure of collagen bundles, figuratively referred to as “dissection of collagen,” is a characteristic feature. Nuclear atypia is always present and may be slight to moderate, but occasional large hyperchromatic cells may be encountered. At this stage, the vascular lumens are generally bloodless, but they may contain free-lying shed malignant cells. In less well-differentiated areas, endothelial cells increase in size and number, forming intraluminal papillary projections where there is enhanced mitotic activity. In poorly differentiated areas, solid sheets of large pleomorphic cells with little or no evidence of luminal differentiation, can resemble metastatic carcinoma or melanoma. Focally, areas showing epithelioid cells are not uncommon. Other areas may simulate a poorly differentiated spindle cell sarcoma. Interstitial hemorrhage and widely dilated blood-filled spaces may sometimes develop.
Diffuse dermal angiomatosis, low power. There is a cellular proliferation in the papillary and upper reticular dermis which is not associated with the overlying epidermis.

Diffuse dermal angiomatosis, medium power. The cellular areas are composed of numerous spindle cells.

Diffuse dermal angiomatosis, high power. The spindle cells are small and bland in appearance. They form small vascular channels.

Diffuse dermal angiomatosis, medium power, CD31 immunoperoxidase stain. CD31 highlights the spindle cells as well as the formation of small vascular channels.

Diffuse dermal angiomatosis, medium power, smooth muscle actin immunoperoxidase stain. A stain for smooth muscle actin highlights the pericyte component of the spindle cell proliferation.
Jagged vascular spaces

Fig. VIC5.r

Intracytoplasmic vacuoles

Fig. VIC5.t

Cutaneous angiosarcoma, low power. The architecture of the dermis is replaced by hemorrhagic tissue within which subtle jagged spaces can be seen.

Fig. VIC5.r

Cutaneous angiosarcoma, high power. Jagged spaces containing erythrocytes and lined by plump, hyperchromatic endothelial cells. This pattern of dissection throughout the reticular dermal collagen is typical of angiosarcoma.

Fig. VIC5.s

Cutaneous angiosarcoma, high power. A population of more epithelioid angiosarcoma cells, with intracytoplasmic vacuoles as a clue to endothelial differentiation.

Fig. VIC5.t

Cutaneous angiosarcoma, high power. Another example, with jagged spaces lined by atypical endothelial cells.

Fig. VIC5.u

Cutaneous angiosarcoma, high power. A characteristic pattern of infiltration among reticular dermis collagen fibers.

Fig. VIC5.v
**Cutaneous Epithelioid Angiomatous Nodule/Epithelioid Hemangioendothelioma**

Cutaneous epithelioid angiomatous nodule is an uncommon vascular proliferation, which presents histologically as a well-circumscribed, mainly unilobular, solid proliferation of endothelial cells with prominent epithelioid features. The cytoplasm is abundant and eosinophilic, and many of the neoplastic cells contain prominent vacuoles. Inflammatory infiltrates are variable. There may be overlap with epithelioid hemangioendothelioma which is a low grade malignancy, however, all the cases reported to date have followed a benign course (107).

**Targetoid Hemosiderotic Hemangioma (Hobnail Hemangioma)**

**CLINICAL SUMMARY.** Targetoid hemosiderotic hemangioma is a benign acquired vascular lesion that presents as a macule with central papule or solitary macule on the trunk or extremities of young to middle-aged adults (108,109). It can have a varied clinical appearance, mimicking a melanocytic nevus, particularly a dysplastic nevus, dermatofibroma, Kaposi’s sarcoma, or even a melanoma. Though not present in the majority of cases, the “classic” clinical morphology is that of a pale, erythematous, or ecchymotic ring measuring 1 to 2 cm with a central red, violaceous, or brown papule measuring 2 to 3 mm, resulting in a targetoid appearance. It is believed to represent a reactive vascular ectasia rather than a true neoplasm, and trauma may be a predisposing factor. A history of waxing and waning with respect to size and color is common, and a changing morphology with the menstrual cycle has been reported.

**HISTOPATHOLOGY.** The histologic appearance may also mimic malignant conditions such as Kaposi’s sarcoma or angiosarcoma. Telangiectatic blood-filled vessels are present in the papillary dermis or superficial reticular dermis, becoming flattened vascular spaces that dissect between

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**Fig. VIC5.w**

*Epithelioid hemangioendothelioma, low power.* There is a relatively well circumscribed but non-encapsulated dome shaped lesion within the dermis. The epidermis is uninvolved and shows an effaced rete ridge pattern.

**Fig. VIC5.x**

*Epithelioid hemangioendothelioma, medium power.* The neoplasm is composed of a solid sheet of uniform, bland-appearing cells associated with small dilated vascular channels which contain erythrocytes.

**Fig. VIC5.y**

*Epithelioid hemangioendothelioma, high power.* The cells contain an abundance of cytoplasm and show intracytoplasmic vacuoles. There may be scattered erythrocytes between the cells, with interstitial hemorrhage. Although significant cytoplasmic atypia is not present, these lesions may have an uncertain prognosis.
Clin. Fig. VIC5.c. Targetoid hemosiderotic hemangioma. Note the violaceous papule (the bull’s eye) surrounded by an erythematous halo.

Fig. VIC5.z. Targetoid hemosiderotic hemangioma, low power. Dilated blood vessels are present in the upper dermis. In the reticular dermis, vessels are often flatter and extend interstitially, resulting in a wedge-shaped architecture. Extravasated red blood cells are present around vessels.

Fig. VIC5.za. Targetoid hemosiderotic hemangioma, medium power. Somewhat flattened vessels dissect between collagen in the reticular dermis. There is an inflammatory component made up mostly of lymphocytes. Red blood cell extravasation can be extensive, and later lesions will show hemosiderin within macrophages, not seen here.

Fig. VIC5.zb. Targetoid hemosiderotic hemangioma, high power. Dilated vascular channels are characteristically lined by hobnail endothelial cells with nuclei that protrude into the lumen.
collagen bundles with deeper, wedge-shaped extension into the reticular dermis and this potentially mimicking angiosarcoma. The endothelial cells lining the vessels are bland, but may have rounded nuclei which project into vascular lumina and resemble hobnails, hence the alternate designation for this lesion. Superficial vessels may also contain fibrin thrombi and papillary projections. Vascular channels in the deeper dermis are often irregular and jagged, with subtle lumina lined by low endothelial cells. Extravasated red blood cells may be present and prominent, and later lesions will often show hemosiderin-laden macrophages. A lymphocytic inflammatory infiltrate can be seen.

**Conditions to be considered in the differential diagnosis:**

- Angiosarcoma
- Kaposi’s sarcoma
- Acroangiodermitis
- Other forms of angioendotheliomatosis

**Angiokeratoma**

See Clin. Fig. VIC5.d and Figs. VIC5.zc, zd.

**Arteriovenous Hemangioma**

See Figs. VIC5.ze, zf.

**Cavernous Hemangioma**

See Figs. VIC5.zg, zh.

**Cherry Hemangioma**

See Figs. VIC5.zi, zj.

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**Clin. Fig. VIC5.d.** *Angiokeratoma.* These small purplish papules are commonly found on the scrotum.

**Fig. VIC5.zc.** *Angiokeratoma, low power.* There is a vascular proliferation predominantly within the papillary dermis. The associated epidermis is hyperplastic and appears to encircle the vascular channels.

**Fig. VIC5.zd.** *Angiokeratoma, medium power.* The vascular channels are thin walled and lined by mature endothelial cells. They are filled with erythrocytes. The hyperplastic epithelium surrounds these vascular channels and occasionally it may appear that the vascular channels are within the epithelium.
Fig. VIC5.ze. *Arteriovenous hemangioma, low power.* There is a well circumscribed vascular proliferation within the superficial dermis.

Fig. VIC5.zf. *Arteriovenous hemangioma, medium power.* The vascular proliferation is composed of mature thick and thin walled vascular channels filled with erythrocytes.

Fig. VIC5.zg. *Cavernous hemangioma, low power.* Within the deep dermis and subcutaneous tissue there is a proliferation of vascular channels filled with erythrocytes. All cavernous hemangiomas are not as well circumscribed as this example.

Fig. VIC5.zh. *Cavernous hemangioma, medium power.* The vascular channels show thin walled endothelial cells without atypia. The channels are filled with erythrocytes.
Fig. VIC5.zi. *Cherry hemangioma, low power.* This dome-shaped papular lesion shows a vascular proliferation within the superficial dermis.

Fig. VIC5.zj. *Cherry hemangioma, medium power.* There is a proliferation of thin walled mature vascular channels filled with erythrocytes. The associated stroma may be edematous or fibrotic.

Fig. VIC5.zk. *Microvenular hemangioma, low power.* At scanning magnification there is increased cellularity throughout the reticular dermis.

Fig. VIC5.zl. *Microvenular hemangioma, medium power.* There is a proliferation of small venules throughout the reticular dermis without formation of lobular aggregates. No large vascular spaces are seen.

Fig. VIC5.zm. *Microvenular hemangioma, high power.* The vessels are all mature small venules without atypia. There is an associated fibrotic stroma.
Microvenular Hemangioma

These benign acquired lesions typically occur as small, enlarging lesions often on the forearm or leg in an adult. Clinically, they are purple to red lesions usually considered to be hemangiomas. Histologically, there are irregular, branching venules with inconspicuous lumina. There is no cytologic atypia (110).

Cutaneous Lymphangioma

See Figs. VIC.5.vn, zo.

Venous Lake

See Fig. VIC.5.zp.

Glomangioma

See Clin. Fig. VIC.5.e and Figs. VIC.5.zr–zt.

Glomus Tumor

See Figs. VIC.5.zu–zw.

Conditions to consider in the differential diagnosis:

- hyperplasias
- intravascular papillary endothelial hyperplasia
- reactive angioendotheliomatosis
- angiolympoid hyperplasia with eosinophilia
- angiommas
- juvenile hemangioendothelioma (strawberry nevus)
Clin. Fig. VIC5.e. **Glomangioma.** These compressible, purplish nodules on the extremity can be inherited in an autosomal dominant fashion.

Fig. VIC5.zr. **Glomangioma, low power.** In the deep reticular dermis there is a neoplasm composed of multiple cystic-like spaces lined by a thickened wall.

Fig. VIC5.zs. **Glomangioma, medium power.** The cystic spaces are lined by several layers of small cuboidal cells.

Fig. VIC5.zt. **Glomangioma, medium power.** Another area of the glomangioma showing cystic spaces lined by cuboidal glomus cells. The individual cells are monotonously bland and lack cytologic atypia. Erythrocytes may be seen in the cavernous spaces.
cherry hemangioma
glomeruloid hemangioma
tufted angioma (angioblastoma)
angiokeratoma
cavernous hemangioma
sinusoidal hemangioma
verrucous hemangioma
microvenular hemangioma
targetoid hemosiderotic (hobnail) hemangioma
cirrhotic aneurysm (A-V hemangioma)
epithelioid hemangioma
pyogenic granuloma
bacillary angiomatosis
lymphangiomas
cavernous lymphangioma & cystic hygroma
lymphangioma circumscriptum

progressive lymphangioma (benign lymphangioendothelioma)
lymphangiomatosis
telangiectases
hereditary hemorrhagic telangiectasia
spider nevus
venous lakes
vascular malformations
angioma serpiginosum
glomus tumors
glomus tumor, glomangioma, glomangiomyoma
infiltrating glomus tumor
glomangiosarcoma
vascular lipomas
angiomyolipoma
angiolipoma

Fig. VIC5.zu. Glomus tumor, low power. This biopsy shows a cellular tumor in the deep dermis. In contrast to a glomangioma, fewer vascular channels are seen, and glomus cells in sheets are the predominant feature.

Fig. VIC5.zv. Glomus tumor, high power. There are both thin cords and solid areas of tumor composed of uniform cuboidal cells with small round nuclei.

Fig. VIC5.zw. Glomus tumor, high power. The tumor is composed of uniform cuboidal cells with small round nuclei.
angiosarcomas
  cutaneous angiosarcoma
  epithelioid angiosarcoma

**Kaposi’s sarcoma**
Kaposi’s sarcoma simulants (see also angiomatoses)
  aneurysmal fibrous histiocytoma
  spindle cell hemangioendothelioma
  Kaposi-like infantile hemangioendothelioma
  acroangiodermatitis (pseudo-Kaposi’s sarcoma)
  multinucleate cell angiohistiocytoma

**hemangioendotheliomas**
  epithelioid hemangioendothelioma
  retiform hemangioendothelioma
  malignant endovascular papillary angioendothelioma (Dabska’s tumor)
  spindle cell hemangioendothelioma
  Kaposi-like infantile hemangioendothelioma

**other vascular tumors**
  diffuse dermal angioendotheliomatosis
  angiomatosis
  hemangiopericytoma
  intravascular lymphoma (malignant angioendotheliomatosis)

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**VIC6 Tumors of Adipose Tissue**

Most tumors of adipose tissue occur in the subcutis or deeper soft tissues, but some may involve the skin. The lesional cells may range from mature adipocytes indistinguishable from those of mature fat in typical lipomas, to more or less undifferentiated round cells or pleomorphic cells in the high-grade liposarcomas. Nevus lipomatosus superficialis is a lipomatous neoplastic or hamartomatous disorder that primarily involves the skin (111).

**Nevus Lipomatosus Superficialis**

**CLINICAL SUMMARY.** Nevus lipomatosus superficialis is a fairly uncommon lesion which may present as groups of soft, flattened papules or nodules that have smooth or wrinkled surfaces and are skin-colored or pale yellow. Characteristically, the lesions are linearly distributed on one hip or buttock (nevus lipomatosus superficialis of Hoffman and Zurhelle), from where they may overlap onto the adjacent skin of the back or the upper thigh. Other areas, such as the thorax or the abdomen, are only rarely affected. The lesions may be present at birth or may begin in infancy (nevus angiolipomatosus of Howell), in which case the replacement of hypoplastic dermis may cause pseudotumorous yellow protrusions and be associated with skeletal and other malformations, but they develop most commonly during the first two decades of life and occasionally later. Multiple lesions may coalesce. Solitary lesions may be diagnosed as nevus lipomatosus superficialis, or as solitary, baglike, soft fibromas or polypoid fibrolipomas. The rather common presence of fat cells within longstanding intradermal melanocytic nevi represents an involutionary phenomenon and not a nevus lipomatosus.

**HISTOPATHOLOGY.** Groups and strands of fat cells are found embedded among the collagen bundles of the

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**Fig. VIC6.a**

**Fig. VIC6.a.** *Nevus lipomatosus superficialis, low power.* Mature adipose tissue extends up into the reticular dermis. There is no associated inflammatory reaction.

**Fig. VIC6.b**

**Fig. VIC6.b.** *Nevus lipomatosus superficialis, medium power.* Mature adipocytes are seen in the superficial and mid reticular dermis.
Fig. VIC6.c. *Lipoma, low power.* This circumscribed neoplasm shows a very thin fibrous capsule. Lipomas reside in the subcutaneous fat. At scanning magnification the lesion is hypocellular.

Fig. VIC6.d. *Lipoma, high power.* A lipoma is composed of uniform adipocytes which are approximately of equal size. The small nucleus is pushed to the side of the cell and is barely visible.

Fig. VIC6.e. *Angiolipoma, low power.* Similar to a lipoma, an angiolipoma is a well circumscribed subcutaneous mass with a very thin fibrous capsule. However, in contrast, this lesion is more cellular than the one seen in Figure VIC6c.

Fig. VIC6.f. *Angiolipoma, medium power.* The increased cellularity in angiolipomas is secondary to a proliferation of small mature vascular channels filled with erythrocytes and fibrin thrombi.

Fig. VIC6.g. *Angiolipoma, high power.* Multiple fibrin thrombi are frequently found in the small vessels of an angiolipoma.
dermis, often as high as the papillary dermis. The proportion of fatty tissue varies greatly. In cases with only small deposits, the fat cells are apt to be situated in small foci around the subpapillary vessels. In instances with relatively large amounts of fat, the fat lobules are irregularly distributed throughout the dermis, and the boundary between the dermis and the hypoderm is ill-defined or lost. The fat cells may all be mature, but in some instances an occasional small, incompletely lipidized cell may be observed. Aside from the presence of fat cells, the dermis may be entirely normal, but in some instances the density of the collagen bundles, the number of fibroblasts, and the vascularity are greater than in normal skin.

**Lipoma**

By definition, lipomas contain mature adipocytes as a principal component. They tend to be located in the subcutis and surrounded by a thin connective tissue capsule and are composed, often entirely, of normal fat cells that are indistinguishable from the fat cells in the subcutaneous tissue.

**Angiolipomas**

Angiolipomas usually occur as encapsulated subcutaneous lesions. As a rule, they arise in young adults. The forearm is the single most common location for this tumor, which is more often multifocal than solitary. They are often tender or painful. Inapparent at the gross level, angiolipomas microscopically show sharp encapsulation, numerous small-caliber vascular channels containing characteristic microthrombi, and variable amounts of mature adipose tissue. The degree of vascularity is quite variable, ranging from only a few small angiomatous foci to lesions with a predominance of dense vascular and stromal tissue.

**Spindle Cell Lipoma**

Clinically, the tumor is a slowly growing, painless nodule centered in the dermis or subcutis and exhibiting a predilection for the posterior neck and shoulder girdle region in men in their sixth decade. Although the lesion is well circumscribed histologically, it is seldom encapsulated. It comprises mature fat cells and uniform, slender spindle...
cells within a mucinous matrix. Spindle cell lipoma is polymorphous as a result of variations in cellularity, collagen content, and the ratio of spindle cells to mature adipocytes.

**Pleomorphic Lipoma**

**CLINICAL SUMMARY.** Like spindle cell lipomas, the great majority of pleomorphic lipomas are solitary tumors of the shoulder girdle and neck in men in the fifth to seventh decade. The lesion presents as a slowly growing, well-circumscribed dermal or subcutaneous mass grossly resembling an ordinary lipoma. Although in some areas one can identify adipocytes, other areas are very cellular. Admixed with the adipocytes are larger cells with large hyperchromatic nuclei many of which have contain vacuoles many of which indent the nucleus, creating a delicate scalloping of the nuclear membrane (monovacular and multivacular lipoblasts). Mitotic figures are also seen.

**Liposarcoma**

Liposarcomas are large tumors of the deep subcutis or deeper soft tissue. As such, they rarely come to the attention of the dermatopathologist.

**Conditions to consider in the differential diagnosis:**

- lipomas
  - spindle cell lipoma
  - pleomorphic lipoma
  - chondroid lipoma
  - angiolipoma
- liposarcomas
  - well-differentiated
  - atypical lipomatous tumor
  - myxoid
  - round cell
  - pleomorphic
- miscellaneous
  - hibernoma
  - benign lipoblastoma
  - nevus lipomatosus superficialis
VIC7 Tumors of Cartilaginous Tissue

Most tumors of cartilaginous tissue occur in the bones and joints or in the deep soft tissues, but some may involve the skin. The lesional cells may range from mature chondrocytes indistinguishable from those of mature cartilage in an enchondroma, to more or less undifferentiated round cells or pleomorphic cells in a high-grade chondrosarcoma. Because of their location, these tumors come to the attention of the dermatopathologist only rarely.

**Conditions to consider in the differential diagnosis:**
- chondroid lipoma
- soft tissue chondroma
- chondrosarcoma

VIC8 Tumors of Osseous Tissue

Metaplastic ossification, disturbances of calcium metabolism, and presumably other poorly understood mechanisms including hereditary abnormalities may lead to local areas of calcification and also to focal or diffuse ossification in the dermis.

**Albright’s Hereditary Osteodystrophy & Osteoma Cutis**

In Albright’s hereditary osteodystrophy (AHO), multiple areas of subcutaneous or intracutaneous ossification are often encountered (112). These may be present at birth or may arise later in life, and have no definite area of predilection. The areas may be small or large (5 cm). Those located in the skin may cause ulceration, and bony

**Clin. Fig. VIC8.** Multiple cutaneous osteomas. A 50-year-old woman developed multiple 2–3 mm flesh-colored and slightly erythematous firm papules on the cheeks.

**Fig. VIC8.a.** Osteoma cutis, low power. Within the superficial dermis there is a well circumscribed zone of eosinophilic to purplish material.

**Fig. VIC8.b.** Osteoma cutis, medium power. Eosinophilic bone shows numerous osteocytes. There is an associated fibrovascular stroma.
spicules may be extruded through the ulcer. In addition to cutaneous and subcutaneous osteomas, bone formation may be observed in some cases along fascial planes. AHO includes the syndromes of pseudohypoparathyroidism and pseudopseudohypoparathyroidism. Patients with AHO have short stature, round facies, and multiple skeletal abnormalities, such as curvature of the radius and shortening of some of the metacarpal bones. As a result of this shortening, some knuckles are absent when the fists are clenched, and depressions or dimples are apparent there instead. This important diagnostic sign is referred to as the Albright dimpling sign. Additional manifestations include basal ganglia calcification and mental retardation. The mode of inheritance is dominant, possibly X-linked dominant.

The term osteoma cutis is applied to cases of primary cutaneous ossification in which there is no evidence of AHO in either the patients or their families. The lesions may present as a solitary or even multiple tumor-like lesions. Clinically inapparent incidental small foci of ossification are commonly seen within the dermis or stroma in other lesions, such as melanocytic nevi or acne scars. The possibility of AHO should be seriously considered in patients with extensive foci of ossification.

HISTOPATHOLOGY. Spicules of bone of various sizes may be found within the dermis or in the subcutaneous tissue. The bone contains fairly numerous osteocytes as well as cement lines that may be accentuated in polarized light. In addition, there are osteoblasts along the surface of the spicules and often, osteoclasts in Howship’s lacunae. The spicules of bone may enclose, either partially or completely, areas of mature fat cells, representing establishment of a medullary cavity. Hematopoietic elements are observed rarely among the fat cells. The histologic findings in osteoma cutis are the same as in primary cutaneous ossification occurring in conjunction with AHO.

Conditions to consider in the differential diagnosis:

- Albright’s hereditary osteodystrophy
- osteoma cutis
- metaplastic ossification
- subungual exostosis

**VID1 Pilar Differentiation**

Cystic proliferations are present in the dermis, these show spaces surrounded by epithelium of follicular origin and differentiation. Keratin is usually seen in the cystic cavity. Associated cells may be sparse or may include lymphocytes and plasma cells.

**Epidermal or Infundibular Cyst**

**CLINICAL SUMMARY.** Epidermal cysts (113) are slowly growing, elevated, round, firm, intradermal or subcutaneous tumors that cease growing after having reached 1 to 5 cm in diameter. Most epidermal cysts arise spontaneously in hair-bearing areas most commonly on the face, scalp, neck, and trunk, but occasionally on the palms or soles and occasionally as a result of trauma. Usually a patient has only one or a few epidermal cysts, rarely many. In Gardner’s syndrome, numerous epidermal cysts occur, especially on the scalp and face.

**HISTOPATHOLOGY.** Epidermal cysts have a wall composed of true epidermis, as seen on the skin surface and in the infundibulum of hair follicles, the infundibulum being the uppermost part of the hair follicle that extends down to the entry of the sebaceous duct. In young epidermal cysts, several layers of squamous and granular cells can usually be recognized. In older epidermal cysts, the wall often is markedly atrophic, either in some areas or in the entire cyst, and may consist of only one or two rows of...
greatly flattened cells. The cyst is filled with horny material arranged in laminated layers. When an epidermal cyst ruptures and the contents of the cyst are released into the dermis, a considerable foreign-body reaction with numerous multinucleated giant cells results, forming a keratin granuloma. The foreign-body reaction usually causes disintegration of the cyst wall. However, it may lead to a pseudoeotheioliomatous proliferation in remnants of the cyst.

**Fig. VID1.a.** Epidermal cyst, low power. Within the dermis there is a well circumscribed cystic structure filled with laminated keratin.

**Fig. VID1.b.** Epidermal cyst, high power. The wall of the cyst is composed of mature squamous epithelium with formation of a granular cell layer. The contents of the cyst are composed of laminated (basket-weave”) orthokeratin.

**Fig. VID1.c.** Trichilemmal (pilar) cyst, low power. In this scalp biopsy there is a well circumscribed cystic structure in the subcutaneous fat. Focal calcification is present; this is a common incidental finding.

**Fig. VID1.d.** Trichilemmal (pilar) cyst, high power. The wall of the cyst is composed of mature squamous epithelium which shows keratinization without formation of a granular layer.
Cysts of the Dermis and Subcutis

Trichilemmal (Pilar) Cyst

Trichilemmal cysts are also known, especially in surgical terminology, as “sebaceous cysts,” however, they do not exhibit sebaceous differentiation. They are derived as retention cysts from the lower part of the hair follicle where the hair sheath or “trichilemmal” keratinizes abruptly without an interposed granular layer. The keratin is compact rather than basket weave as in an epidermal cyst.

Steatocystoma

See Clin. Fig. VID1.b and Figs. VID1.e–g.

Vellus Hair Cyst

See Figs. VID1.h, i.

Clin. Fig. VID1.b. Steatocystoma multiplex. This uncommon autosomal dominant disorder results in the development of multiple, sebum-draining, dermal cysts.

Fig. VID1.e. Steatocystoma, low power. Steatocystoma may show a solitary cystic space or a multiloculated appearance with numerous infoldings of the cyst wall.

Fig. VID1.f. Steatocystoma, medium power. Mature sebaceous lobules are seen arising from the wall of the cyst.

Fig. VID1.g. Steatocystoma, high power. The epithelial wall of the steatocystoma shows a corrugated luminal surface associated with an eosinophilic cuticle.
VI. Tumors and Cysts of the Dermis and Subcutis

Conditions to consider in the differential diagnosis:
- epidermal cyst
- milia
- trichilemmal cyst
- steatocystoma multiplex
- pigmented follicular cyst
- dermoid cyst
- bronchogenic and thyroglossal duct cysts
- eruptive vellus hair cyst
- pilar sheath acanthoma
- dilated pore of Winer

**Eccrine and Similar Differentiation**

Cystic proliferations are present in the dermis, these show spaces surrounded by eccrine epithelium (small dark epithelial cells). The epithelium of ciliated and bronchogenic cysts is not eccrine but may resemble that of an eccrine cyst. Eccrine hidrocystoma is the prototype (114).

**Eccrine Hidrocystoma**

**CLINICAL SUMMARY.** In this condition, usually one lesion, but occasionally several, and rarely numerous lesions

**Fig. VID1.h.** Vellus hair cyst, low power. The wall of this cyst is lined by mature squamous epithelium. There may be formation of a granular cell layer, changes indistinguishable from the lining of an epidermal inclusion cyst.

**Fig. VID1.i.** Vellus hair cyst, medium power. There are numerous small (vellus) hair shafts within the cavity of the cyst.

**Clin. Fig. VID2.** Eccrine hidrocystoma. An elderly woman developed compressible blue translucent papules on the lower eyelid.

**Fig. VID2.a.** Eccrine hidrocystoma, low power. Multiple sections of a thin-walled cystic structure.
are present on the face. The lesions are small, translucent, cystic nodules 1 to 3 mm in diameter that often have a bluish hue. In some patients with numerous lesions, the number of cysts increases in warm weather and decreases during winter.

**Histopathology.** Eccrine hidrocystoma shows a single cystic cavity located in the dermis. The cyst wall usually shows two layers of small, cuboidal epithelial cells. In some areas, only a single layer of flattened epithelial cells can be seen, their flattened nuclei extending parallel to the cyst wall. Small papillary projections extending into the cavity of the cyst are observed only rarely. Eccrine secretory tubules and ducts are often located below the cyst and in close approximation to it, and, on serial sections, one may find an eccrine duct leading into the cyst from below. However, no connection can be found between the cyst and the epidermis.

**Median Raphe Cyst**

See Figs. VID2.d, e.
VI. Tumors and Cysts of the Dermis and Subcutis

**Fig. VID2.f.** Bronchogenic cyst, low power. Within the dermis there is a solitary cyst with a slightly papilliferous wall.

**Fig. VID2.g.** Bronchogenic cyst, medium power. The projections are lined by pseudostratified columnar epithelium. There is a fibrotic stroma which may contain smooth muscle.

**Fig. VID2.h.** Bronchogenic cyst, high power. The pseudostratified columnar epithelial wall shows numerous cilia extending into the lumen. Goblet cells are also present.

**Fig. VID2.i.** Cutaneous endometriosis, low power. This well circumscribed nodular tumor-like lesion is present in the deep dermis and subcutaneous fat. It is composed of two elements, glandular structures and a prominent stroma, embedded in dense fibrous tissue.

**Fig. VID2.j.** Cutaneous endometriosis, medium power. Numerous glandular structures are embedded in a well vascularized and hypercellular stroma. In some areas, as on the right side of this photomicrograph, the stroma is fibrotic.

**Fig. VID2.k.** Cutaneous endometriosis, high power. The glandular component and the associated specialized and here focally hemorrhagic stroma resemble uterine endometrium during the phases of the menstrual cycle.
**Bronchogenic Cyst**

The most common location for these very uncommon lesions is the suprasternal notch and presternal area, followed by the neck, and scapula. Histologic findings include a ciliated pseudostratified epithelial lining with the presence of smooth muscle cells, goblet cells, and occasionally cartilage (115).

**Cutaneous Endometriosis**

See Figs. VID2.i–k.

**Conditions to consider in the differential diagnosis:**
- eccrine hidrocystoma
- cutaneous ciliated cyst
- bronchogenic and thyroglossal duct cysts
- median raphe cyst of the penis
- cutaneous endometriosis

![Fig. VID3.a. Apocrine hidrocystoma, low power.](image)

Within the dermis there is a well circumscribed cystic structure.

![Fig. VID3.b. Apocrine hidrocystoma, high power.](image)

The wall of this cystic structure is composed of one or more layers of bland-appearing cuboidal cells. The cells show decapitation secretion manifested by small droplets of cytoplasm on their luminal surface.

**VID3 Apocrine Differentiation**

Cystic proliferations are present in the dermis; these show spaces surrounded by apocrine epithelium (large pink cells with decapitation secretion). There may be lymphocytes and plasma cells (syringocystadenoma). Apocrine hidrocystoma (116) and hidradenoma papilliferum are prototypic (117).

**Apocrine Hidrocystoma**

**CLINICAL SUMMARY.** Apocrine hidrocystoma presents as a solitary translucent cystic nodule, between 3 and 15 mm in diameter. The lesion may be skin-colored, or may have a blue hue resembling a blue nevus. The usual location is on the face, but also on the ears, scalp, chest, or shoulders. Multiple apocrine hidrocystomas are rare.

**HISTOPATHOLOGY.** The dermis contains one or several large cystic spaces into which papillary projections often extend. The inner surface of the wall and the papillary projections are lined by a row of secretory cells of variable height showing “decapitation” secretion indicative of apocrine secretion. There is an outer layer of elongated myoepithelial cells, their long axes running parallel to the cyst wall.

**Hidradenoma Papilliferum**

**CLINICAL SUMMARY.** Hidradenoma papilliferum occurs only in women, usually on the labia majora or in the perineal or perianal region. The tumor is covered by normal skin and measures only a few millimeters in diameter. Malignant changes are extremely rare.

**HISTOPATHOLOGY.** The tumor represents an adenoma with apocrine differentiation. It is located in the dermis, is well circumscribed, is surrounded by a fibrous capsule, and has no connection with the overlying epidermis. Some tumors have a peripheral epithelial wall with areas of keratinization. Within the tumor, there are tubular and cystic structures. Papillary folds project into the cystic spaces. Usually, the lumina are surrounded by a double layer of cells consisting of a luminal layer of secretory cells and of an outer layer of small cuboidal cells with deeply basophilic nuclei. These are myoepithelial cells. The lumina are lined...
occasionally with only a single row of columnar cells, which show an oval, pale-staining nucleus located near the base, a faintly eosinophilic cytoplasm, and active decapitation secretion as seen in the secretory cells of apocrine glands.

Conditions to consider in the differential diagnosis:
- *hidradenoma papilliferum*
- syringocystadenoma papilliferum
- apocrine hidrocystoma

References

Inflammatory and Other Benign Disorders of Skin Appendages

The hair, sebaceous glands, eccrine glands, apocrine glands, and nails may be involved in inflammatory processes (e.g., hidradenitis, folliculitis). Some neoplasms may masquerade as inflammatory processes.
Inflammatory processes may present as alopecia, or as follicular localization of inflammatory rashes. Acne and related conditions present as dilatation of follicles which are filled with keratin (1,2).

1. Scant Inflammation
2. Lymphocytes Predominant
3. With Prominent Eosinophils
4. Neutrophils Prominent
5. Plasma Cells Prominent
6. Fibrosing and Suppurative Follicular Disorders

**TABLE VII.1. Non-scarring Alopecia (Normal Follicular Density)**

<table>
<thead>
<tr>
<th>Clinical Pattern</th>
<th>Degree of Miniaturization (0–+++)</th>
<th>Telogen Count</th>
<th>Inflammation</th>
<th>Other Histo Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary/androgenetic alopecia (AGA)</td>
<td>Males: thinning of vertex, crown, bitemporal Females: thinning of crown, retention of frontal hairline</td>
<td>++</td>
<td>16.8% avg.</td>
<td>Lymphocytic; superficial perivascular (37% of cases)</td>
</tr>
<tr>
<td>Alopecia Areata (AA)</td>
<td>Round bald patches, diffuse absence of scalp hair (talis), diffuse absence of scalp and body hair (universalis). May see exclamation point hairs.</td>
<td>+++</td>
<td>27% avg.; &gt;50% favors AA</td>
<td>Lymphocytic; peribulbar (“swarm of bees”) around terminal hairs (acute) and miniaturized hairs (chronic, recurrent)</td>
</tr>
<tr>
<td>Telogen Effluvium: Acute</td>
<td>Diffuse thinning</td>
<td>None</td>
<td>&gt;15%-suggestive &gt;20%-presumptive &gt;25%-definitive (usually not &gt;50%)</td>
<td>Absent</td>
</tr>
<tr>
<td>Telogen Effluvium: Chronic</td>
<td>Diffuse thinning</td>
<td>None</td>
<td>11% avg.</td>
<td>Absent</td>
</tr>
<tr>
<td>Trichotillomania</td>
<td>Patchy or diffuse. Hairs of irregular length, broken hairs.</td>
<td>None</td>
<td>Elevated (&gt;15%)</td>
<td>Absent</td>
</tr>
</tbody>
</table>

**Androgenetic Alopecia**

**CLINICAL SUMMARY.** The expression of androgenetic alopecia (AGA) frequently shows a familial and probably genetic inheritance pattern. Hair shafts become progressively finer and shorter, with true alopecia occurring only as a later event. This involutional process slowly evolves to
become so severe that the scalp skin becomes exposed to a greater or lesser extent. This process can also occur in women, although much less frequently and with lesser severity so that significant balding is quite unusual.

**HISTOPATHOLOGY.** Evaluation of this condition can be achieved best from transverse sectioning of punch biopsy material (3,4). Diminution of follicular size, most effectively measured by assessment of mean hair shaft diameter, can be obtained with relative simplicity using an optical micrometer. Since this approach allows assessment of all follicles in the specimen, direct counting of anagen, telogen, and catagen follicles can be undertaken and the percentages of each obtained (5). Reduction of follicular size appears to be randomized, so that, initially, normal-size follicles coexist with an increased number of smaller ones, whereas, ultimately, follicular reduction becomes more persistent and obvious. Associated with this reduction in follicular size,

**Clin. Fig. VIIA1.a.** Androgenetic Alopecia. Affected hairs, commonly seen on the vertex in males, undergo a shortened anagen phase resulting in a gradual transformation of terminal to vellus-like hairs.

**Fig. VIIA1.a.** Androgenetic alopecia, medium power, horizontal section. Within the superficial subcutis, one sees the lower segment of terminal anagen follicles and an increased number of fibrous streamers.

**Fig. VIIA1.b.** Androgenetic alopecia, high power, horizontal section. A streamer is characterized by a concentric arrangement of loose, fibrovascular tissue resembling a collapsed fibrous sheath. Streamers result from shortening of follicles, either from follicular miniaturization or an increased percentage of follicles in the resting (telogen) phase.

**Fig. VIIA1.c.** Androgenetic alopecia, medium power, horizontal section. Early in the course of this disorder the density of follicles remains normal. There is great variation in follicular size, with an increased number of indeterminate and vellus follicles. An increase in the percentage of catagen and telogen follicles can sometimes be seen. (continues)
there is a progressive increase in the percentage of telogen follicles, both of normal club pattern and with increasing severity, diminutive or persistent telogen epithelial remnants (telogen germinal units). These structures appear to represent epithelial remnants of telogen follicles that no longer respond to the stimulus to return to anagen growth. Ultimately, there may be a reduction in the density of follicles. Peri-infundibular fibroplasia ultimately leading to focal follicular scarring may be the explanation for the reduced follicular density. The diminution of follicles leads to a substantial increase in the number of empty follicular sheaths in the deeper dermis and subcutaneous tissue.

**Trichotillomania**

**CLINICAL SUMMARY.** Compulsive avulsion of hair shafts leads to zones of thin, ragged, broken stubble on the affected scalp. If the damage is done in localized fashion it can occasionally mimic alopecia areata. Follicular breakage and loss may occasionally be associated with evidence of damage to the scalp by erosions or crusts.

**HISTOPATHOLOGY.** The most important findings in biopsy specimens are an increase in catagen hairs (up to 75%), pigmented defects and casts, evidence of traumatized hair bulbs, and trichomalacia (a complete but distorted, fully developed terminal hair in its bulb) (6). Occasionally, follicles may be identified still in anagen but empty because of hair shaft avulsion. Follicles can show considerable distortion of the bulb epithelium and sometimes conspicuous hemorrhage. Hair shaft avulsion may deposit melanin pigment in the hair papilla and peribulbar connective tissue. Pigment casts are also frequently identified in the isthmus or infundibulum. Trichomalacia, if present, is specific for trichotillomania. Longitudinal splitting of a hair shaft with blood sandwiched in between has been called the “hamburger sign” (7). These various injuries to the bulbous portions of follicles are not accompanied by significant inflammatory infiltrates. Trichotillomania is not associated with miniaturization of follicles or with deep perifollicular infiltrates, features that usually serve to differentiate it from alopecia areata. Histologic findings in early traction alopecia are said to be identical with those of trichotillomania, but fewer follicles are involved, the changes are less dramatic, and vellus hairs are preserved.

**Telogen Effluvium**

**CLINICAL SUMMARY.** Telogen effluvium represents the increased or excessive shedding of hair in the telogen phase of the growth cycle. This condition has several precipitating causes or associated conditions, including chemotherapy and debilitating diseases of various kinds, which may cause alopecia by eliciting changes in the length of the anagen period of growth, and in the active process of release of hair shafts in telogen. Plucked or shed telogen hairs have a club-like appearance at the bottom of the shaft, and are therefore often known as “club hairs.”

**HISTOPATHOLOGY.** Telogen effluvium does not show significant dermal inflammatory infiltrates, nor should there be evidence of diminution of follicular and hair shaft size, unless telogen effluvium occurs in patients with established androgenetic or another form of involutional alopecia (8). Proportions of normal telogen follicles in excess of 15% to 25% are considered to be abnormal and
Trichotillomania. “Plucking” of hairs by a middle aged female with a delusional disorder resulted in well-demarcated patches of alopecia in a diffuse distribution.

At scanning magnification there is a normal number of hair follicles per cross-section. There is a mild, predominantly superficial inflammatory infiltrate.

One frequently sees distortion of the hair follicle, as manifested here by the twisted contour of the follicular canal.

A characteristic finding in trichotillomania is the presence of pigment casts (clumps of pigment) which are present in the follicular canal. (continues)
suggest the likely presence of telogen. If a biopsy is obtained in the very early stages of recovery, early anagen regeneration follicles will also be present, while if recovery is substantial, the appearances may be entirely normal (9).

**Keratosis Pilaris**

Keratosis pilaris (KP) is a common inherited disorder of follicular hyperkeratosis, which is characterized by small, folliculocentric keratotic papules that may have surrounding erythema, most commonly affecting the extensor aspects of the upper arms, upper legs, and buttocks. The small papules impart a stippled appearance to the skin resembling gooseflesh. Associated/related conditions may include keratosis pilaris atrophicans, erythromelanosis follicularis faciei et colli, and ichthyosis vulgaris (10).

**Fig. VIIA.1.i.** Trichotillomania, high power. Brown pigment casts in a cross section.

**Fig. VIIA.1.j.** Telogen effluvium, low power, horizontal section. At scanning magnification there is a normal density of follicles with uniform diameters. An increased percentage of catagen and telogen follicles, as is seen in the early phases, is best appreciated at or just below the level of the isthmus. Inflammation is not seen here or in deeper levels within the fat.

**Fig. VIIA.1.k.** Telogen effluvium, high power, horizontal section. A telogen (club) hair, on the left, is readily identifiable by a hair shaft which fills the follicular canal and merges with the outer root sheath via an eosinophilic zone, a consequence of trichilemmal keratinization.

**Fig. VIIA.1.l.** Telogen effluvium, medium power, horizontal section. The irregular island of basaloid epithelium represents a telogen germinal unit, an epithelial remnant of a telogen follicle. Such structures may be increased in telogen effluvium.
**Fig. VIIA.1.m.** Keratosis pilaris, low power. In the center of this biopsy is the edge of a hair follicle which is manifested by an invagination of epithelium. This is associated with marked hyperkeratosis of the follicular orifice.

**Fig. VIIA.1.n.** Keratosis pilaris, medium power. The follicular epithelium and the adjacent epidermis are mildly acanthotic. The characteristic hyperkeratotic scale may be both ortho and parakeratotic. There is only minimal inflammation in the surrounding dermis.

**Fig. VIIA.1.o.** Scurvy, medium power. A horizontally sectioned biopsy from the leg shows a terminal follicle with eccentric placement of the hair shaft and focal thinning of the outer root sheath epithelium. There is perifollicular fibrosis, a lymphocytic infiltrate, and extravasated red blood cells to the right of the follicle.

**Fig. VIIA.1.p.** Scurvy, medium power. In another section, the follicular canal is distorted and shows hyperkeratosis and a few neutrophils. Extravasated red blood cells are present in the surrounding stroma.

**Fig. VIIA.1.q.** Scurvy. A plucked leg hair from the same patient shows the characteristic corkscrew morphology.
**Scurvy**

See Figs. VIIA.1.o–q.

**Conditions to consider in the differential diagnosis:**

- **Follicular maturation disorders**
  - androgenetic alopecia
  - telogen effluvium
  - trichotillomania
  - scurvy
  - vitamin A deficiency (phrynoderma)

- **Follicular keratinization disorders**
  - keratosis pilaris
  - lichen spinulosus
  - trichorrhexis invaginata (Netherton’s syndrome)
  - trichostasis spinulosa
  - acne vulgaris
  - Favre–Racouchot syndrome (nodular elastosis with cysts and comedones)
  - nevus comedonicus
  - Bazex syndrome (follicular atrophoderma)

**VIIA2 | Lymphocytes Predominant**

There is follicular alteration with an inflammatory infiltrate mainly of lymphocytes. Conditions associated with inflammation may in many instances result in scarring alopecia in which hairs are lost and replaced by fibrosis (see Table VII.2).

**Alopecia Areata**

**CLINICAL SUMMARY.** Alopecia areata is characterized by complete or nearly complete absence of hair in one or more circumscribed areas of the scalp (11). Inflammatory change is not clinically obvious, and the follicular openings are preserved. Complete scalp involvement (alopecia totalis), or complete or nearly complete loss of the entire body hair (alopecia universalis) can occur. Involvement of the eyebrows and eyelashes and a pitted defect in the nail plates are additional features of this condition. Most patients undergo spontaneous resolution, but a few patients have permanent hair loss. In the areas of active hair shedding, a short, fractured hair shaft may be identified—the characteristic “exclamation point” hair.

**HISTOPATHOLOGY.** The critical diagnostic pathologic sign is lymphocytic infiltrates in the peribulbar area of anagen follicles, or follicles in early catagen (12). The lymphocytic infiltrates are present around the receding epithelial remnant but also in the area of the collapsing follicular sheaths. While still in anagen, lymphocytes may be seen sparsely infiltrating the matrix epithelium. Follicular structures diminish in size rapidly and become miniaturized, and as a result are identified more superficially in the dermis (13). The diminutive follicles are observed predominantly in early or late catagen. During the recovery phase, diminutive anagen follicles may be quite numerous, many showing some peribulbar lymphocytic infiltrates. In long-standing cases, the inflammatory infiltrates appear to diminish. In severe alopecia universalis and totalis of long duration (a decade or more), functional follicular structures may be diminished in number and some scarring of the follicular sheaths may be identified. Dilated follicular infundibula, which on horizontal sectioning bears resemblance to Swiss cheese, is another helpful clue in alopecia areata (14). When biopsy specimens are sectioned transversely early in the disease, it can be demonstrated that the number of follicles is not diminished but that follicles enter a persistent phase of telogen (telogen germinal units) and that there is a diminution of normal club telogen follicles.

**Lichen Planopilaris**

**CLINICAL SUMMARY.** Lichen planopilaris is lichen planus with follicular involvement in some or all of the lesions. This type of lichen planus predominantly affects the scalp. Initially, there may be only follicular papules or perifollicular erythema; however, with progressive hair loss irregularly shaped atrophic patches of scarring alopecia develop on the scalp (15). The axillae and the pubic region may also be affected and the alopecia in these areas may be cicatricial. Hyperkeratotic follicular papules may also be seen on glabrous skin. The association of scarring alopecia of hair-bearing areas and hyperkeratotic follicular papules on glabrous skin is known as Graham Little syndrome. Lichen planopilaris may also coexist with typical lichen planus lesions on skin, mucous membranes, or nails. Linear lichen planopilaris of the face resolving with scarring has also been described.

Frontal fibrosing alopecia is a variant of lichen planopilaris that occurs in a band over the frontal scalp, typically in postmenopausal females (16). Recent research has shown that the characteristic histologic findings also involve vellus hair follicles on the face, clinically presenting as small papules (17).

**HISTOPATHOLOGY.** Most early lesions of lichen planopilaris show a focally dense, band-like perifollicular lymphocytic infiltrate at the level of the infundibulum and the isthmus where the hair “bulge” is located (18). Initially, the inferior segment of the hair follicle is spared. Vacular changes of the basal layer of the outer root sheath and necrotic keratinocytes are often seen. In addition, orthokeratosis and follicular plugging are observed. A few biopsies exhibit simultaneous involvement of the interfollicular epidermis and the hair follicles. In more developed lesions perifollicular fibrosis and epithelial atrophy at the level of the infundibulum and isthmus are characteristic findings. Damage to the hair bulge, the site where stem cells of the hair follicle reside, results in permanent scarring alopecia. Advanced cases show alopecia with vertically oriented fibrotic tracts containing clumps of degenerated elastic fibers replacing the destroyed hair follicles. This end-stage scarring alopecia in which no visible hair follicles remain has been designated by some as pseudopelade of Brocq.
<table>
<thead>
<tr>
<th>Clinical Pattern</th>
<th>Inflammation Type</th>
<th>Site of Follicular Inflammation</th>
<th>Other Histo Features</th>
<th>Elastic Stain (VVG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen Planopilaris (LPP) (and variants)</td>
<td>Irregularly shaped patches of hair loss scattered over the scalp. Perifollicular scale and erythema.</td>
<td>Lymphocytic</td>
<td>Isthmus and lower infundibulum; lichenoid/ interface with occasional colloid bodies. Sometimes inter-follicular epidermis involved.</td>
<td>Hypergranulosis of infundibula. Cleft between follicular epithelium and dermis-often. Perivascular and perieccrine inflammation absent.</td>
</tr>
<tr>
<td>Discoid Lupus Erythematosus (DLE)</td>
<td>Classic lesions show alopecic areas with erythema, atrophy, dilated and plugged infundibula. May show central hypopigmentation.</td>
<td>Lymphoplasmacytic</td>
<td>Typically infundibulum but may involve entire follicle; interface-vacuolar or lichenoid; colloid bodies less common than LPP. Epidermal involvement more common than LPP.</td>
<td>Superficial and deep perivascular and perieccrine inflammation. Dermal mucin is often increased. Epidermis may show thickened basement membrane zone.</td>
</tr>
<tr>
<td>Central Centrifugal Cicatricial Alopecia (CCCA)</td>
<td>Area of alopecia centered on the crown or vertex; progresses centrifugally.</td>
<td>Lymphocytic</td>
<td>Lower infundibulum and isthmus, without interface alteration.</td>
<td>Early finding is premature desquamation of the inner root sheath. Eccentric thinning of the outer root sheath and concentric lamellar fibrosis ensues.</td>
</tr>
<tr>
<td>Folliculitis Decalvans</td>
<td>Multifocal pustules, or larger alopecic patch on the crown with erythema, pustules, and crusting at the periphery.</td>
<td>Lymphocytic and lymphocytic</td>
<td>Intrafollicular and perifollicular involving the infundibulum and isthmus.</td>
<td>Resembles a bacterial folliculitis (may represent inflammatory stage of CCCA).</td>
</tr>
<tr>
<td>Acne Keloidalis</td>
<td>Papules, pustules, and small areas of alopecia involving the posterior neck and occiput. In advanced cases, keloidal plaques form</td>
<td>Lymphoplasmacytic (neutrophils if a pustule is biopsied)</td>
<td>Lower infundibulum and isthmus.</td>
<td>As follicles are destroyed, hair shaft fragments may serve as a stimulus for fibrosis.</td>
</tr>
<tr>
<td>Dissecting Scalp Cellulitis</td>
<td>Firm and fluctuant nodules, with areas of purulent drainage, primarily over the crown and vertex.</td>
<td>Lymphocytic, neutrophilic, and plasmacytic</td>
<td>Initially, perifollicular inflammation in the lower dermis and subcutaneous fat. Later, superficial parts of follicle are affected.</td>
<td>Early on, alopecia is due to conversion to catagen/ telogen hairs. Later, follicles are destroyed; granulation tissue, sinus tracts, and fibrosis develop. Sebaceous glands destroyed late.</td>
</tr>
</tbody>
</table>
Clin. Fig. VIIA2.a. *Alopecia Areata.* Well circumscribed patch of alopecia with “exclamation” (!) hairs (tapering at proximal end) at the periphery typically respond to intralesional corticosteroids.

Fig. VIIA2.a. *Alopecia areata, low power, vertical section.* There are three catagen follicles, as indicated by a prominent eosinophilic cuticle. Beneath one of the catagen follicles, there is a terminal anagen follicle with perifollicular inflammation within the subcutis. Catagen follicles are infrequently seen on vertical sectioning unless increased in number.

Fig. VIIA2.b. *Alopecia areata, high power, vertical section.* A dense lymphocytic infiltrate (“swarm of bees”) hugs the bulb of the terminal anagen follicle seen in the previous figure.

Fig. VIIA2.c. *Alopecia areata, low power, horizontal section.* Most of the hairs present in this figure show varying degrees of eosinophilic change of the hair shaft, indicating that they are in various stages of transition from catagen to telogen hairs. At this level of sectioning, the lymphocytes are not present and the differential diagnosis would include telogen effluvium.
Central Centrifugal Cicatricial Alopecia

CLINICAL SUMMARY. Since many forms of scarring alopecia share clinical and histologic features that make them difficult to distinguish with certainty, a unifying concept of central centrifugal cicatrical alopecia (CCCA) was proposed to reflect the overlap (19). CCCA encompasses several types of permanent hair loss which have in common the following features: alopecia centered on the crown or vertex of the scalp; progressive chronic disease with eventual “burnout”; fairly symmetrical expansion with the most active areas at the periphery; and clinical and microscopic evidence of inflammation in these active sites (20).

HISTOPATHOLOGY. CCCA displays all of the following histologic features: eccentric thinning of the outer root sheath epithelium, most prominent at the level of the isthmus and lower infundibulum, associated with close

Fig. VIIA.2. Alopecia areata, medium power, horizontal section. The increased percentage of resting follicles is reflected by the numerous streamers seen near the dermal–subcutaneous junction. A lymphoid infiltrate is apparent, concentrated about the streamers.

Fig. VIIA.2. Alopecia areata, high power, horizontal section. Perifollicular lymphocytes can be seen affecting catagen and telogen follicles as they retreat upward into the dermis. The eosinophilic vitreous membrane is characteristic of this catagen follicle.

Fig. VIIA.2. Alopecia areata, low power, horizontal section. In longstanding alopecia areata, there is an increased number of catagen and telogen follicles. In addition, follicular miniaturization begins to occur.

Fig. VIIA.2. Alopecia areata, medium power, horizontal section. Peribulbar lymphocytic inflammation is easily seen on horizontal sections within the subcutis. Since all of the follicles in the biopsy specimen can be visualized on horizontal sections, an increased number of streamers and catagen follicles can be easily assessed.
VII. Inflammatory and Other Benign Disorders of Skin Appendages

Perifollicular infiltrates

![Fig. VIIA2.h](image1)

Vacuolar change

![Fig. VIIA2.i](image2)

Fibrosed follicle

![Fig. VIIA2.j](image3)

Dyskeratotic/apoptotic cells

![Fig. VIIA2.l](image4)

**Fig. VIIA2.h.** Lichen planopilaris, low power, vertical section. A dense, mostly perifollicular lymphoid infiltrate affecting predominantly the isthmus and lower infundibulum is seen on scanning magnification. The interfollicular epidermis, which is best visualized on vertical sections, is largely unaffected.

**Fig. VIIA2.i.** Lichen planopilaris, medium power, vertical section. The lymphocytic infiltrate is associated with vacuolar alteration of the outer layers of the follicular epithelium.

**Fig. VIIA2.j.** Lichen planopilaris, low power, horizontal section. Follicular loss (i.e., scarring) is best identified on horizontal sections. A perifollicular lymphoid infiltrate is also apparent.

**Fig. VIIA2.k.** Lichen planopilaris, medium power, horizontal section. At the level of the isthmus, vacuolar change, perifollicular fibrosis and inflammation are most prominent.

**Fig. VIIA2.l.** Lichen planopilaris, high power, horizontal section. The lymphocytic infiltrate is associated with blurring of the interface between the follicular epithelium and dermis, keratinocyte vacuolization, and dyskeratosis/apoptosis.
apposition of the hair shaft and follicular contents to the dermis; concentric lamellar fibroplasia (“onion skin” fibrosis); and chronic inflammation composed of lymphocytes and plasma cells surrounding the zone of fibroplasia (21). Eventually, the hair shaft migrates into the dermis, inciting granulomatous inflammation and additional epithelial destruction. Finally, the follicle is replaced by a vertical band of connective tissue, resulting in a “follicular scar.” Singly, these histologic features may be found in other types of scarring alopecia.

CCCA may also show one of three histologic patterns of disease: follicular degeneration syndrome, pseudopelade pattern (a “modern” use of the term, not pseudopelade of Brocq), and folliculitis decalvans (22). Features may be

Clin. Fig. VIIA2.b. Central centrifugal cicatricial alopecia. This condition occurs most commonly in African-Americans and affects the crown and vertex scalp. Hair loss is permanent.

Fig. VIIA2.m,n. Central centrifugal cicatricial alopecia, transverse section. In the upper dermis, the affected follicles show eccentric thinning of the outer root sheath (ORS) epithelium and perifollicular fibrosis manifested by concentric lamellar fibroplasia. There is lymphoplasmacytic inflammation peripheral to the fibrosis. Sebaceous glands, normally seen at this level, are notably absent.

Fig. VIIA2.o. Central centrifugal cicatricial alopecia, transverse section. The affected follicles show early perifollicular fibrosis with some mononuclear inflammation. (continues)
present that allow sub-classification into one of these patterns. For instance, African American patients with CCCA who display characteristics of the follicular degeneration syndrome pattern tend to show premature desquamation of the inner root sheath (23). A characteristic histologic feature of the folliculitis decalvans pattern is folliculocentric neutrophilic inflammation, typically seen if a pustule from the expanding margin is biopsied.

**Discoid Lupus Erythematosus of the Scalp**

See Clin. Fig.VIIA2.c and Figs.VIIA2.q–v.

**Alopecia Mucinosa**

Alopecia mucinosa can be seen in childhood but is more common in adults. It may occur in three settings: a primary idiopathic form, a form associated with malignancy, and a form secondary to inflammatory conditions. The histologic

**Clin. Fig. VIIA2.c.** Discoid lupus erythematosus. The inflammation in this hyperpigmented plaque with follicular plugging led to permanent hair loss.

**Fig. VIIA2.q.** Discoid lupus erythematosus of the scalp, low power. A superficial and deep often quite prominent perivascular and perifollicular inflammatory infiltrate is seen at low magnification.

**Fig. VIIA2.r.** Discoid lupus erythematosus, low power. In some examples, as here, the infiltrate can be quite sparse. The number of hair follicles is diminished at scanning magnification.

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Fig. VIIA2.p

**Fig. VIIA2.p.** Central centrifugal cicatricial alopecia, transverse section. The follicular epithelium may be completely destroyed, resulting in naked hair shafts which incite a granulomatous response.

Fig. VIIA2.q

**Fig. VIIA2.q.** Discoid lupus erythematosus of the scalp, low power.

Clin. Fig. VIIA2.c

**Clin. Fig. VIIA2.c.** Discoid lupus erythematosus. The inflammation in this hyperpigmented plaque with follicular plugging led to permanent hair loss.
Fig. VIIA2.s. Discoid lupus erythematosus, medium power. As in other forms of lupus erythematosus, the epidermis reveals atrophy, vacuolar alteration and an interface dermatitis. This superficial infiltrate is composed primarily of lymphocytes and there is prominent pigment incontinence.

Fig. VIIA2.t. Discoid lupus erythematosus, high power. Close examination of the epidermis reveals hyperkeratosis and thickening of the basement membrane zone. Pigment laden macrophages are seen in the papillary dermis.

Fig. VIIA2.u. Discoid lupus erythematosus, medium power. The perifollicular infiltrate is associated with eventual scarring and fibrosis at the site of hair follicles.

Fig. VIIA2.v. Discoid lupus erythematosus, medium power. Pigment laden macrophages may be seen in the subcutaneous fat at the site of previous hair follicles. However, this finding is not specific to this diagnosis and can be seen in other forms of alopecia.
hallmark is follicular mucinosis, the accumulation of mucin in the follicular epithelium (24).

**Rosacea**

Rosacea is a very common condition, of unknown etiology although theories abound. It is most often characterized by transient or persistent central facial erythema, visible blood vessels, and often papules and pustules. Rosacea can be classified into 4 broad subtypes: erythematotelangiectatic, papulopustular, phymatous (characterized by thickening e.g. rhinophyma, otothyma, etc), and ocular (e.g. blepharitis, conjunctivitis, etc) (25).

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**Fig. VIIA2.w**

Spaces formed by increased mucin

**Fig. VIIA2.x**

*Fig. VIIA2.w. Follicular mucinosis, low power.* At scanning magnification the follicular epithelium appears widened by multiple clear spaces. The overlying epidermis is uninvolved (23).

**Fig. VIIA2.x**

*Alopecia mucinosa, medium power.* The follicular keratinocytes are pale and in many areas are separated from adjacent keratinocytes. There is a surrounding perivascular and perifollicular lymphoid infiltrate.

**Fig. VIIA2.y**

*Alopecia mucinosa, high power.* The follicular epithelium appears clear because of extensive deposition of acid mucopolysaccharide. The epithelium is also infiltrated by small lymphoid cells which lack significant cytologic atypia. The acid mucopolysaccharide can be demonstrated using Alcian blue or colloidal iron stains. The predominant component is hyaluronic acid which can be removed with digestion with hyaluronidase.
**Fig. VIIA.2.z.** *Rosacea, low power.* This biopsy from facial skin reveals prominent sebaceous glands, a lymphoid infiltrate, and telangiectasia.

**Fig. VIIA.2.za.** *Rosacea, high power.* The infiltrate may be perivascular, interstitial, and perifollicular.

**Fig. VIIA.2.zb.** *Rosacea, high power.* Here the infiltrate is vaguely granulomatous.
Conditions to consider in the differential diagnosis:
alopecia areata
discoid lupus erythematosus
alopecia mucinosa/follicular mucinosis
folliculotropic mycosis fungoides
lichen planopilaris
Fox–Fordyce disease
syringolymphoid hyperplasia with alopecia
lichen striatus
chronic folliculitis
rosacea
perioral dermatitis
disseminate and recurrent infundibular folliculitis
acne varioliformis (acne necrotica)

VIIA3 With Prominent Eosinophils

Eosinophils are prominent in the infiltrate and may infiltrate the follicular structures. Eosinophilic pustular folliculitis is prototypic (26).

Eosinophilic Pustular Folliculitis

CLINICAL SUMMARY. This condition demonstrates broad patches of itchy follicular papules and pustules involving particularly the face, trunk, and arms. The involved areas may take on various configurations; there may be central healing and peripheral spread. The condition occurs also in patients with HIV infection (27). Extra-follicular lesions with involvement of both palms and soles, and scarring alopecia through scalp involvement may occur. Moderate leukocytosis and eosinophilia in the peripheral blood are also present.

HISTOPATHOLOGY. Involved follicles may show spongotic change with exocytosis extending from the sebaceous gland and its duct throughout the infundibular zone (28). Lymphocytes with some eosinophils migrate into the epidermis initially in a somewhat diffuse pattern, but micropustular aggregation develops and the ultimate lesion is an infundibular eosinophilic pustule (29). The epidermis adjacent to the follicle may be involved with eosinophilic microabscess formation. In the adjacent dermis, there are perivascular infiltrates of lymphocytes and numerous eosinophils.

Conditions to consider in the differential diagnosis:
eosinophilic pustular folliculitis
erthema toxicum neonatorum
Ofuji’s syndrome
fungal folliculitis

Clin. Fig. VIIA3

Clin. Fig. VIIA3. Eosinophilic pustular folliculitis. Pruritic erythematous papules commonly seen on the face of HIV infected patients characterize this recalcitrant condition.

Fig. VIIA3.a. Eosinophilic pustular folliculitis, low power. In the center of this punch biopsy, a hair follicle shows an intense inflammatory infiltrate involving the upper half of the follicular epithelium.
**VIIA4 Neutrophils Prominent**

There is a follicular inflammatory infiltrate containing neutrophils, which may result in disruption of the follicle. Furuncle is prototypic (30).

**Acute Deep Folliculitis (Furuncle)**

**CLINICAL SUMMARY.** A furuncle is caused by staphylococci and consists of a tender, red, perifollicular swelling terminating in the discharge of pus and of a necrotic plug.

**HISTOPATHOLOGY.** A furuncle shows an area of perifollicular necrosis containing fibrinoid material and many neutrophils. At the deep end of the necrotic plug, in the subcutaneous tissue, is a large abscess. A Gram stain shows small clusters of staphylococci in the center of the abscess.

**Tinea Capitis**

This term refers to dermatophyte fungal infections occurring in the scalp and involving hairs. The involvement can be “endothrix” (within the hair shaft) or “ectothrix”.

**Majocchi’s Granuloma**

**CLINICAL SUMMARY.** Occasionally, *Trichophyton rubrum* causes an asymptomatic nodular perifolliculitis in circumscribed areas, often called “Majocchi granuloma.” It was first described as a scalp infection seen in children, but is seen most commonly on the legs in association with an infection of the soles, particularly in women who shave their legs (31).

**HISTOPATHOLOGY.** Sections show a nodular folliculitis and perifolliculitis forming an abscess in the dermis. On staining with PAS or methenamine silver, numerous hyphae and spores are seen within hairs and hair follicles and in the inflammatory infiltrate of the dermis, measuring up to 6 mm in the dermis, though usually smaller in the follicles. The fungal elements reach the dermis through a break in the follicular wall. The dermal infiltrate shows lymphoid cells, macrophages, epithelioid cells, and scattered multinucleated giant cells around and within an area of central necrosis and occasionally also suppuration.

**Herpes Simplex Viral Folliculitis**

Viral folliculitis can be caused by both herpes simplex virus and varicella-zoster virus, though varicella-zoster more commonly involves follicles. In early lesions, herpes folliculitis presents as lymphocytic folliculitis which may be devoid of epithelial changes considered to be diagnostic of herpes virus infections. Exclusive involvement of follicles is not uncommon in zoster (32,33).

**Conditions to consider in the differential diagnosis:**

- superficial folliculitis
  - acute bacterial folliculitis
  - impetigo Bockhart
  - pseudomonas folliculitis
  - acne vulgaris
  - alopecia of secondary syphilis
- deep folliculitis
  - furuncle, carbuncle
  - folliculitis barbae, decalvans
**Clin. Fig. VIIA4.a.** *Furuncle.* An inflamed tender nodule represents the acute stage of a furuncle caused by *Staphylococcus aureus.*

**Fig. VIIA4.a.** *Acute folliculitis.* Scanning magnification is essentially indistinguishable from eosinophilic pustular folliculitis. The hair follicle shows intense infiltration of its epithelium by an inflammatory cell reaction. There is a surrounding perivascular infiltrate.

**Fig. VIIA4.b.** *Acute folliculitis, high power.* The infiltrate within the follicular epithelium is composed predominantly of neutrophils. Eosinophils may be seen but not to the extent that they are present in eosinophilic pustular folliculitis. There are yeast forms consistent with *Pityrosporum* organisms which are generally saprophytic but may be etiologic in some cases.

**Clin. Fig. VIIA4.b.** *Tinea capitis.* Scaly patches with associated hair loss is a common presentation of tinea capitis in African-American children.

**Fig. VIIA4.c.** *Tinea capitis, low power, horizontal section.* The extensive inflammation in this case has lead to follicular destruction and scarring.
Pathology Involving Hair Follicles

**Fig. VIIA.4.d.** *Tinea capitis, medium power, horizontal section.* The dense inflammatory infiltrate contains mixed cell types.

**Fig. VIIA.4.e.** *Tinea capitis, high power, horizontal section.* Neutrophils and other inflammatory cells surround this small follicle. Fungal elements are present within the hair shaft, constituting an endothrix infection.

**Clin. Fig. VIIA.4.c.** *Majocchi’s granuloma.* KOH scraping of these scaly papules contained within an annular plaque confirmed the diagnosis.

**Fig. VIIA.4.f.** *Majocchi’s granuloma, low power.* Scanning magnification reveals an abscess in the superficial dermis.

**Fig. VIIA.4.g.** *Majocchi’s granuloma, medium power.* Beneath this abscess, the hair follicles show an intense inflammatory reaction.
Fig. VIIA4.h. Majocchi’s granuloma, high power. Upon close examination of the hair shaft on the H&E stained sections, one can identify pale blue-staining fungal hyphae within the hair shaft.

Fig. VIIA4.i. Majocchi’s granuloma, high power. PAS stains reveal multiple organisms which have replaced a fragment of hair shaft embedded in a sea of neutrophils (abscess).

Fig. VIIA4.j. Herpes simplex viral folliculitis, low power. Scanning magnification reveals epidermal ulceration and a perivascular and perifollicular inflammatory infiltrate which is generally mixed, including both acute and chronic inflammatory cells. Early lesions often show a lymphocytic folliculitis without epidermal changes.

Fig. VIIA4.k. Herpes simplex viral folliculitis, high power. The follicular epithelium shows extensive necrosis and destruction associated with the inflammatory infiltrate that contains many neutrophils. Follicular keratinocytes show peripheral rimming of nuclear chromatin and may show multinucleation. These changes may also be seen in the overlying epidermis.
pseudofolliculitis of the beard
pyoderma gangrenosum
**follicular occlusion disorders**
dissecting cellulitis/perifolliculitis capitis abscedens et suffodiens
hidradenitis suppurativa
acne conglobata
**fungal folliculitis**
Majocchi granuloma (*T. rubrum*)
favus (*Trichophyton schoenleinii*)
pityrosporum folliculitis
viral folliculitis
acne fulminans

**VIIA5** Plasma Cells Prominent

Plasma cells are seen in abundance in the infiltrate. In most instances they are admixed with lymphocytes. Acne keloidalis is prototypic.

**Folliculitis (Acne) Keloidal Nuchae**

**CLINICAL SUMMARY.** Folliculitis keloidalis nuchae represents a chronic folliculitis on the nape of the neck in men that causes hypertrophic scarring (34). In early cases, there are follicular papules, pustules, and occasionally abscesses. The lesions are replaced gradually by indurated fibrous nodules (35).

**HISTOPATHOLOGY.** Deep folliculitis progresses to follicular destruction and dermal fibrosis. Late-stage lesions show extensive fibrosis and scarring, only sometimes with keloidal collagen.

**Tinea Capitis**

Plasma cells may be quite prominent in the infiltrate associated with tinea capitis, which can mimic many causes of scarring alopecia, including folliculitis, chronic furuncles, folliculitis decalvans, perifolliculitis capitis, dissecting cellulitis, discoid lupus erythematosus, and traction alopecia, as well as eczema and psoriasis (36).

**Conditions to consider in the differential diagnosis:**

- acne keloidalis
- fungal folliculitis
- alopecia of secondary syphilis

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**Fig. VIIA5.a.** Acne keloidalis nuchae, low power. Several hair shafts are seen within the deep dermis surrounded by chronic inflammation and extensive scarring.

**Fig. VIIA5.b.** Acne keloidalis nuchae, medium power. The dermis becomes fibrotic secondary to chronic inflammation. Free hair shafts are surrounded by granulomatous inflammation. (continues)
VII. Inflammatory and Other Benign Disorders of Skin Appendages

**Fig. VIIA5.c.** Acne keloidalis nuchae, high power. A portion of a hair shaft is being engulfed by a multinucleated giant cell. The infiltrate also contains numerous plasma cells.

**Fig. VIIA5.d.** Acne keloidalis nuchae, medium power. In a late lesion, free hair shafts have incited chronic inflammation leading to dense fibrosis in the dermis.

**Fig. VIIA5.e.** Tinea capitis, low power, horizontal section. The infiltrate in this example is perifollicular and interstitial, and is composed predominantly of lymphocytes and plasma cells.

**Fig. VIIA5.f.** Tinea capitis, high power, horizontal section. This PAS-stained section highlights the fungal spores and hyphae in cross section that characterize this endothrix infection with *Trichophyton tonsurans*. Horizontal sections demonstrate that not every follicle is involved.
Fibrosing and Suppurative Follicular Disorders

There is extensive fibrosis of the dermis, often with keratin tunnels of follicular origin, and with embedded hairs with associated foreign body inflammation. Neutrophils and plasma cells are seen in abundance in the infiltrate, in addition to lymphocytes.

Follicular Occlusion Triad (Hidradenitis Suppurativa, Acne Conglobata, and Perifolliculitis Capitis Abscedens et Suffodiens)

CLINICAL SUMMARY. The three diseases included in the follicular occlusion triad are similar. Quite frequently, two or three of the diseases are encountered in the same patient. All three diseases represent a chronic, recurrent, deep-seated folliculitis resulting in abscesses and followed by the formation of sinus tracts and scarring. In hidradenitis suppurativa, the axillary and anogenital regions are affected (37). In acute lesions there are red, tender nodules that become fluctuant and heal after discharging pus. In chronic cases, deep-seated abscesses lead to the discharge of pus through sinus tracts, resulting in severe scarring. Acne conglobata occurs mainly on the back, buttocks, and chest and only rarely on the face or the extremities. In addition to comedones, fluctuant nodules discharging pus or a mucoid material occur, as well as deep-seated abscesses that discharge through interconnecting sinus tracts. In perifolliculitis capitis abscedens et suffodiens, which involves the scalp and neck, nodules and abscesses as described above occur in the scalp, also known as dissecting cellulitis of the scalp (38,39). Pilonidal sinus is also often considered to be a part of this group of disorders (“follicular occlusion tetrad”).

HISTOPATHOLOGY. Early lesions show follicular hyperkeratosis with plugging and dilatation of the follicle. The follicular epithelium may proliferate or may be destroyed. At first there is little inflammation, but eventually a perifolliculitis develops with an extensive deep reticular dermal or subcutaneous infiltrate composed of neutrophils, lymphocytes, and histiocytes. Abscess formation results and leads to the destruction first of the pilosebaceous structures and later also of the other cutaneous appendages. Apocrine glands in hidradenitis suppurativa of the axillae or groin regions may be secondarily involved by the inflammatory process. In response to this destruction, granulation tissue containing lymphoid and plasma cells, and foreign body giant cells related to fragments of keratin and to embedded hairs, infiltrate the area near the remnants of hair follicles. As the abscesses extend deeper into the subcutaneous tissue, draining sinus tracts develop that are lined with epidermis. In areas of healing, there is extensive fibrosis.

Hidradenitis Suppurativa

See Clin. Fig.VIIA6.a and Figs.VIIA6.a–d.

Dissecting Cellulitis of the Scalp

See Figs.VIIA6.e–g.

Folliculitis Decalvans

CLINICAL SUMMARY. In folliculitis decalvans, scattered through the scalp are slowly enlarging, bald, atrophic areas with follicular pustules at their peripheries (40). In some instances, other hairy areas, such as the bearded and pubic regions, axillae, eyebrows and eyelashes, are also involved. It may represent a highly inflammatory stage of CCCA with pustules, erythema, crusting and bacterial superinfection.

HISTOPATHOLOGY. As in the other forms of chronic deep folliculitis, folliculitis keloidalis nuchae and folliculitis barbae, in early lesions there is a perifollicular infiltrate composed largely of neutrophils but also containing lymphoid cells, histiocytes, and plasma cells (41). The infiltrate develops into a perifollicular abscess leading to destruction of the hair and hair follicles. Older lesions show chronic granulation tissue containing numerous plasma cells, as well as lymphoid cells and fibroblasts. Often, foreign body giant cells are present around remnants of hair follicles, and particles of keratin may be located near the giant cells. As healing takes place, fibrosis is observed. If there is hypertrophic scar formation, as in folliculitis keloidalis nuchae, numerous thick bundles of sclerotic collagen are present.

Conditions to consider in the differential diagnosis:

- acne keloidalis
- follicular occlusion disorders
- pilonidal sinus
- hidradenitis suppurativa

Clin. Fig. VIIA6.a

Clin. Fig. VIIA6.a. Hidradenitis suppurativa. Draining sinus tracts were present in the axillae, characteristic of hidradenitis suppurativa. (continues)
Fig. VIIA6.a. *Hidradenitis suppurativa, low power.* There is an area of epidermal ulceration associated with an invagination of epithelium. There is a dense inflammatory reaction throughout the dermis.

Fig. VIIA6.b. *Hidradenitis suppurativa, medium power.* At the edge of the ulceration the epithelium shows hyperplasia. The infiltrate is intense and frequently forms abscesses composed of neutrophils.

Fig. VIIA6.c. *Hidradenitis suppurativa, high power.* The dermis, as seen here, may show granulation tissue-like changes with a mixed acute and chronic inflammatory infiltrate. One may also see extensive fibrosis and granulomatous inflammation, changes which may be indistinguishable from a ruptured epidermal cyst.

Fig. VIIA6.d. *Hidradenitis suppurativa, high power.* There may be flakes of keratin (often gray in color as here), here eliciting a neutrophilic and often a granulomatous response.
**Fig. VIIA6.e.** Dissecting cellulitis of the scalp, low power. Early lesions may show follicular plugging with acute perifollicular inflammation. Eventually the follicle is destroyed and replaced by dense mixed inflammation. The appearances are indistinguishable from hidradenitis suppurativa.

**Fig. VIIA6.f.** Dissecting cellulitis of the scalp, medium power. Perifollicular fibrosis ensues and is accompanied by granulomatous inflammation to follicular contents. Advanced lesions may show sinus tract formation.

**Fig. VIIA6.g.** Dissecting cellulitis of the scalp, high power. The follicular epithelium is almost completely destroyed, leaving the hair shaft exposed to the dermis and a mixed infiltrate of neutrophils, lymphocytes, histiocytes, and plasma cells.

**Clin. Fig. VIIA6.b.** Folliculitis decalvans. An area of scarring alopecia in a middle-aged man, associated with a hyperkeratotic scale-crust with follicular hyperkeratosis and erythema, and follicular pustules.
**VII. Inflammatory and Other Benign Disorders of Skin Appendages**

**Perifollicular mixed inflammatory infiltrate**

**Fig. VIIA6.h**

**Fig. VIIA6.i**

**Hair shaft**

**Fig. VIIA6.j**

**Fig. VIIA6.k**

**Fig. VIIA6.h.** *Folliculitis decalvans, medium power, vertical section.* Early lesions show a follicular-based pustule with perifollicular inflammation composed predominantly of neutrophils, with chronic inflammatory cells as well.

**Fig. VIIA6.i.** *Folliculitis decalvans, low power, vertical section.* A later lesion shows destruction of the follicle with a perifollicular microabscess and fibrosis in the surrounding dermis.

**Fig. VIIA6.j.** *Folliculitis decalvans, high power, vertical section.* As the hair shaft and follicular keratin come in contact with the dermis, chronic and granulomatous inflammation ensues.

**Fig. VIIA6.k.** *Folliculitis decalvans, high power, Gram stain.* Pustular lesions may develop as a consequence of bacterial superinfection. The Gram stain shows clusters of Gram-positive cocci amid the perifollicular neutrophils.
Pathology Involving Sweat Glands

The sebaceous glands, eccrine glands, and apocrine glands may be involved in inflammatory processes (hidradenitis).

1. Scant inflammation
2. Lymphocytes Predominant
   2a. With Plasma Cells
   2b. With Eosinophils
   2c. Neutrophils Predominant

**Scant inflammation**

Sweat glands are abnormal in color or size and number, but there is little or no inflammation.

**Eccrine Nevus**

**CLINICAL SUMMARY.** Eccrine nevi are very rare. They may show a circumscribed area of hyperhidrosis, a solitary sweat-discharging pore, or papular lesions in a linear arrangement (42). In the so-called eccrine angiomatous hamartoma, there may be one or several nodules or a solitary large plaque. The lesions are generally present on an extremity at birth. Hyperhidrosis and/or pain may be apparent.

**HISTOPATHOLOGY.** Eccrine nevi show an increase in the size of the eccrine coil or in both the size and the number of coils. In other cases there is ductal hyperplasia consisting of thickening of the walls and dilatation of the lumina. Eccrine angiomatous hamartomas show increased numbers of eccrine structures and numerous capillary channels surrounding or intermingled with the eccrine structures. These hamartomas may also contain fatty tissue and pilar structures.

**Conditions to consider in the differential diagnosis:**

- argyria
- syringosquamous metaplasia

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**Fig. VIIIB1.a.** Eccrine angiomatous hamartoma, low power. In the deep dermis, there is an increased number of eccrine glands in a mucinous stroma.

**Fig. VIIIB1.b.** Eccrine angiomatous hamartoma, medium power. The eccrine glands may be dilated, as seen here; there is an increased number of mature vascular channels.
Lichen Striatus

**CLINICAL SUMMARY.** This fairly uncommon dermatitis occurs as a rule in children. It presents as a unilateral eruption along Blaschko's lines (44) on the extremities, trunk, or neck as either a continuous or an interrupted band composed of minute, slightly raised, erythematous papules, which may have a scaly surface. The lesions appear suddenly and usually involute within a year. They are occasionally pruritic.

**VIIIB2** **Lymphocytes Predominant**

There is a predominantly lymphocytic infiltrate in and around the sweat glands. Lichen striatus is a prototypic example (43).
HISTOPATHOLOGY. Although the histologic picture is highly variable, there is usually a superficial perivascular inflammatory infiltrate of lymphocytes admixed with a variable number of histiocytes (45). Plasma cells and eosinophils are rare. Focally, in the papillary dermis, the infiltrate may have a band-like distribution with extension into the lower portion of the epidermis, with vacuolar alteration of the basal layer and necrotic keratinocytes. Additional epidermal changes consist of spongiosis and intracellular edema often associated with exocytosis of lymphocytes and focal parakeratosis. Less frequently, there are scattered necrotic/apoptotic keratinocytes in the spino- nous layer as well as subcorneal spongiotic vesicles filled with Langerhans’ cells. A very distinctive feature is the presence of an inflammatory infiltrate in the reticuldermis around hair follicles and eccrine glands.

Conditions to consider in the differential diagnosis:

- *lupus erythematosus*
- syringolymphoid hyperplasia with alopecia
- lichen striatus
- erythema annulare centrifugum
- erythema chronicum migrans

**VII B2a With Plasma Cells**

There is a predominantly lymphocytic infiltrate in and around the sweat glands. Plasma cells are also present as a minority population.

**Lupus Erythematosus**

See additional discussion in IIIH.4.

HISTOPATHOLOGY. In lupus, the inflammatory infiltrate in the dermis is usually lymphocytic with or without an admixture of plasma cells (46,47). Its distribution is a clue to the diagnosis of lupus. Lymphocytic and plasmacytic inflammation around eccrine coils is a characteristic finding. In hair-bearing areas, there is a similar infiltrate located around hair follicles and the sebaceous glands. Frequently, there are hydropic changes in the basal layer of the hair follicles, which may be of diagnostic value in the absence of dermal–epidermal changes. By impinging on pilosebaceous units, the infiltrate causes their gradual atrophy and disappearance. A patchy inflammatory infiltrate may also be present in the upper dermis in an interstitial pattern and occasionally, the infiltrate extends into the subcutaneous fat.

**Conditions to consider in the differential diagnosis:**

- *lupus erythematosus*
- syphilis
- secondary syphilis
- cheilitis glandularis
- erythema chronicum migrans

**VII B2b With Eosinophils**

There is an inflammatory infiltrate with lymphocytes and eosinophils in and around the sweat glands (48).

**Arthropod Bite**

See Figs. VII B2b.a, b.
Fig. VIIB2b.b. Arthropod bite, high power. The inflammatory reaction is present around eccrine glands; however, generally there are numerous eosinophils, a clue to the diagnosis.

Conditions to consider in the differential diagnosis:
- insect bite reactions
- drug reaction

[VIIB2c] Neutrophils Predominant

There is an inflammatory infiltrate with neutrophils in and around the sweat glands.

Neutrophilic Eccrine Hidradenitis

CLINICAL SUMMARY. This condition may present with erythematous, often acral, plaques several days after cytoreductive chemotherapy for hematologic malignancy (49). The description of cases occurring before the diagnosis of the malignancy, of cases in individuals treated with granulocyte colony-stimulating factor, and in patients with other malignancies, suggests that NEH may be related to Sweet’s syndrome as a part of the spectrum of neutrophilic diseases (see also VC2). The cutaneous lesions of NEH may be single or multiple and characteristically present as infiltrated or edematous papules or plaques of variable size, which may be asymptomatic or painful, and may resemble

Clin. Fig. VIIB2c. Neutrophilic eccrine hidradenitis. A young child with acute lymphocytic leukemia developed erythematous papules and plaques while on maintenance chemotherapy.

Fig. VIIB2c.a. Neutrophilic eccrine hidradenitis, low power. There is a sparse, perivascular and perieccrine infiltrate which is seen predominantly at the dermal-subcutaneous junction.
lesions of Sweet’s syndrome. The lesions are usually erythematous, or may be pigmented or purpuric. There are typically no epidermal changes; however, pustules may occasionally occur.

**HISTOPATHOLOGY.** There is variable infiltration of the eccrine coil by neutrophils and lymphocytes with necrosis of secretory epithelium (50). Individual cells or whole coils show increased cytoplasmic eosinophilia, degeneration of nuclei and loss of integrity of cell walls.

**Idiopathic Recurrent Palmoplantar Hidradenitis**

**CLINICAL SUMMARY.** Idiopathic recurrent palmo-plantar hidradenitis is an entity that is histologically indistinguishable from neutrophilic eccrine hidradenitis (NEH). Idiopathic palmo-plantar hidradenitis occurs primarily in children and presents as multiple tender erythematous nodules on the palms, soles, or both (51). It occurs in otherwise healthy patients. There is a slight predominance of females, and the mean age of onset is 6 years (52). Some patients have an associated low-grade fever. In most cases, the lesions spontaneously resolve in approximately 3 weeks, but may recur. Unlike NEH, there is no association with chemotherapy use and/or leukemia. The etiology is unknown but some authors have speculated the possibility of moisture and/or trauma producing rupture of eccrine glands and subsequently inciting a neutrophil-rich inflammatory process. There have been a few reports of similar clinical lesions that have been associated with infections including *Pseudomonas* (53), *Serratia, Enterobacter, Staphylococcus, Nocardia,* and HIV.

**HISTOPATHOLOGY.** The epidermis is essentially unremarkable. Within the dermis is a moderately intense neutrophilic infiltrate that shows preferential involvement of eccrine coils in the deep dermis (54). Neutrophils can also be seen perivascularly and interstitially in the dermis and focally in the subcutaneous tissue. Neutrophils can be seen within the eccrine epithelium and there may be associated degeneration and/or necrosis of the epithelium. Vasculitis and/or leukocytoclasia is not seen. Special stains for infectious organisms are typically negative. The differential diagnosis includes other neutrophil–rich dermal inflammatory processes, such as an early lesion of Sweet’s syndrome. This latter entity shows a more intense neutrophilic infiltrate associated with prominent papillary dermal edema. Urticaria should also be considered; however, urticaria will reveal eosinophils and lymphocytes in addition to neutrophils. The histopathology is indistinguishable from the chemotherapy-associated NEH.

**Conditions to consider in the differential diagnosis:**

- insect bite reactions
- *neutrophilic eccrine hidradenitis*
- secondary syphilis
- idiopathic recurrent palmo-plantar hidradenitis
- urticaria
- Sweet’s syndrome
- infectious etiologies with bacteria, atypical mycobacteria, and fungi
VII. Inflammatory and Other Benign Disorders of Skin Appendages

Pathology Involving Nerves

Specific inflammatory involvement of nerves is uncommon in dermatopathology.

1. Lymphocytic Infiltrates
2. Mixed Inflammatory Infiltrates
3. Neoplastic Infiltrates

**VIIC1 Lymphocytic Infiltrates**

Neurotropic spread of neoplasms, especially neurotropic melanoma, may be associated with a dense lymphocytic infiltrate that may tend to obscure a subtle infiltrate of neoplastic spindle cells. Any of the infections listed below may present as a pure (or predominant) lymphocytic neuritis.

**Fig. VIIB2c.d.** Idiopathic recurrent palmoplantar hidradenitis, low power. There is sparse superficial and deep inflammatory infiltrate which is perivascular, perieccrine, and focally interstitial.

**Fig. VIIB2c.e.** Idiopathic recurrent palmoplantar hidradenitis, high power. The neutrophilic infiltrate concentrates around eccrine coils and may be seen within the eccrine epithelium.

**Fig. VIIB2c.f.** Idiopathic recurrent palmoplantar hidradenitis, high power. The infiltrate is composed almost exclusively of neutrophils.

**Fig. VIIC1.a.** Neurotropic melanoma, high power (see also VIIC3). The presence of a lymphocytic infiltrate can call attention to nerve involvement in a melanoma (inset).
Conditions to consider in the differential diagnosis:

- neurotropic melanoma
- leprosy
- polyneuritis
- leprosy
- erythema chronicum migrans
- arthropod bite reaction

**VIIC2** Mixed Inflammatory Infiltrates

There is a mixed inflammatory infiltrate involving nerves.

**Nerve Involvement in Leprosy**

**CLINICAL SUMMARY.** Nerve involvement can be demonstrated in most lesions of leprosy (55), but is most

**Fig. VIIC2.a.**  *Tuberculoid leprosy, medium power.* Within the dermis there is an intense granulomatous infiltrate.

**Fig. VIIC2.b.**  *Tuberculoid leprosy, high power.* This granulomatous inflammation surrounds small cutaneous nerves.

**Fig. VIIC2.c.**  *Erythema chronica migrans, low power.* There is a superficial and deep perivascular and perineural infiltrate without a significant interstitial component.

**Fig. VIIC2.d.**  *Erythema chronica migrans, high power.* This infiltrate which is composed predominantly of lymphocytes and occasional plasma cells (not shown), may surround small nerves as well as eccrine units.
prominent in the tuberculoid type (TT). In the various patterns of leprosy, the major peripheral nerves often undergo parallel pathologies. The inflammation is similar, and the same classification system is applied. However, the density of acid-fast bacilli is often a logarithm higher than in the nearby skin. The skin lesions of TT leprosy are scanty, dry, erythematous, hypopigmented papules, or plaques with sharply defined edges. Anesthesia is prominent (except on the face). Thickened local peripheral nerves may be found. The lesions heal rapidly on chemotherapy.

**HISTOPATHOLOGY.** Primary TT leprosy has large epithelioid cells arranged in compact granulomas along with neurovascular bundles, with dense peripheral lymphocyte accumulation. Langhans’ giant cells are typically absent. Dermal nerves may be absent (obliterated) or surrounded and eroded by dense lymphocyte cuffs. Acid-fast bacilli are rarely found, even in nerves. A second pattern of TT leprosy is found in certain reactional states (see later).

**Erythema Chronium Migrans With Nerve Involvement**

Erythema chronicum migrans, the rash associated with Lyme disease, presents with a lymphocytic infiltrate, often with plasma cells, that is typically perivascular and may also involve skin appendages including nerves.

**Arthropod Bite Reaction With Nerve Involvement**

See Fig. VIIC2.e.

**Conditions to consider in the differential diagnosis:**
- leprosy
- erythema chronicum migrans
- *arthropod bite reaction*

**Neoplastic Infiltrates**

Many neoplasms may occasionally involve nerves. The involvement by carcinomas (basal cell, squamous cell, metastatic) is commonly in the perineural space, while involvement by neurotropic melanoma tends to occupy...
the endoneurium and to be associated with a dense lymphocytic infiltrate that may tend to obscure a subtle infiltrate of neoplastic spindle cells.

**Neurotropic Melanoma**

**CLINICAL SUMMARY.** Neurotropic melanoma is defined as a melanoma that invades nerves. Usually, there are no specific clinical stigmata of nerve involvement, but occasionally pain or paresthesias may be reported by the patient. Neurotropism in a primary melanoma is associated with increased risk for local recurrence, even after standard “definitive” therapy, and also with increased mortality.

**HISTOPATHOLOGY.** Neurotropism is often seen in a desmoplastic melanoma (56). There are fascicles of neoplastic spindle cells that have invaded cutaneous nerves, usually in a spindle-cell vertical component with fibrosis. However, some neurotropic melanomas lack these latter features of desmoplastic melanoma. Many of these are spindle-cell tumorigenic melanomas of acral lentiginous or lentigo maligna type, but some are composed of epithelioid cells. Although the neoplastic cells in the nerves are often highly atypical, in some cases the involvement may be subtle because the malignant cells may be sparsely distributed within the endoneurium of the nerve. In some cases, the presence of a lymphocytic infiltrate in the nerve may draw attention to the neoplastic involvement.

**Conditions to consider in the differential diagnosis:**

- neurotropic melanoma
- neurotropic carcinomas and other tumors

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**VIID PATHOLOGY OF THE NAILS**

Several inflammatory dermatoses more often seen elsewhere in the skin may present incidentally or exclusively in the nails. The reaction patterns have overlapping features with those seen in other areas of the cutaneous surface, but also have histologic features distinct to the nail unit.

1. Lymphocytic Infiltrates
2. Lymphocytes with Neutrophils
3. Vesculobullous Diseases
4. Parasitic Infestations

**VIID1 Lymphocytic Infiltrates**

There is an increased number of lymphocytes in the nail bed and matrix. They may be arranged in a perivascular or diffuse pattern, and may be confined to the dermis, or may involve the epithelium in a lichenoid, spongiotic, or other pattern.

**Acral Lentiginous Melanoma**

The periphery of an in situ component of acral-lentiginous melanoma may mimic a lymphocytic infiltrate, because brisk infiltrating lymphocytes in a lichenoid pattern may obscure the lesional neoplastic melanocytes in focal areas of the lesion, especially when viewed at low power.

**Conditions to consider in the differential diagnosis:**

- spongiotic dermatitis
- lichen planus
- acral lentiginous melanoma

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**Clin. Fig. VIID1.** Subungual acral lentiginous melanoma. There is a very broad and variegated pigmented lesion which extends from the nail to the surrounding skin. This extension of pigmentation from the nail to the skin is termed Hutchinson’s sign.

**Fig. VIID1.a.** Subungual acral lentiginous melanoma, low power: This excisional biopsy of the nail unit shows only subtle changes at the dermal–epithelial junction of the nail matrix at scanning magnification. (continues)
III2 Lymphocytes With Neutrophils

Neutrophils may be present in the dermis in acute infections and in gangrenous necrosis. As in the skin proper, neutrophils in the nail plate should suggest fungus infection, or may be indicative of psoriasis or a related condition (57).

Onychomycosis

CLINICAL SUMMARY. Fungal infection of the nails may be the most common nail disorder (58). There are four main types: distal lateral subungual onychomycosis, proximal subungual onychomycosis, white superficial onychomycosis, and candidal onychomycosis. Distal lateral

Clin. Fig. VIID2. Onychomycosis. Chronic infection with Trichophyton rubrum resulted in thickened, yellowish nails with subungual debris.

Fig. VIID2.a. Onychomycosis, low power. This photomicrograph shows a nail plate composed of laminated keratin. The ventral surface shows a papillomatous architecture with parakeratin. No nail bed or nail matrix is seen in this biopsy.
subungual onychomycosis is the most common form and is usually caused by *T. rubrum*. The fungus initially invades the hyponychium and lateral nail folds, causing yellowing, onycholysis, and eventual subungual hyperkeratosis.

**HISTOPATHOLOGY.** Most commonly, onychomycosis is diagnosed histologically by a nail clipping. Biopsy of the nail plate shows hyperkeratosis. A PAS stain should be performed on all nail biopsies. This stain reveals fungal organisms that are usually located in the lower stratum corneum near the nail bed epidermis and on the nail plate. The nail bed epidermis shows acanthosis, spongiosis, and exocytosis of lymphocytes and histiocytes. In proximal subungual onychomycosis, infection initially involves the area of the proximal nail fold. Superficial white onychomycosis is caused by *Trichophyton mentagrophytes*, located on the superficial nail plate only. The nail must be damaged for this to occur. In HIV-infected persons, superficial white onychomycosis is usually caused by *T. rubrum*. *Candida* may involve the nail plate and nail bed in patients with chronic mucocutaneous candidiasis and in HIV-infected patients.

**Conditions to consider in the differential diagnosis:**
- psoriasis
- *tinea unguium*, onychomycosis

**VII D3 Vesiculobullous Diseases**

Vesiculobullous disease more commonly seen elsewhere in the skin may also involve the nails. Darier’s disease commonly involves the nail with characteristic clinical findings that are not often biopsied.

**Darier’s Disease**

**CLINICAL SUMMARY.** Nail changes usually occur in association with other clinical findings. Rarely, involvement may be limited to the nail alone. Nail changes may occur in the proximal nail fold, matrix, nail bed, and hypoinychium. Involvement of the nail matrix in Darier–White disease is usually located in the distal lunula. The nails show characteristic changes of V-shaped nicking, linear striations, onycholysis, and subungual keratotic reaction. See clinical image in Clinical Figure IVD1.b.

**HISTOPATHOLOGY.** The proximal nail fold may show keratotic papules that are histologically similar to those of acrokeratosis verruciformis of Hopf. However, in addition to papillary epidermal hyperplasia, focal areas of suprabasilar acantholysis may be seen. Histologically, the leukonychia is due to foci of persistent parakeratosis in the lower nail plate related to the usual histology of Darier–White disease of the distal matrix (59).

**Conditions to consider in the differential diagnosis:**
- *Darier’s disease*
- pemphigus
- erythema multiforme
- toxic epidermal necrolysis
- epidermolysis bullosa
- bullous pemphigoid
Parasitic Infestations

Scabies is an example of a parasitic infection that may involve the nails (60).

Scabies

CLINICAL SUMMARY AND HISTOPATHOLOGY. *Sarcopes scabiei* may involve the nail unit. Organisms are often present in distal subungual hyperkeratotic debris found in the hyponychium and may be a cause of persistent epidemics of scabies (61). Norwegian scabies may cause severe involvement of the nail folds.

Conditions to consider in the differential diagnosis:

- scabies
- Norwegian scabies

References


The reactions in the subcutis are mostly inflammatory, although tumors of the subcutis do occur. Pathologic conditions arising in the dermis may extend to the subcutis. The conditions can be classified according to their septal or lobular location, and the presence or absence of vasculitis (1). Even though all panniculitides are somewhat mixed because the inflammatory infiltrate involves both the septa and lobules, the differential diagnosis between a mostly septal and a mostly lobular panniculitis is usually straightforward at scanning magnification (2). A recent report described clinical overlap and the significance of biopsy findings in a series of 55 panniculitis cases from Saudi Arabia. A definite panniculitis diagnosis was made in 53 cases including erythema nodosum (28 cases), leukocytoclastic vasculitis (seven cases), nodular vasculitis (four cases), superficial thrombophlebitis (two cases), eosinophilic panniculitis (three cases), infection-related panniculitis (five cases), and one case each of erythema nodosum leprosum (ENL), lupus panniculitis, pancreatic fat necrosis and acne conglobata with two cases remaining unclassified. Histologically, “predominantly septal” and “mixed panniculitis” were the chief inflammatory patterns in erythema nodosum cases, while mixed panniculitis was seen in most leukocytoclastic vasculitis cases and predominantly lobular and mixed panniculitis in nodular vasculitis cases (3).

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### A. Subcutaneous Vasculitis and Vasculopathy (Septal or Lobular) 492

1. Neutrophilic Vasculitis 492
   - Cutaneous/Subcutaneous Polyarteritis Nodosa 492
2. Lymphocytic “Vasculitis” 493
3. Granulomatous “Vasculitis”
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**VIIIA**

**SUBCUTANEOUS VASCULITIS AND VASCULOPATHY (SEPTAL OR LOBULAR)**

True vasculitis is defined by the presence of necrosis and inflammation in vessel walls. Other forms of vasculopathy include thrombosis and thrombophlebitis, fibrointimal hyperplasia, calcification, and neoplastic infiltration of vessel walls.

1. Neutrophilic Vasculitis
2. Lymphocytic “Vasculitis”
3. Granulomatous “Vasculitis”

**VIIIA1** Neutrophilic Vasculitis

Neutrophils and disrupted nuclei are present in the wall of the vessel, with associated eosinophilic “fibrinoid” necrosis.

**Cutaneous/Subcutaneous Polyarteritis Nodosa (See Also VB3)**

Cutaneous polyarteritis nodosa is a vasculitis involving arteries and arterioles of the septa of the dermis or subcutaneous fat with few or relatively minor systemic manifestations, such as fever, malaise, myalgias, arthralgias, and neuropathy. Cutaneous vasculitis may present as a component of systemic vasculitic syndromes such as rheumatoid vasculitis or anti-neutrophil cytoplasmic antibody (ANCA)-associated primary vasculitic syndromes, which include Wegener granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis, and may have overlapping histology (4). Systemic polyarteritis nodosa frequently may present first in the skin, and demonstration of multi-organ involvement, particularly in the kidneys, heart, and liver, is necessary to make the distinction. As recently reviewed, a biopsy diagnosis of vasculitis must be correlated with clinical history, physical and laboratory findings and/or angiographic features to arrive at specific diagnosis (5). Diagnosis of any individual case therefore depends on clinicopathologic correlation (6). Vasculitis extending deep into the reticular dermis or subcutaneous tissue seems to be associated more often with systemic disease such as malignancy or connective tissue disease (7). A recent review has emphasized the importance of distinguishing between superficial thrombophlebitis and arteritis. Veins in the lower legs may have a compact concentric smooth
muscle pattern with a round lumen and an intimal elastic fiber proliferation that may mimic the characteristic features of arteries; however, elastic fibers are prominent between the bundles of smooth muscle in vein walls, while being sparse in the medial muscular layer in arteries (8).

**Conditions to consider in the differential diagnosis:**
- leukocytoclastic vasculitis
- subcutaneous polyarteritis nodosa
- superficial migratory thrombophlebitis
- erythema nodosum leprosum (ENL)

**VIII A2 Lymphocytic “Vasculitis”**

The concept of “lymphocytic vasculitis” is a controversial one. Many disorders characterized by lymphocytes within the walls of vessels are best classified as lymphocytic infiltrates. The term “vasculitis” may be appropriate when there is vessel wall damage, as in nodular vasculitis, even in the absence of neutrophils and “fibrinoid” changes (9).

**Conditions to consider in the differential diagnosis:**
- nodular vasculitis
- perniosis (see VB2)
- angiocentric lymphomas

**VIII A3 Granulomatous “Vasculitis”**

The inflammatory infiltrate in the vessel walls is composed of mixed cells including more or less epithelioid histiocytes, and giant cells. Other cell types including lymphocytes and plasma cells, and sometimes neutrophils and eosinophils, are also commonly present.

**Erythema Induratum (Nodular Vasculitis)**

**CLINICAL SUMMARY.** The lesions of erythema induratum (10), also known as “nodular vasculitis,” consist of painless but somewhat tender, deep-seated, circumscribed, nodular, subcutaneous infiltrations of the lower legs, especially on the calves. Gradually, the infiltrations extend toward the surface, forming blue-red plaques that can ulcerate before healing with atrophy and scarring. Recurrences are common and often are precipitated by the onset of cold weather. Women are more commonly affected than men. Many cases are associated with detectable sequences of *Mycobacterium tuberculosis* in lesional tissue by PCR, with a prevalence that varies geographically, perhaps related to the prevalence of tuberculosis in the community (11,12). “Nodular vasculitis” has been proposed as a term for those cases with erythema induratum-like lesions that were not associated with tuberculosis.

**HISTOPATHOLOGY.** In contrast to erythema nodosum that is mainly a septal panniculitis, erythema induratum (nodular vasculitis) initially is mainly a lobular panniculitis characterized by inflammation and necrosis of the fat lobule with relatively less involvement of the structures of the septa. It is controversial whether vasculitis should be required as a necessary diagnostic feature, but nevertheless some form of vasculitis is present in most cases (13). The fat necrosis elicits granulomatous inflammation. Epithelioid cells and giant cells and/or lymphocytes and plasma cells form broad zones of inflammation surrounding the necrosis and extending between the fat cells but also can form well-delimited granulomas of the tuberculoid type. Ziehl–Neelsen stains are negative for mycobacteria. Vascular...
changes are typically extensive and severe. The walls of small- and medium-sized arteries and veins are infiltrated by a dense lymphoid or granulomatous inflammatory infiltrate, associated with endothelial swelling and edema of the vessel walls, fibrous thickening of the intima and, often, thrombosis of the lumen. Compromise of the lumen produces ischemic and caseous fat necrosis, which when extensive may lead to involvement of the overlying dermis and ulceration. In the necrotic fat there may be fat cysts, with surrounding amorphous, finely granular, eosinophilic material containing some pyknotic nuclei. Later lesions contain many foamy histiocytes surrounding the areas of fat necrosis.

**Conditions to consider in the differential diagnosis:**
- Erythema induratum/nodular vasculitis
- ENL (Type 2 leprosy reaction)
- Wegener’s granulomatosis
- Churg–Strauss vasculitis
- Crohn’s disease
- giant cell arteritis

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**Clin. Fig. VIII A3.** Erythema induratum. A young female presented with a tender ulcerated nodule in the left pretibial area. Cultures for tuberculosis were negative.

**Fig. VIII A3.a.** Erythema induratum/nodular vasculitis, low power. There is inflammation involving the subcutaneous lobules with little or no inflammation in the overlying epidermis and dermis.

**Fig. VIII A3.b.** Erythema induratum/nodular vasculitis, medium power. This is a predominantly lobular panniculitis with less intense involvement of the subcutaneous septae.
VIIIB. Septal Panniculitis Without Vasculitis

The inflammation is mainly confined to the septa, although there may be some lobular involvement.

1. Septal Panniculitis, Lymphocytes, and Mixed Infiltrates
2. Septal Panniculitis, Granulomatous
3. Septal Panniculitis, Sclerotic

VIIIB1 Septal Panniculitis, Lymphocytes, and Mixed Infiltrates

The inflammation predominantly involves the subcutaneous septa, although there may be “spillover” into the fat lobules. The infiltrate is mainly lymphocytic although other cells can be found including plasma cells and acute inflammatory cells.

Erythema Nodosum

CLINICAL SUMMARY. Although the causes of erythema nodosum (14,15) are multiple and cannot always be determined, streptococcal infection is the most common. In the acute form of erythema nodosum, there is a sudden appearance of tender, bright red or dusky red-purple nodules that only slightly elevate the level of the skin surface and have a strong predilection for the anterior surfaces of the lower legs, although they also may occur elsewhere, but mostly on dependent regions. The lesions do not ulcerate and generally involute within a few weeks, while new lesions may intermittently appear for several months. The lesions are tender and warm, and the acute disease is often accompanied by fever, malaise, leukocytosis, and arthralgic. Focal hemorrhages are common and can cause the lesions to resemble bruises (erythema contusiforme). The chronic form of erythema nodosum may last from a few months to a few years and is also known as erythema nodosum migrans or subacute nodular migratory panniculitis. There are one or several red, slightly tender subcutaneous nodules that are found, usually unilaterally, on the lower leg. Most of the patients are women with a solitary lesion and a recent history of sore throat and arthralgia. The nodules enlarge by peripheral extension into plaques, often with central clearing.

HISTOPATHOLOGY. In early acute lesions there is edema of the subcutaneous septa with a lymphohistiocytic infiltrate, having a slight admixture of neutrophils and eosinophils. Focal fibrin deposition and extravasation of erythrocytes occur frequently. Often the inflammation is most intense at the periphery of the edematous septa and extends into the periphery of the fat lobules between individual fat cells in a lace-like fashion without prominent necrosis of the fat. Clusters of macrophages around small blood vessels, or a slit-like space, occur in early lesions and are known as Miescher’s radial nodules. The degree of vascular involvement is variable, but usually falls short of true vasculitis. Often the inflammation is most intense at the periphery of the edematous septa and extends into the periphery of the fat lobules between individual fat cells in a lace-like fashion without prominent necrosis of the fat. Clusters of macrophages around small blood vessels, or a slit-like space, occur in early lesions and are known as Miescher’s radial nodules. The degree of vascular involvement is variable, but usually falls short of true vasculitis. Later acute lesions show widening of the septa, often with fibrosis and with inflammation at the periphery of the fat lobules. Neutrophils usually are absent and there are more macrophages in the infiltrate. Macrophages at the edges of the fat lobules have a “foam-cell” appearance from phagocytozed lipid. Loosely formed granulomas comprised of macrophages and giant cells, without lipid deposition, are more frequent in late lesions compared to the early ones. The oldest lesions have septal widening and fibrosis.
**Clin. Fig. VIIIB1.** Erythema nodosum. Tender erythematous nodules on the shins is a classic presentation.

**Fig. VIIIB1.a.** Erythema nodosum, low power. Scanning magnification reveals thickening of the fibrous septa.

**Fig. VIIIB1.b.** Erythema nodosum, medium power. The septa are edematous and fibrotic. There is a mixed inflammatory infiltrate in this mid-stage lesion that begins to extend into the adjacent fat lobules.

**Fig. VIIIB1.c.** Erythema nodosum, high power. Vasculitis is absent. The septa are fibrotic.

**Fig. VIIIB1.d.** Erythema nodosum, high power. Lymphocytes and histiocytes are present in the expanded septa.
with a decrease in all of the inflammatory cells, except for a few persisting at the periphery of the fat lobules.

In chronic erythema nodosum, the histologic findings are generally the same as those of the late stages of acute erythema nodosum. However, granuloma and lipogranuloma formation often is more pronounced. There is vascular proliferation and thickening of the endothelium with extravasation of erythrocytes.

**Conditions to consider in the differential diagnosis:**
- *erythema nodosum and variants*
- Crohn’s disease
- *morphea*

**VIIIB2 Septal Panniculitis, Granulomatous**

Subcutaneous granulomas may present as ill-defined collections of epithelioid histiocytes, as well-formed epithelioid-cell granulomas, and as palisading granulomas in which histiocytes are radially arranged around areas of necrosis or necrobiosis. Most of the conditions in this list may also present as mixed lobular/septal panniculitis (see VIIIC5).

**Subcutaneous Granuloma Annulare**

**CLINICAL SUMMARY.** In this disorder, subcutaneous nodules occur, especially in children, either alone or in association with intradermal lesions (16). The subcutaneous nodules clinically resemble rheumatoid nodules, although there is a greater tendency to occur on the legs and feet, and there is no history of arthritis. A very rare, deep, destructive form of granuloma annulare has also been described. This lesion might also be considered in the section on mixed septal and lobular involvement (see VIIID6).

**HISTOPATHOLOGY.** The subcutaneous nodules of granuloma annulare usually show large foci of palisaded histiocytes surrounding areas of degenerated collagen and prominent mucin with a pale appearance; however, biopsies in which mucin was not apparent or the central area...
VIII. Disorders of the Subcutis

Table VIII.1. Selected Panniculitides

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Erythema Nodosum</th>
<th>Erythema Induratum</th>
<th>Polyarteritis Nodosa</th>
<th>Sarcoidosis</th>
<th>Granuloma Annulare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Nodules on shins, tender</td>
<td>Nodules on calves, tender</td>
<td>Preferentially on lower extremity</td>
<td>Nodules wide distribution</td>
<td>Nodules wide distribution</td>
</tr>
<tr>
<td>Ulceration</td>
<td>No</td>
<td>Possible</td>
<td>Possible</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Distribution</td>
<td>Septal</td>
<td>Lobular</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Mixed</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>No</td>
<td>Large and small, veins and arteries</td>
<td>Large vessels, arteries</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Histology</td>
<td>Neutrophils, histiocytes</td>
<td>Fat necrosis, histiocytes</td>
<td>Tissue necrosis, neutrophils</td>
<td>Noncaseating granulomas</td>
<td>Palisading histiocytes, necrobiosis</td>
</tr>
</tbody>
</table>

Fig. VIIIB2.b. Subcutaneous granuloma annulare, medium power. In the subcutaneous septum, there is palisaded granulomatous inflammation.

Fig. VIIIB2.c,d. Subcutaneous granuloma annulare, high power. The altered (necrobiotic) collagen is surrounded by a palisade of histiocytes as well as fibrosis.

Fig. VIIIB2.b

Fig. VIIIB2.c

Fig. VIIIB2.d

TABLE VIII.1. Selected Panniculitides

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Erythema Nodosum</th>
<th>Erythema Induratum</th>
<th>Polyarteritis Nodosa</th>
<th>Sarcoidosis</th>
<th>Granuloma Annulare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section</td>
<td>VIIIB1</td>
<td>VIIIA3</td>
<td>VIIIA1</td>
<td>VIIIC7b</td>
<td>VIIIB7</td>
</tr>
</tbody>
</table>
appeared more fibrinoid have also been reported. The histopathologic differential diagnosis includes rheumatoid nodule, necrobiosis lipoidica, and epithelioid sarcoma (17). Especially in the pediatric population, it is important to consider subcutaneous granuloma annulare before making a diagnosis of rheumatoid nodule.

**Conditions to consider in the differential diagnosis:**
- palisaded granulomas
- subcutaneous granuloma annulare
- rheumatoid nodules
- sarcoidosis
- lichen scrofulosorum
- Crohn’s disease
- subcutaneous infections
- syphilis
- tuberculosis

**VIIIB. Septal Panniculitis, Sclerotic**

Sclerosis of the panniculitis may begin as a septal process and extend into the lobules.

**Scleroderma and Morphea**

**CLINICAL SUMMARY.** (See also VF1). Morphea is also known as localized scleroderma, and is differentiated from systemic sclerosis based on the absence of sclerodactyly,
Raynaud phenomenon, and nailfold capillary changes (18). Many patients with morphea have systemic manifestations, such as malaise, fatigue, arthralgias, and myalgias, and positive autoantibody serologies. The pathogenesis of morphea is not understood at this time, but ultimately results in an imbalance of collagen production and destruction.

**HISTOPATHOLOGY.** Changes in the subcutis are prominent in both scleroderma and morphea (19). The inflammatory infiltrate involving the subcutaneous fat in morphea is often much more pronounced than that in the dermis. It consists of lymphocytes and plasma cells, and extends upward toward the eccrine glands. Trabeculae subdividing the subcutaneous fat are thickened by an inflammatory infiltrate and deposition of new collagen. Large areas of subcutaneous fat are replaced by newly formed collagen composed of fine, wavy fibers. Vascular changes in the early inflammatory stage may consist of endothelial swelling and edema of the walls of the vessels. In the late sclerotic stage, as seen in the center of old morphea lesions, the inflammatory infiltrate has disappeared almost completely, except in some areas of the subcutis. The fascia and striated muscles underlying lesions of morphea may be affected in the linear, segmental, subcutaneous, and generalized types, showing fibrosis and sclerosis similar to that seen in subcutaneous tissue. The muscle fibers appear vacuolated and separated from one another by edema and focal collections of inflammatory cells. Aggregates of calcium may also be seen in the late stage within areas of sclerotic, homogeneous collagen of the subcutaneous tissue.

In early lesions of systemic scleroderma, the inflammatory reaction is less pronounced than in morphea. The vascular changes in early lesions are slight, as in morphea. In contrast, in the late stage, systemic scleroderma shows more pronounced vascular changes than morphea, particularly in the subcutis. These changes include a paucity of blood vessels, thickening and hyalinization of their walls, and narrowing of the lumen.

**Conditions to consider in the differential diagnosis:**
- scleroderma, morphea
- eosinophilic fasciitis
- ischemic liposclerosis
- lipodermatosclerosis
- toxins

### VIIIIC Lobular Panniculitis, Without Vasculitis

The inflammation is mainly confined to the lobules, although there may be some septal involvement.

1. Lobular Panniculitis, Lymphocytes Predominant
2. Lobular Panniculitis, Lymphocytes, and Plasma Cells
3. Lobular Panniculitis, Neutrophilic
4. Lobular Panniculitis, Eosinophils Prominent
5. Lobular Panniculitis, Histiocytes Prominent
6. Lobular Panniculitis, Mixed with Foam Cells
7. Lobular Panniculitis, Granulomatous
8. Lobular Panniculitis, Crystal Deposits, Calcifications
9. Lobular Panniculitis, Necrosis Prominent
10. Lobular Panniculitis, Embryonic Fat Pattern
11. Lobular Panniculitis, Lipomembranous

#### VIIIIC1 Lobular Panniculitis, Lymphocytes Predominant

Lymphocytes are the primary infiltrating cells.

**Lupus Erythematosus Panniculitis**

**CLINICAL SUMMARY.** In patients with chronic cutaneous lupus erythematosus, the lesions can be deep and can involve the panniculus either alone or accompanied by dermal lesions (20). The patients can have either chronic discoid lupus erythematosus or systemic lupus erythematosus. Most commonly, the skin lesions are firm, indurated subcutaneous nodules and plaques that tend to involve the skin of the trunk and proximal extremities, particularly the lateral aspects of the upper arms, thighs, and buttocks. The overlying skin shows no specific changes. The lesions are painful and have a tendency to ulcerate and to heal leaving depressed scars. When the overlying skin is involved there is a loss of hair, erythema, poikiloderma, and epidermal atrophy. The patients may present with localized depressions of lipoatrophy alone. The term “lupus profundus” has been used both for lupus panniculitis and also for discoid lupus erythematosus lesions that involve the dermis and extend deeply into the subcutis.

**HISTOPATHOLOGY.** The histologic sections show a deep lymphocytic infiltrate in the fat lobules and in the septa. Lymphoid aggregates, nodules, and germinal centers are common. Usually there is mucinous edema of the septa and of the overlying dermis. The dermis can have a superficial and deep perivascular lymphocytic infiltrate with plasma cells or all of the changes of lesions of discoid lupus erythematosus may be present. A distinctive feature is the so-called “hyaline necrosis” of the fat, in which portions of the fat lobule have lost nuclear staining of the fat cells and there is an accumulation of fibrin and other proteins in a homogeneous eosinophilic matrix between residual fat cells and extracellular fat globules. Blood vessels are infiltrated by lymphoid cells and can have restriction of their lumen diameter. Calcification may be present in older lesions. The differential diagnosis includes subcutaneous panniculitis-like T-cell lymphoma.

In a recent study, features helpful in making this distinction included the presence of involvement of the...
Clin. Fig. VIIIC1. *Lupus panniculitis.* A patient with discoid lupus erythematosus developed an indurated subcutaneous area with postinflammatory hyper/hypopigmentation on the lateral thigh.

Fig. VIIIC1.a. *Lupus panniculitis, low power.* An intense inflammatory infiltrate is present at the dermal–subcutaneous junction, extending into the adipose tissue in an interstitial pattern (C. Jaworsky).

Fig. VIIIC1.b. *Lupus panniculitis, medium power.* The inflammatory infiltrate outlines individual adipocytes, creating a lace-like pattern (C. Jaworsky).

Fig. VIIIC1.c. *Lupus panniculitis, high power.* Foam cells indicate adipocyte injury. Note also the hyaline matrix between adipocytes (“hyaline fat necrosis”) (C. Jaworsky).
epidermis, lymphoid follicles with reactive germinal centers, mixed cell infiltrate with prominent plasma cells, clusters of B lymphocytes, and polyclonal T cell receptor gene rearrangements (21). Monoclonal gene rearrangements have been described in rare cases, and clear distinction between these entities may require observation over time in some difficult cases (22).

**Conditions to consider in the differential diagnosis:**

- lupus panniculitis
- lupus profundus
- nodular vasculitis/erythema induratum, inapparent vasculitis
- post-steroid panniculitis
- subcutaneous lymphoma-leukemia

### VIIIC3 Lobular Panniculitis, Neutrophilic

Lymphocytes and neutrophils are the primary infiltrating cells. The conditions listed below are more likely to present as a mixed lobular and sepal panniculitis (see VIIID1), and may also involve the dermis. In some cases with pancreatic enzyme panniculitis, possibly with early lesions, biopsies of subcutaneous nodules show only a nonspecific pattern of a necrotizing panniculitis with a neutrophilic inflammatory response. If there is no necrosis and if other entities can be ruled out, and in an appropriate clinical setting, the diagnosis for a neutrophilic panniculitis may be subcutaneous Sweet’s syndrome (23).

**Conditions to consider in the differential diagnosis:**

- infection (cellulitis)
- necrotizing fascitis
- ruptured follicles and cysts
- pancreatic fat necrosis
- traumatic panniculitis
- subcutaneous Sweet’s syndrome

### VIIIC4 Lobular Panniculitis, Eosinophils Prominent

Lymphocytes and eosinophils are the primary infiltrating cells. The conditions listed below are more likely to present as a mixed lobular and sepal panniculitis (see VIIID3), and may also involve the dermis.

**Conditions to consider in the differential diagnosis:**

- eosinophilic fascitis
- eosinophilic panniculitis
- arthropod assault reactions
- parasites
- hypersensitivity reactions
- Well’s syndrome

### VIIIC5 Lobular Panniculitis, Histiocytes Prominent

Lymphocytes and histiocytes are the primary infiltrating cells. The conditions listed below are more likely to present as a mixed lobular and sepal panniculitis (see also VIIID4).

**Histiocytic Cytophagic Panniculitis (Subcutaneous T-Cell Lymphoma With Hemophagocytic Syndrome)**

**CLINICAL SUMMARY.** Histiocytic cytophagic panniculitis (24,25) is a frequently fatal systemic disease that is characterized by recurrent, widely distributed, painful subcutaneous nodules associated with malaise and fever. The nodules can be hemorrhagic and may ulcerate. Hepatosplenomegaly, pancytopenia, and progressive liver dysfunction develop in most cases. The patients may follow a
long chronic course or the disease can be fulminant. The patients usually die a hemorrhagic death due to depletion of blood coagulation factors. In some patients, the disease seems limited to the skin and subcutaneous tissue and follows a more benign course. Some of these cases may be virally associated.

In most instances, the cytophagic panniculitis is the result of a malignant lymphoma in which the abnormal lymphocyte population has stimulated benign macrophages to engage in fulminant hemophagocytosis. Lymphoma may or may not be evident in any given biopsy of skin and/or subcutaneous tissue. The natural killer (NK) cell marker CD56 is an important marker for distinguishing two major patterns of subcutaneous lymphomas with features of cytotoxic T-cell and NK/T-cell lymphomas. CD56-negative cases tend to be mainly in the younger age group and have systemic subcutaneous nodules without ulceration, with subcutaneous invasion by medium-sized lymphoma cells, scattered erythrophagocytosis, patchy necrosis, and little tumor invasion in the superficial dermis, and a somewhat better prognosis. CD56-positive cases tend to have systemic ulcerative skin tumors composed of pleomorphic lymphoma cells with massive necrosis and little erythrophagocytosis, involving the subcutis and also often the whole dermis, with a relatively poor prognosis (26).

**HISTOPATHOLOGY.** A deep biopsy usually shows both subcutaneous and dermal nodules composed of macrophages

---

Clin. Fig. VIIIC5. *Histiocytic cytophagic panniculitis.* This cross-sectioned skin nodule shows both septal and lobular infiltration and hemorrhage. Note also the dermal hemorrhage (N.S. McNutt, A. Moreno, F. Contreras).

Fig. VIIIC5.a. *Histiocytic cytophagic panniculitis, medium power.* There is hemorrhagic necrosis of the fat, with an infiltrate of lymphocytes and macrophages (N.S. McNutt, A. Moreno, F. Contreras).

Fig. VIIIC5.b. *Histiocytic cytophagic panniculitis, high power.* Macrophages and multinucleated cells ingest lymphocytes and erythrocytes to form so-called “bean-bag cells” (N.S. McNutt, A. Moreno, F. Contreras).
and a mixed inflammatory infiltrate. In the subcutis the inflammation is both septal and lobular. Often there is necrosis and hemorrhage. The nuclei of the macrophages are without significant atypia. In some areas the macrophages become so engorged by phagocytosis of erythrocytes, lymphocytes, and cell fragments (termed "emperiploisis") that they have been named "bean bag cells." In some patients early lesions contain a rather dense infiltrate of small lymphocytes and only focal areas with cytophagic histiocytes. Overt lymphoma may not be evident in biopsies of early stage lesions. The involvement of other organs by similar cytophagic macrophages leads to diffuse infiltration of liver, bone marrow, spleen, lymph nodes, myocardium, lungs, and gastrointestinal tract. The cytophagic macrophages can deplete almost all of the bone marrow elements.

**Conditions to consider in the differential diagnosis:**
- cytophagic histiocytic panniculitis
- Rosai–Dorfman disease
- subcutaneous histiocytoid Sweet's syndrome
- atypical mycobacteria
- lepromatous leprosy
- sarcoidosis

**Lobular Panniculitis, Mixed With Foam Cells**

Lymphocytes, plasma cells, and a variety of infiltrating cells can be seen including giant cells and foamy histiocytes.

**Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber–Christian Disease)**

**CLINICAL SUMMARY.** The diagnosis of Weber–Christian disease (27) is a diagnosis of exclusion. It is made much less frequently now than it was in the past, probably due to the greater power of current laboratory testing to reveal lupus erythematosus panniculitis, alpha-1-antitrypsin (AAT) deficiency panniculitis, histiocytic cytophagic panniculitis, or infectious etiologies in cases that might previously have been classified as Weber–Christian disease. The classical clinical description is of a disease characterized by the appearance of crops of tender nodules and plaques in the subcutaneous fat, usually in association with mild fever. The lower extremities are favored sites, but lesions can occur also on the trunk, the upper extremities, and rarely on the face. The lesions may ulcerate; as they involute, they leave depressions in the skin surface. The overlying skin usually shows no involvement other than mild erythema. In general, the prognosis is good, with the attacks gradually becoming less severe and ultimately ceasing. The name Weber–Christian disease has been used in such a general fashion by some authors that the term loses meaning beyond being a clinical syndrome with nodular panniculitis for which the etiology has not yet been determined (28).

**HISTOPATHOLOGY.** The histopathologic appearance itself is not sufficiently specific to exclude the other diseases mentioned above. The classical description is that of a lobular panniculitis that evolves through three phases. The first phase is acute inflammation of the fat lobules with degeneration of fat cells accompanied by an infiltrate of neutrophils, lymphocytes, and macrophages. Neutrophils may predominate, but abscesses do not occur. In the second phase, after the lesions have been present for several days, the infiltrate is discretely localized to the fat lobules and consists mainly of foamy macrophages, usually also with a few lymphocytes and plasma cells. The foam cells can be large and often some of them are multinucleated. Foamy macrophages replace the fat lobules and extracellular lipid masses ("microcysts") result from lysis of the fat. In some cases, the lesions perforate the skin surface and discharge a sterile, oily liquid. The third phase, in clinical lesions that are depressed and indurated, shows many fibroblasts and scattered lymphocytes and a few plasma cells that have replaced the fat; dense fibrosis results.

Systemic lesions that may be seen in Weber–Christian disease include involvement of the mesenteric and omental fat; involvement of intravisceral adipose tissue, causing focal necroses in liver or spleen; involvement of the bone marrow; and accumulation of large amounts of oily fluid in either the peritoneal or pleural cavity.

**Conditions to consider in the differential diagnosis:**
- AAT deficiency panniculitis
- Weber–Christian disease
- traumatic fat necrosis
- cold panniculitis
- injection granuloma
- factitious panniculitis
- necrobiotic xanthogranuloma with paraproteinemia

![Clin. Fig. VIIIC6](image-url)

**Clin. Fig. VIIIC6.** “Weber–Christian disease.” An indurated nodule on the leg has developed a perforation and drains a turbid, sterile, oily fluid with necrotic tissue (N.S. McNutt, A. Moreno, F. Contreras).
Fig. VIIIC6.a. *Lobular panniculitis consistent with “Weber–Christian disease,” low power.* A dense lymphocytic infiltrate is sharply localized to the fat lobules without vasculitis.

Fig. VIIIC6.b. *Lobular panniculitis consistent with “Weber–Christian disease,” high power.* The infiltrate is composed mainly of lymphocytes and macrophages with variable numbers of neutrophils.

Fig. VIIIC6.c. *Lobular panniculitis consistent with “Weber–Christian disease,” high power.* An ill-defined granuloma is present. There is no vasculitis. Infection should be ruled out.

Fig. VIIIC6.d. *Lobular panniculitis consistent with “Weber–Christian disease,” later lesion, medium power.* The fat is necrotic and has been extensively replaced by lipid-laden macrophages or “foam cells.”
VIII. Disorders of the Subcutis

VIIIC7 Lobular Panniculitis, Granulomatous

Lymphocytes and histiocytes are the primary infiltrating cells. Except for erythema induratum, discussed in VIIIA3 because it is usually associated with evident vasculitis, most of the conditions in this list may more usually present as mixed lobular/septal panniculitis (see VIIIC5).

Subcutaneous Sarcoidosis

Sarcoidosis may present as a subcutaneous nodule, characterized as in other sites by noncaseating epithelioid cell granulomas, usually with only slight associated lymphocytic inflammation. The diagnosis should be based on exclusion of other granulomatous disorders, especially infection, with clinicopathologic correlation.

Conditions to consider in the differential diagnosis:
- erythema induratum/nodular vasculitis (if vasculitis is inapparent)
- palisaded granulomas
- subcutaneous granuloma annulare/pseudorheumatoid nodule
- rheumatoid nodules
- subcutaneous sarcoidosis
- tuberculosis
- Crohn’s disease

VIIIC8 Lobular Panniculitis, Crystal Deposits, Calcifications

Crystalline deposits derived from free fatty acids or other precipitated salts are present in the fat lobules.

Subcutaneous Fat Necrosis of the Newborn

CLINICAL FEATURES. Subcutaneous fat necrosis of the newborn usually occurs in premature or full-term infants, often in the past after delivery with forceps (29), or after a history of fetal distress (30). Indurated nodules and plaques appear in the subcutis a few days after birth. Rarely, in cases with numerous nodules, the lesions may discharge a caseous material. The patient’s health generally is good and the nodules resolve spontaneously after a few weeks or months.

HISTOPATHOLOGY. Focal areas of fat necrosis are present in the fat lobules and are infiltrated by macrophages and foreign-body giant cells. The fat deposits in the macrophages and giant cells contain crystalline fat, which forms needle-shaped clefts in a radial arrangement. Calcium deposits are usually scattered in the necrotic fat. An important histologic differential diagnosis is sclerema neonatorum, which shows less inflammation than subcutaneous fat necrosis of the newborn, and occurs in severely ill infants.

Calcifying Panniculitis (Calciphylaxis)

CLINICAL FEATURES. Calciphylaxis is an uncommon complication of renal failure usually in combination with secondary or tertiary hyperparathyroidism. Obesity, female gender, and poor nutritional status are some putative risk factors. Painful violaceous lesions that may be indurated often develop in areas of livedo reticularis on the trunk and extremities and can rapidly progress to form bullae, ulcers, eschars, and gangrene. The prognosis is extremely poor, especially for proximal disease, even with aggressive...
Clin. Fig. VIIIC8.a. Subcutaneous fat necrosis of the newborn. A healthy full term infant developed an indurated plaque with alopecia on the scalp, an unusual presentation (P. Honig).

Fig. VIIIC8.a. Subcutaneous fat necrosis of the newborn, low power. Scanning magnification reveals a predominantly lobular panniculitis. The overlying epidermis and dermis show almost no inflammation.

Fig. VIIIC8.b. Subcutaneous fat necrosis of the newborn, medium power. Within the subcutaneous lobules there is a lymphoid infiltrate associated with large giant cells. Occasionally, as seen here, they may be numerous.

Fig. VIIIC8.c. Subcutaneous fat necrosis of the newborn, high power. The giant cells show numerous needle-shaped clefts in a radial array, a characteristic finding in this disease.
treatment by parathyroidectomy. Fulminant sepsis may develop from infection of necrotic or gangrenous tissue.

**HISTOPATHOLOGY.** The principal histologic findings include (1) calcification of soft tissue and small vessels, (2) nonspecific intimal proliferation of small vessels, often resulting in luminal narrowing, (3) variable fibrin thrombi, and (4) frequent ischemic necrosis of skin and subcutis. The small vessels involved by this process cannot be identified as either arterial or venous. Small vessel vasculitic changes may also be seen in some cases. Foreign body-giant cell reaction to calcium and mixed inflammatory cell infiltrates that are neutrophil-rich may be seen. The relationships between the calcification and thrombosis, and the ischemic necrosis in calciphylaxis are unclear. Some similar cases have been described with subcutaneous thrombotic vasculopathy but without calcification, and may represent an early stage or a related lesion (31). Although vascular calcification is common in uremic patients, calciphylaxis is rare. Elevation of the calcium and phosphorous product along with a poorly defined precipitating or challenging event or agent are hypothesized to be necessary for calcium deposition in cutaneous tissues. Although they are relatively nonspecific when considered

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**Clin. Fig. VIIIIC8.b.** *Calcifying panniculitis.* This patient with hyperparathyroidism developed erythematous, hemorrhagic, indurated plaques that were cold to touch (N.S. McNutt, A. Moreno, F. Contreras).

**Clin. Fig. VIIIIC8.c.** *Calciphylaxis.* An x-ray of a skin biopsy from a patient with calciphylaxis reveals linear calcifications in vessel walls.

**Fig. VIIIIC8.d.** *Calcifying panniculitis, low power.* Although the subcutis appears relatively unaffected at low power, gangrenous necrosis of the epidermis and dermis suggests vascular injury at a deeper level.

**Fig. VIIIIC8.e.** *Calcifying panniculitis, high power.* In addition to lipomembranous change, small vessels within the subcutis are seen to contain basophilic granular material consistent with calcium within their walls.
in isolation, the cited histopathologic features of cutaneous calciphylaxis allow for the diagnosis of this potentially lethal disorder when seen in combination with one another, particularly if detailed clinical data also are available (32).

**Conditions to consider in the differential diagnosis:**
- sclerema neonatorum
- subcutaneous fat necrosis of the newborn
- gout
- oxalosis
- calcifying panniculitis

**VIIIC9 Lobular Panniculitis, Necrosis Prominent**

There is fat necrosis with a resulting infiltrate that is mixed.

**Subcutaneous Nodular Fat Necrosis in Pancreatic Disease**

**CLINICAL SUMMARY.** In patients with pancreatitis or pancreatic neoplasms, the release of lipase enzymes into the blood can lead to nodules of fat necrosis in the subcutis (33). The pretibial region is the most common site of the nodules, but they may occur on the thighs, buttocks, and elsewhere. The nodules usually are tender and red and may be fluctuant, but they only rarely discharge oily fluid through fistulae. Abdominal pain is present in most cases of pancreatitis but may be absent in pancreatic carcinoma when the nodules appear. Arthralgia in the ankles is a common early symptom.

**HISTOPATHOLOGY.** The histologic appearance of the subcutaneous nodules in pancreatic disease is characteristic in most instances. In the foci of fat necrosis, there are ghost-like fat cells having thick, faintly stained cell peripheries and no nuclear staining. Calcification forms basophilic granules in the cytoplasm of the necrotic fat cells, and sometimes lamellar deposits around individual fat cells or patchy basophilic deposits at the periphery of the fat necrosis. A polymorphous infiltrate surrounds the foci of fat necrosis and consists of neutrophils, lymphoid cells, macrophages, foam cells, and foreign-body giant cells. There can be extensive hemorrhage into the lesions. Older lesions have fibrosis and hemosiderin deposition in addition to the inflammatory infiltrates. In some cases with pancreatic enzyme panniculitis, possibly with early lesions, biopsies of subcutaneous nodules show only a nonspecific pattern of a necrotizing panniculitis with a neutrophilic inflammatory response.

**Conditions to consider in the differential diagnosis:**
- pancreatic panniculitis
- erythema induratum, inapparent vasculitis
- necrobiotic xanthogranuloma with paraproteinemia
- gummatous syphilis
- infarct
- abscess
VIII. Disorders of the Subcutis

Viiic10 Lobular Panniculitis, Embryonic Fat Pattern

Due to atrophy or to failure of normal morphogenesis, immature small fat cells are present in the lobules.

Localized Lipoatrophy and Lipodystrophy

CLINICAL SUMMARY. Both localized lipoatrophy (34) and lipodystrophy can have lesions with a similar clinical appearance; however, lipoatrophy usually involves one or several circumscribed, round, depressed areas, from one to several centimeters in diameter. In contrast, lipodystrophy produces the loss of large areas of subcutaneous fat. Most cases of lipodystrophy are of the cephalothoracic type and involve the face, neck, upper extremities, and upper trunk. Lipodystrophy may occur with diabetes and with glomerulonephritis (35). Lipoatrophic panniculitis also occurs in connective tissue panniculitis.

Clin. Fig. VIIIC9. Pancreatic panniculitis. Erythematous nodules appear most commonly on the lower legs (N.S. McNutt, A. Moreno, F. Contreras).

Fig. VIIIC9.a. Pancreatic panniculitis, low power. Calcification forms granular basophilic material. Focal hemorrhage is frequent (N.S. McNutt, A. Moreno, F. Contreras).

Fig. VIIIC9.b. Pancreatic panniculitis, high power. Necrotic fat cells contain eosinophilic deposits of partially hydrolyzed fat (N.S. McNutt, A. Moreno, F. Contreras).

Fig. VIIIC9.c. Pancreatic panniculitis, high power. Many neutrophils are present at the margin of the zone of calcification and fat necrosis.
Clin. Fig. VIIIC10. Lipoatrophy. Insulin resistance and hypertriglyceridemia were present in this middle-aged male who presented with loss of subcutaneous fat leading to the appearance of hypertrophic muscles.

Fig. VIIIC10.a. Lipoatrophy, low power. At this magnification the subcutaneous fat appears fibrotic and the lobules appear shrunken and hypercellular.

Fig. VIIIC10.b. Lipoatrophy, high power. The individual adipocytes are small and the fat is not truly hypercellular but appears such because the individual nuclei are closer to one another.

Fig. VIIIC10.c. Lipoatrophy, high power. The fat cells are reduced in size.
Lesions of lipodystrophy are described with total loss of the subcutaneous fat producing dermis adjacent to fascia. However, localized lipoatrophy has been described as having two types: inflammatory and noninflammatory or “involutional” types. In the inflammatory type, multiple lesions are common and have a lymphocytic infiltrate around the blood vessels and scattered diffusely in the fat lobules. Areas of fat necrosis can be present with infiltration by macrophages. In the involutional type, usually there is only a solitary lesion that exhibits a decrease in size of the individual adipocytes. They are separated from each other by abundant eosinophilic, hyaline material, or in some instances by mucoid material.

**Conditions to consider in the differential diagnosis:**
- lipoatrophy
- lipodystrophy

**Lobular Panniculitis, Lipomembranous**

Lymphocytes, plasma cells, and a variety of infiltrating cells can be seen including giant cells and histiocytes.

**Lipomembranous Change or Lipomembranous Panniculitis**

**CLINICAL SUMMARY.** Patients with severe stasis, diabetes, and other causes of arterial vascular insufficiency to the lower legs can develop indurated plaques in the subcutis. They are depressed and painful, but rarely ulcerate (36).

**HISTOPATHOLOGY.** The lesions are defined microscopically by the presence of lipomembranes around fat deposits or “cysts” (37). Biopsies deep into the fat show a lobular panniculitis with focal macrophage infiltration and fibrosis around the shrunken lobules. At the border of the lobules with the septa there are fat cysts that are lined by a thin eosinophilic layer of protein that has fine, feathery projections into the fat cavity. This layer is called a lipomembrane and is positive on periodic acid-Schiff (PAS) and elastic-tissue stains. Early lesions have focal areas of fat necrosis, such as those produced by partial ischemia. Lipomembranous change has been found also in lupus erythematosus panniculitis and in morphea.

**Conditions to consider in the differential diagnosis:**
- lipomembranous panniculitis
- lipogranulomatosis of Rothmann–Makai
- granulomatous panniculitis in light-chain disease

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**Fig. VIIIC11.a.** Lipomembranous panniculitis, low power. The subcutaneous tissue shows fibrosis of both septae and lobules with cystic space formation, associated with a mild chronic inflammatory infiltrate.

**Fig. VIIIC11.b.** Lipomembranous panniculitis, medium power. Within the fat one can see variably sized cystic structures that are surrounded by eosinophilic material.
Fig. VIIIC11.c.  *Lipomembranous panniculitis, medium power.* The fat cells vary in size and shape.

Fig. VIIIC11.d.  *Lipomembranous panniculitis, high power.* The cysts are surrounded by feathery eosinophilic material which is frequently positive with PAS stains.

early stages of pyoderma gangrenosum
necrobiotic xanthogranuloma
lipodermatosclerosis

**VIIID**

**MIXED LOBULAR AND SEPTAL PANNICULITIS**

Neoplastic infiltrates and inflammation due to trauma or infection do not respect anatomic compartments of the subcutis.

1. With Hemorrhage or Sclerosis
2. With Many Neutrophils
3. With Many Eosinophils
4. With Many Lymphocytes
5. With Cytophagic Histiocytes
6. With Granulomas

**VIIID1**  **With Hemorrhage or Sclerosis**

Inflammation due to trauma is likely to be associated with hemorrhage, neutrophilic inflammation, and sclerosis in late lesions.

**Panniculitis Due to Physical or Chemical Agents**

**CLINICAL SUMMARY.** Trauma may be due to physical injury or chemical injury, such as that produced by injection of noxious substances. Physical injury can be produced by blunt pressure or impact, cold (38) or excessive heat, or electrical injury. All of these factors can produce firm nodules in the subcutaneous fat. Suggestitious injections of noxious substances can produce bizarre clinical and histologic patterns of lesions. Insulin injections, often on the thigh and lower abdomen, can result in subcutaneous lesions. Meperidine hydrochloride or Demerol and pentazocine or Talwin injections are known to produce traumatic panniculitis. The introduction of oily substances such as paraffin or silicone for cosmetic effects can produce a panniculitis (39). Mentally ill persons and drug addicts may purposely or inadvertently inject themselves with foreign substances, such as feces or milk, sometimes used to dilute or cut narcotics (40). These various physical or chemical traumas lead to indurated subcutaneous nodules that may undergo liquefaction, ulcerate, and discharge pus or a thick oily fluid. Healing leaves depressed scars. Lesions produced by extreme cold may include nodules or plaques that appear from one to three days after exposure and subside spontaneously within two weeks. Excessive
heat and electrical injury are usually accompanied by ulceration and eschar formation.

**HISTOPATHOLOGY.** The injection of various toxic agents will produce a variable histologic picture of acute inflammation, with aggregation of neutrophils and focal fat necrosis with hemorrhage. Older lesions have infiltrates of lymphocytes and macrophages with fibrosis. Vasculitis usually is absent. Polarized light may reveal foreign material in injection sites. The injection of oily liquids leads to the formation of many pockets of fatty material “fat cysts,” often with a surrounding fibrous reaction containing foamy macrophages, that produces a “Swiss-cheese appearance” after the fat is extracted during routine histologic processing. Trauma due to cold injury initially has an infiltrate of lymphocytes and macrophages near the blood vessels of the deep plexus at the junction of dermis and subcutis. Such changes have also been described in perniosis. Biopsies at the third day, the height of the reaction, show rupture of the fat cells with fat pockets in the tissue surrounded by an infiltrate of lymphocytes, macrophages, neutrophils, and occasional eosinophils.

**Conditions to consider in the differential diagnosis:**

- *traumatic panniculitis*
- cold panniculitis
- injections including factitial panniculitis
- blunt trauma: sclerosing lipogranuloma
- scleroderma/morphea
- lipodermatosclerosis

**With Many Neutrophils**

Neutrophilic inflammation diffusely involves the subcutis and extends along fascial planes.

**Necrotizing Fasciitis**

**CLINICAL SUMMARY.** Necrotizing fasciitis is caused most commonly by group A beta-hemolytic streptococci,
Mixed Lobular and Septal Panniculitis

Disorders of the Subcutis

and it typically presents with rapidly spreading erythema and pain (41). The erythema is more ill-defined than that of erysipelas and progresses to painless ulceration and necrosis along fascial planes. Whereas erysipelas involves the more superficial layers of the skin, fasciitis extends more deeply into the subcutaneous tissues. Although virtually all cases of erysipelas are caused by beta-hemolytic streptococci, primarily group A, the list of causative agents of cellulitis is much more extensive (42).

HISTOPATHOLOGY. The histologic picture is characterized by acute and chronic inflammation with necrosis. Often there is thrombosis of blood vessels as the result of damage to vessel walls from the inflammatory process. The key feature in distinguishing necrotizing fasciitis from a less threatening superficial cellulitis is the location of the inflammation. In the former, the inflammation involves the subcutaneous fat, fascia, and muscle in addition to the dermis. A biopsy may be submitted at the time of surgical debridement for frozen section examination. In an appropriate setting, the presence of edema and neutrophils in these deep locations supports the diagnosis. Frank necrosis may not be demonstrable, and bacteria are frequently not evident in an initial biopsy.

Conditions to consider in the differential diagnosis:
- necrotizing fasciitis (bacterial infection)
- abscesses
- North American blastomycosis
- pyoderma gangrenosum (involves dermis also)
- ecthyma gangrenosum
- AAT deficiency
- infection (cellulitis)
- dissecting cellulitis of the scalp (perifolliculitis abscedens et suffodiens)
- hidradenitis suppurativa
- ruptured follicles and cysts

Fig. VIIID2.a. Necrotizing fasciitis, low power. Necrosis of muscle and fascia in a patient with a staphylococcal infection complicating a hysterectomy.
Fig. VIIID2.b. Necrotizing fasciitis, high power. Necrotic muscle infiltrated by degenerating neutrophils.
Fig. VIIID2.c. Necrotizing fasciitis, high power. Fascia with focal edema and neutrophils. Presence of neutrophils in the fascia is compatible with this diagnosis in an appropriate clinical setting, even in the absence of necrosis in a particular biopsy specimen.
VIII. Disorders of the Subcutis

VIIID3 With Many Eosinophils

Few to many eosinophils are present in subcutaneous lobules and septa.

Eosinophilic Fasciitis (Shulman’s Syndrome)

CLINICAL SUMMARY. Eosinophilic fasciitis (43) is a scleroderma-like disorder characterized by inflammation and thickening of the deep fascia. It has a rapid onset often after exercise, associated with pain, swelling, and progressive induration of the skin leading to exaggerated deep grooving of the skin around superficial veins. This disorder is often accompanied by peripheral eosinophilia and hypergammaglobulinemia, and has been associated with aplastic anemia. Eosinophilic fasciitis often involves one or more extremities. There are lesions on the trunk in only a few cases, and the face is almost invariably spared. In nearly all reported cases, Raynaud’s phenomenon and visceral lesions of scleroderma have been absent. The disorder has a varied course: some patients improve spontaneously, others improve with corticosteroids, while still others may have relapses and remissions. Eosinophilic fasciitis shares many features with generalized morphea: they both may show inflammation and fibrosis of the fascia, as well as blood eosinophilia and hypergammaglobulinemia. Also, antinuclear antibodies are present in a significant number of cases. The term morphea profunda, analogous to lupus erythematosus profundus, has been applied to this disorder.

HISTOPATHOLOGY. The fascia is markedly thickened, appears homogeneous, and is permeated by a mononuclear inflammatory infiltrate. In some instances the infiltrate in the fascia contains an admixture of eosinophils. The underlying skeletal muscle in some cases shows myofiber degeneration, severe inflammation with a component of eosinophils, and focal scarring; in other cases, however, it is not involved. In most cases the fibrous septa separating deeply located fat lobules are thicker, paler-staining, and more homogeneous and hyaline than normal subcutaneous connective tissue. In other cases, the collagen in the lower reticular dermis appears pale and homogeneous, and the entire subcutaneous fat is replaced by horizontally oriented, thick, homogeneous collagen containing only few fibroblasts and merging with the fascia.

Conditions to consider in the differential diagnosis:
- eosinophilic fasciitis
- eosinophilic panniculitis
- arthropod bites
- parasites

Clin. Fig. VIIID3.a. Eosinophilic fasciitis. The outer thigh skin is swollen and indurated.

Clin. Fig. VIIID3.b. Eosinophilic fasciitis. The skin appears sclerotic with surface dimpling. Morphea is in the differential diagnosis.
**VIIID**  Mixed Lobular and Septal Panniculitis

**VIIID4  With Many Lymphocytes**

Lymphocytic infiltrates diffusely involve the subcutis.

**Subcutaneous Panniculitic or Lipotropic T-Cell Lymphoma**

**CLINICAL SUMMARY.** Subcutaneous panniculitic or lipotropic T-cell lymphomas (44) may present with subcutaneous nodules, usually on the extremities. Some patients with this condition have associated hemophagocytic syndrome.

**HISTOPATHOLOGY.** The morphologic pattern overlaps with angiocentric lymphoma, as infiltration of vessel walls often accompanies subcutaneous infiltrates. Histopathologic features include a dense, subcutaneous infiltrate with a mixed septal and lobular distribution. The neoplastic cells have cytologic features similar to those of...
medium-sized or large-cell pleomorphic T-cell lymphoma, with irregularly shaped, variably sized hyperchromatic nuclei, with small nucleoli; rarely, anaplastic large cells are prominent. In cases with hemophagocytic element, phagocytosis of erythrocytes by non-neoplastic macrophages is present in the subcutaneous infiltrate or the bone marrow. Foci of karyorrhexis and fat necrosis can occur and can be associated with a granulomatous inflammatory reaction. The neoplastic cells express a mature helper T-cell phenotype but can show loss of CD5 and CD7. Subcutaneous T-cell lymphomas resemble panniculitis at scanning magnification, and in the cases in which small pleomorphic T cells predominate, their infiltrates may not be obviously malignant, even under close scrutiny. Subcutaneous lobular lymphoid infiltrates, termed lymphocytic lobular panniculitis (LLP), have recently been characterized as representing a spectrum of histologic, immunophenotypic, and molecular abnormalities that range from the clearly benign to the clearly neoplastic. Lymphoid atypia, erythrophagocytosis, loss of certain pan T-cell markers, a reduced CD4/8 ratio and TCR rearrangement are attributes that help to define these subcuticular T-cell lymphoid dyscrasias; however, some cases continue to defy precise classification (45).

Cutaneous gamma/delta T-cell lymphoma (CGD-TCL) has been included in the World Health Organization (WHO) lymphoma classification as a provisional entity (47).

**Conditions to consider in the differential diagnosis:**
- lupus panniculitis
- chronic lymphocytic leukemia
- subcutaneous T-cell lymphoma
- histiocytic cytophagic panniculitis (early lesion)

**Sinus Histiocytosis With Massive Lymphadenopathy (SHML, Rosai–Dorfman)**

**CLINICAL SUMMARY.** Massive cervical lymphadenopathy, usually bilateral and painless, is the most common manifestation. This is generally a benign disorder in spite of a propensity to form large masses and to disseminate to both nodal and extranodal sites. In most patients the disease resolves spontaneously, others have persistent problems, and very few die. Skin is the most common extranodal site, with more than 10% of patients having cutaneous involvement. The lesions are typically papules or nodules. A similar percentage has soft tissue involvement, usually of the subcutaneous tissue. Occasionally the soft tissue lesion may present as a breast mass or panniculitis. Although the disorders are clearly related, the cutaneous form of the
Mixed Lobular and Septal Panniculitis

Disorders of the Subcutis

Disease occurs in an older and ethnically more diverse group and is less likely to be associated with systemic symptoms than the systemic form (48).

Histopathology. The skin lesions contain a polymorphous infiltrate in which histiocytes with abundant cytoplasm are the most prominent element. Occasionally they may be multi-nucleated or have a foamy cytoplasm. However, the hallmark histologic feature is emperipolesis of lymphocytes. On occasion, red cells can also be taken up. In the lymph nodes, the sinuses are greatly dilated and crowded with inflammatory cells, particularly histiocytes. Here they tend to have an abundant foamy cytoplasm and also display emperipolesis. The histiocytes are S-100-positive but CD1a-negative, and do not contain Birbeck granules. About 50% are CD30-positive.

Conditions to consider in the differential diagnosis:
- AAT deficiency (late lesion)
- Histiocytic cytophagic panniculitis (late lesion)
- Rosai–Dorfman disease (SHML)

VIII With Granulomas

There is granulomatous inflammation involving the subcutis.

Mycobacterial Panniculitis

Mycobacterial infection of the fat can produce a mycobacterial panniculitis that can mimic erythema nodosum as well as erythema induratum. Special stains for acid-fast bacteria and cultures are important for the identification of the mycobacteria that are responsible. Often nontuberculous mycobacteria are involved in countries with a low incidence of tuberculosis, and in immunodeficient subjects (49). Granulomas may be inconspicuous or absent in many of these situations. A high index of suspicion is important, and modified acid-fast staining may be required to demonstrate the organisms.

Erythema Nodosum Leprosum
(Type 2 Leprosy Reaction)

Clinical Summary. ENL occurs most commonly in lepromatous leprosy (LL) and less frequently in borderline
lepromatous (BL) leprosy (50). Immune complex production and deposition as well as complement activation are regarded as the principal pathogenetic mechanism, while new data show that cell-mediated immunity is also important. ENL is characterized by an inflammatory infiltrate of neutrophils with vasculitis and/or panniculitis. There is deposition of immune complexes and complement together with Mycobacterium leprae antigens in the skin. The major T-cell subtype in ENL is the CD4 cell, in contrast to lepromatous leprosy where CD8 cells predominate (51). It may be observed in patients under treatment or in untreated patients. Clinically, there is a widespread eruption accompanied by fever, malaise, arthralgia, and leukocytosis. On the skin there are tender, red plaques and nodules together with areas of erythema and occasionally also purpura and vesicles. Ulceration, however, is rare.

**HISTOPATHOLOGY.** The skin and subcutaneous lesions are foci of acute inflammation superimposed on chronic multibacillary leprosy. Polymorph neutrophils may be scanty or so abundant as to form a dermal abscess with ulceration. Whereas foamy macrophages containing fragmented bacilli are usual, in some patients no bacilli remain and macrophages have a granular pink hue on Wade-Fite staining, indicating mycobacterial debris. A necrotizing vasculitis affecting arterioles, venules, and capillaries occurs in some cases; these patients may have superficial ulceration.

**Conditions to consider in the differential diagnosis:**
- tuberculosis
- Crohn’s disease
- gummatous tertiary syphilis
- ENL
Fig. VIIID6.d. *Erythema nodosum leprosum, low power.* The architecture on scanning magnification may resemble erythema nodosum. Superiorly there is a large vessel within a fat lobule which is occluded and surrounded by a dense infiltrate.

Fig. VIIID6.e. *Erythema nodosum leprosum, low power.* This profile demonstrates dense inflammation within the septa and focally within the lobules. Vascular involvement is also evident.

Fig. VIIID6.f. *Erythema nodosum leprosum, medium power.* A granuloma composed of histiocytes and giant cells is present at the edge of a fat lobule. Clear spaces are identifiable within histiocytes.

Fig. VIIID6.g. *Erythema nodosum leprosum, high power.* Close inspection of the clear spaces within foamy macrophages and giant cells reveals numerous clumps of fragmented bacilli (“globi”) within the foamy cells, which are known as “lepra” or “Virchow” cells. Neutrophils are scattered throughout this granuloma.

chronic erythema nodosum
palisaded granulomas
subcutaneous granuloma annulare/pseudorheumatoid nodule
rheumatoid nodules
*mycobacterial panniculitis*
subcutaneous sarcoidosis

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**VIII SUBCUTANEOUS ABSCESSSES**

A collection of neutrophils and necrotic material in the subcutis, usually surrounded by granulation tissue and fibrosis.
**With Neutrophils**

The center of the abscess contains pus, which is viscous because of the presence of DNA fragments derived from neutrophils and dead organisms.

**Phaeohyphomycotic Cyst**

**CLINICAL SUMMARY.** Phaeohyphomycosis (52) has been defined as a subcutaneous or systemic infection by dematiaceous, mycelia-forming fungi, that is, those fungi having dark-walled hyphae. This is a histopathologic definition of a disease process that can be caused by many different organisms and that can have multiple different clinical presentations. Subcutaneous phaeohyphomycosis typically presents as a solitary abscess or nodule on the extremity of an adult male. A history of trauma or a splinter can sometimes be elicited.

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**Fig. VIII1.e1.a.** Phaeohyphomycotic "cyst" (abscess). A subcutaneous nodule was comprised of sheets of neutrophils, with demonstrable fungal hyphae at higher magnification.

**Fig. VIII1.e1.b.** Phaeohyphomycotic cyst, low power. There is a dense infiltrate in the dermis with a central collection of neutrophils surrounded by granulomatous inflammation.

**Fig. VIII1.e1.c.** Phaeohyphomycotic cyst, medium power. There are alternating zones of neutrophilic abscesses and granulomatous inflammation with histiocytes and multinucleated giant cells.

**Fig. VIII1.e1.d.** Phaeohyphomycotic cyst, high power. Fungal forms may be most likely to be found in the areas of neutrophilic inflammation. The fungi may or may not contain brown pigment.
Lesions of subcutaneous phaeohyphomycosis start as small, often stellate foci of suppurative granulomatous inflammation. The area of inflammation gradually enlarges and usually forms a single large cavity with a surrounding fibrous capsule, the so-called phaeohyphomycotic cyst. The central space is filled with pus formed of polymorphonuclear leukocytes and fibrin. There is a surrounding granulomatous reaction composed of histiocytes, including epithelioid cells and multinucleated giant cells, lymphocytes, and plasma cells. Diligent search may identify an associated splinter in the tissue or liquid pus. The organisms are found within the cavity and at its edge, often within histiocytes. The hyphae often have irregularly placed branches and show constrictions around their septae. Mycelia, if present, are more loosely arranged than the compact masses of hyphae seen in eumycetoma. Pigment is not always obvious.

**Conditions to consider in the differential diagnosis:**

- acute or chronic bacterial abscesses
- deep fungal infections
  - *phaeohyphomycotic cyst*
  - North American blastomycosis
  - chromoblastomycosis
  - cutaneous alternariosis
  - paracoccidioidomycosis
  - coccidioidomycosis
  - sporotrichosis
  - protothecosis
  - mycobacterial panniculitis

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