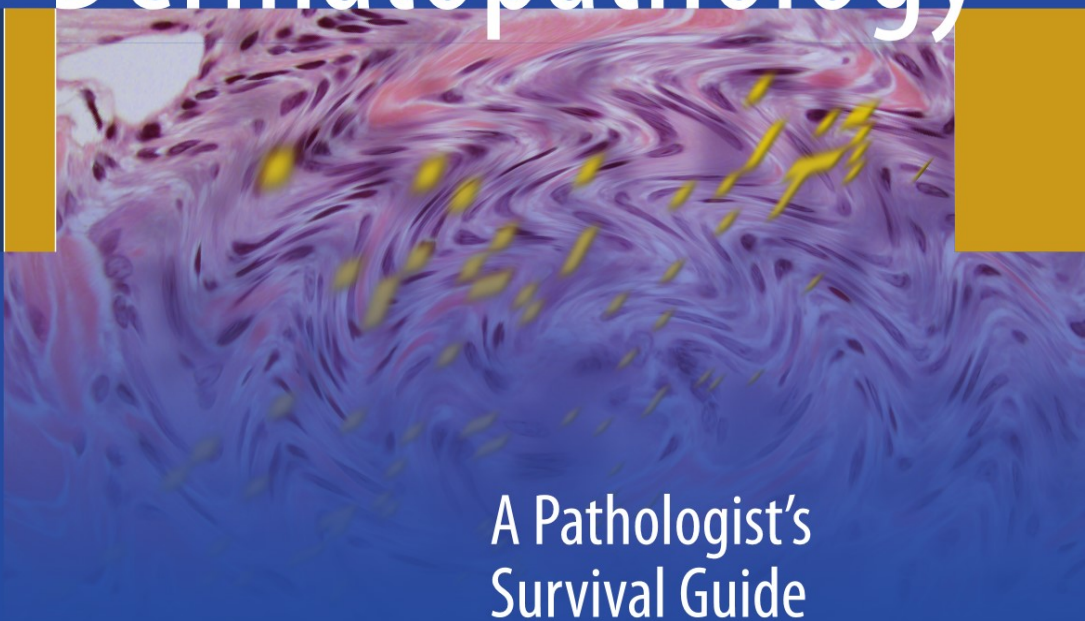
Steven D. Billings
Jenny Cotton

Inflammatory Dermatopathology



A Pathologist's Survival Guide

Springer

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Steven D. Billings, MD
Anatomic Pathology
Cleveland Clinic
9500 Euclid Avenue, L25
Cleveland, OH 44195
USA
billins@ccf.org

Jenny Cotton, MD, PhD
St. Joseph Mercy Hospital
5301 East Huron River Drive
Ann Arbor, MI 48106
USA

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This book is dedicated to my wife, Beth, and daughter, Maeve. I am ever grateful for all the joy you bring me and for your love and support.

Thank you:

I especially want to thank Drs. Yu-Hung Wu and Jasmin Jamora. This book would not have been written without your help. I would also like to thank my residents and fellows who always teach me as much as I teach them.

Steven D. Billings

To the three wonderful men in my life: my husband, Andrew and my sons Nathan and Jackson.

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Jenny Cotton

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Preface

When I was a first year resident, I emerged from my first dermatopathology conference with only one thought in mind: I would never study dermatopathology. It was all too confusing. Everything looked alike, and the terminology was impenetrable. Never say never. Somehow I was able to overcome that first shock with the help of my colleague Dr. Cotton and my mentor Dr. Antoinette Hood. Several years later, I am now charged with teaching dermatopathology to residents and fellows as well as CME courses for practicing pathologists and other dermatopathologists.

This brings us to this book. Clearly, there are other much more encyclopedic dermatopathology textbooks out there than this relatively thin tome. So, why this book? Probably because I keep running into residents and practicing pathologists who have the same reaction I had when I first encountered the subspecialty of dermatopathology. There is hope. Dermatopathology is hard, but it is not as hard as it is made out to be. A quick weekend of reading this book should help demystify inflammatory dermatopathology. It is meant to be a practical resource, a survival guide if you will, for surgical pathologists and residents for the approach of inflammatory diseases of the skin. Most of the entities commonly encountered in daily practice are covered in this book, with an emphasis on practical points that are useful in everyday practice. To increase the practical usefulness, we have also included a novel aspect. While most pathology texts do an admirable job describing histologic features and discussing differential diagnoses, writing the report is an art never discussed. Therefore, to increase the usefulness of the text, we have also included sample reports at the end of each chapter to provide examples on how we approach signing out our cases. We hope you enjoy this book. More importantly, we hope you find it useful in your practice.

Contents

Chapter 1
Introduction

Keywords Reaction pattern • Pathology report • Descriptive diagnosis

Dermatopathology is a hard subject and inflammatory dermatopathology is especially vexing. There is significant histologic overlap between the entities. The terminology can border on the impenetrable, and so, a specific diagnosis is often elusive. As a result we rely on diagnoses such as non-specific chronic dermatitis. Therein lies the problem. There is nothing that dermatologists or other clinicians hate more than the diagnosis of "non-specific chronic dermatitis." It does not have to be this way. One can still make a descriptive diagnosis that is actually helpful to the clinician.

The key to interpreting biopsies of inflammatory dermatoses lies in understanding the concept of the basic reaction patterns. This book is generally organized according to these reaction patterns with some exceptions. Broadly speaking, most inflammatory dermatoses can be divided into two categories: epidermal and dermal patterns. In the epidermal patterns, there are three primary patterns: spongiotic, psoriasiform, and interface patterns. The spongiotic pattern is characterized by intraepidermal accumulation of edema fluid. The psoriasiform pattern is characterized by epidermal hyperplasia. The interface pattern is characterized by damage to the basal layer of the epidermis by an inflammatory infiltrate. The spongiotic and psoriasiform patterns frequently co-exist. Overlap with the interface pattern may also be seen.

The dermal patterns lack significant epidermal change. The dermal patterns can generally be divided into perivascular, nodular and diffuse, palisading granulomatous, and sclerosing patterns. As expected, the perivascular pattern demonstrates an inflammatory infiltrate predominantly around dermal blood vessels in a superficial, or superficial and deep distribution. In the nodular and diffuse pattern, the infiltrate is less vasculocentric. There may be significant overlap between perivascular and nodular and diffuse patterns. The palisading granulomatous pattern has an infiltrate that surrounds zones of altered collagen. Sclerosing dermatoses are characterized by fibrosis of the dermis, usually with relatively little inflammation.

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As a general rule the epidermal patterns trump the dermal patterns. In other words, if there is significant epidermal change, the lesion belongs to one of the epidermal patterns, and not one of the dermal patterns. Within the epidermal patterns, the interface pattern trumps the other two epidermal patterns. One must be careful not to overinterpret basilar spongiosis as true interface change. In general, interface change shows at least focal evidence of keratinocyte destruction.

There are also special patterns that are unique unto themselves. Panniculitis does not belong to the aforementioned patterns, but is subdivided into septal and lobular patterns. Similarly bullous disease has is its own patterns, divided into subepidermal and intraepidermal patterns.

Knowledge of these patterns and the common entities in the patterns is crucial in creating a good pathology report. What makes up an ideal surgical pathology report of an inflammatory dermatosis? In our opinion, all reports from biopsies of inflammatory dermatoses require three elements: (1) diagnosis, (2) microscopic description, and (3) comment.

Obviously, a diagnosis is required for any report. When possible, it is important to provide a specific diagnosis. Unfortunately, a specific diagnosis is often not possible. In such cases, it is perfectly acceptable to provide a descriptive diagnosis. However, the descriptive diagnosis needs to be couched in the appropriate terms. In other words, the diagnosis needs to be framed using the reaction pattern that is present (e.g., spongiotic dermatitis) rather than overly general terms such as "chronic dermatitis." What gives meaning to the descriptive diagnosis are the accompanying microscopic description and the comment section of the report.

As a specialty, pathologists are increasingly turning away from microscopic descriptions and it is becoming a lost art. However, it is still important to provide this in pathology reports for inflammatory skin diseases for a number of reasons. First and foremost, dermatologists as a general rule are relatively high-end consumers of pathology reports. Unlike some surgeons, they often read the entire report. They expect a microscopic description and are looking for key descriptive terms in the body of the report. Sometimes a microscopic description will provide additional insights into a case for the clinician and might even prompt consideration of alternate clinical possibilities. Another reason to provide a report is the nature of inflammatory processes in general. Inflammatory skin disease is dynamic. A particular entity may have a completely different appearance early in the course of the disease from what it looks like late in the disease process. Occasionally, multiple biopsies may be required, and the descriptive historical record can be helpful in deciphering the diagnosis. As a general rule, we incorporate the microscopic description as the first part of the comment section. Part of the reason for doing it this way is the layout of the report format we use. The choice in the construction of your report is up to you.

In the comment section of the report, especially in cases where a descriptive diagnosis is rendered, one should provide a differential diagnosis if possible and what is favored if possible. The comment section is frequently the most important section of the report. It is the pathologist's chance to truly enter a dialog with the clinician. As mentioned above, we combine the microscopic

description with the comment section. The first half of the comment section is the microscopic description while the second half is the discussion of the case.

When constructing a report, we recommend brevity. In general, the microscopic description/comment section can be provided in a handful of sentences. Verbose language is rarely required. Remember the axiom that the more you write, the less the consumer of the report reads. Another tip for generating effective reports is good communication with the clinician. Too often, pathologists forget to use one of tier most important tools: the telephone. Rarely does a day go by where we do not pick up a phone and call a contributor to seek additional information to clarify the clinical situation of a case. It must be remembered that clinicians rarely fill out the specimen requisitions. Often it is a nurse or assistant who fills out the form and certain key information can be missing. Furthermore, the physical space on the specimen requisitions may be too small to provide sufficiently detailed important information. A brief 5-minute phone call can often clear up these matters. It also helps build a working relationship with the clinician, a vital aspect of successful practice for any pathologist or dermatopathologist.

To provide additional guideline in the formation of effective reports, there are sample reports at the end of each chapter. These sample reports merely represent guidelines and not specific 'report language' that can be used in the readers' reports. As always, one must assess each case individually and apply observations unique to the individual case.

Chapter 2
Spongiotic Dermatitis

Keywords Spongiosis • Spongiotic dermatitis • Eczema • Atopic dermatitis • Contact dermatitis • Nummular dermatitis • Dyshidrotic eczema • Drug eruption • Mycosis fungoides • Pityriasis rosea • Stasis dermatitis • Psoriasiform dermatitis

Spongiotic Dermatitis

A variety of entities are in this group of inflammatory diseases. This chapter will focus on the group of entities encompassing the eczematous family of dermatitis, but also discuss other important and distinct diseases with spongiosis as its predominant finding.

The spongiotic reaction pattern is characterized by epidermal changes related to the accumulation of intraepidermal edema. The resulting hydrostatic forces cause separation of the keratinocytes revealing the intercellular desmosomal attachments. This appearance has been likened to the cut surface of a sponge, hence the term spongiotic (Fig. 2.1). The epidermal change in spongiotic dermatitis is a dynamic process that evolves over time. It can be divided into three phases: acute, subacute, and chronic. It should be recognized that these divisions are somewhat arbitrary and merely represent a means to conceptualize the histological changes.

Acute Spongiotic Dermatitis

This represents the earliest phase and consequently the least frequently biopsied phase. In the earliest timeframe the epidermis retains its normal basket-weave stratum corneum. The epidermis proper has variable amounts of spongiosis ranging from minimal to spongiotic microvesicles (Fig. 2.2). Spongiotic microvesicles are collections of edema fluid in the epidermis. They form when the hydrostatic pressure from the intraepidermal edema fluid is such that the intercellular junctions between keratinocytes

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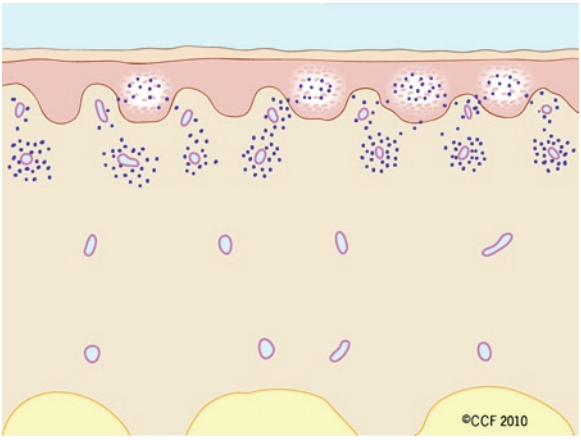

Fig. 2.1 *Schematic presentation of spongiotic pattern*. In the spongiotic reaction pattern there is accumulation of edema fluid within the epidermis resulting in the keratinocytes being pulled apart. Typically, there is an associated superficial perivascular inflammatory infiltrate

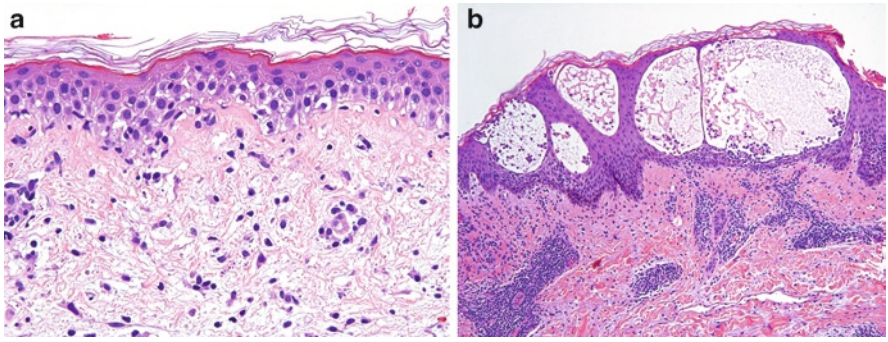

Fig. 2.2 *Acute spongiotic dermatitis*. (**a**) In the earliest phase of acute spongiotic epidermis, the epidermis shows spongiosis but does not show spongiotic microvesicles or acanthosis. (**b**) This case demonstrates spongiotic microvesicle formation

are ruptured. Clinically, this can result in the appearance of blisters. In addition to the intraepidermal spongiosis, there is usually a superficial perivascular inflammatory infiltrate composed of a mixture of lymphocytes, some histiocytes, and often some eosinophils. In some cases, a few neutrophils may be present. The infiltrate is usually concentrated around the superficial vascular plexus, but the pattern of the infiltrate can be somewhat variable. In lesions with an intense infiltrate, it can have the appearance of a more lichenoid pattern. There may also be some extension of the inflammation into the mid-dermis. There is usually some exocytosis of inflammatory cells into the overlying epidermis, usually lymphocytes, but can be other inflammatory cells as well. The superficial dermis usually shows some edema in the earlier phases of the process (Table 2.1).

Table 2.1 Acute spongiotic dermatitis: key microscopic features

- Normal basket-weave stratum corneum
- Epidermal spongiosis with or without spongiotic microvesicles
- Variable papillary derma edema
- Superficial perivascular inflammatory infiltrate of lymphocytes and often with admixed eosinophils

Subacute Spongiotic Dermatitis

One of the ways the epidermis reacts to inflammatory insults is by proliferation. This results in additional changes including acanthosis (hyperplasia) and parakeratosis (Fig. 2.3). In subacute spongiotic dermatitis the epidermis has had time to react to the inflammatory process. The epidermis shows variable parakeratosis and acanthosis. There is spongiosis, but it varies. There can be spongiotic microvesicles, but more often, the degree of spongiosis is less than what is seen in acute spongiotic dermatitis. Within the dermis, there is less edema, but otherwise a similar pattern of inflammation (Table 2.2).

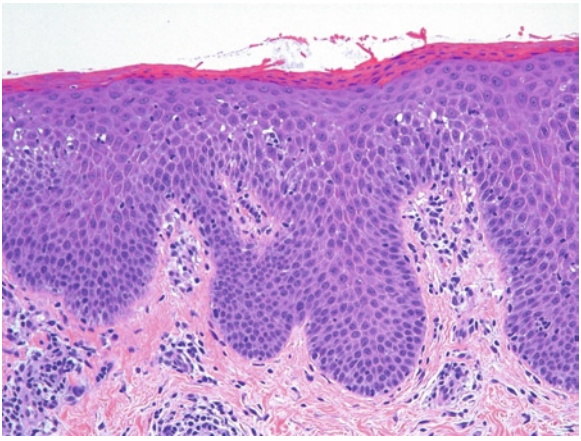

Fig. 2.3 *Subacute spongiotic dermatitis*. There is prominent parakeratosis, a diminished granular layer, acanthosis, and mild spongiosis. Within the dermis there is a superficial perivascular infiltrate. The infiltrate generally primarily consists of lymphocytes, but eosinophils are commonly present as well

Table 2.2 Subacute spongiotic dermatitis: key microscopic features

- Parakeratosis
- Spongiosis
- Acanthosis
- Little to no papillary dermal edema
- Superficial perivascular inflammatory infiltrate of lymphocytes and often with admixed eosinophils

Chronic Spongiotic Dermatitis

In chronic spongiotic dermatitis, there is much less spongiosis. The spongiosis is minimal to mild in nature. In this phase, the reactive epidermal changes are more prominent (Fig. 2.4). There is compact hyperkeratosis, variable parakeratosis, thickening of the granular layer, and more pronounced acanthosis. The superficial dermis does not demonstrate evidence of edema and may be slightly fibrotic. The inflammatory infiltrate is less intense but otherwise composed of the same constituent cells (Table 2.3).

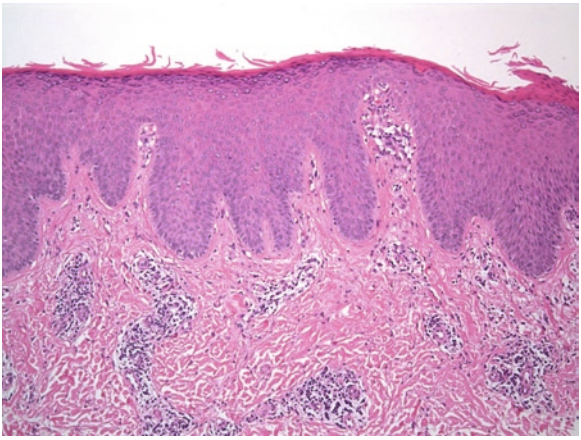

Fig. 2.4 *Chronic spongiotic dermatitis*. In chronic spongiotic dermatitis, there is compact hyperkeratosis with no or minimal parakeratosis. The epidermis is acanthotic and there is little to no apparent spongiosis. The papillary dermis may be fibrotic and there is a variable, usually mild, superficial perivascular infiltrate

Table 2.3 Chronic spongiotic dermatitis: key microscopic features

- Compact hyperkeratosis and variable parakeratosis
- Acanthosis
- Minimal spongiosis
- Superficial perivascular inflammatory infiltrate of lymphocytes and often with admixed eosinophils. Usually mild in nature
- Variable superficial dermal fibrosis

Overlap With Psoriasiform Pattern

In subacute and chronic spongiotic dermatitis, the acanthosis of the epidermis can cause significant overlap with the psoriasiform pattern (Chap. 3). This issue is primarily an issue in construction of the pathology report and will be dealt with at the end of the chapter.

Eczematous Dermatitides

The group of inflammatory disorders in the eczematous family of skin diseases includes a wide range of entities including, atopic dermatitis, nummular dermatitis, contact dermatitis (both allergic and irritant contact dermatitis), dyshidrotic dermatitis (pompholyx), id reaction, and eczematous drug eruptions. Here is one of the secrets of dermatopathology: all of these entities are essentially histologically identical. They all can demonstrate the three patterns of spongiotic dermatitis depending on when the lesion is biopsied. With some of the entities, there can be clues to the diagnosis histologically, but clinical information is often crucial to the diagnosis. With that in mind, it is important to review some of the clinical aspects of these diseases.

Atopic Dermatitis

Atopic dermatitis is a chronic, relapsing, pruritic dermatitis in patients with a familial history of atopy. Atopy is characterized by variable combinations of dermatitis, asthma, sinusitis, and allergic rhinitis. In children, the eruption favors flexural areas such as the antecubital fossa. In adults, the presentation is more variable including very mild periorbital dermatitis to full body erythroderma.

Contact Dermatitis

Contact dermatitis is a result of an exogenous stimulus and can be subdivided into allergic or irritant types. Allergic contact dermatitis is the result of a type IV hypersensitivity reaction that requires exposure to a specific antigen. The prototypical allergic contact dermatitis includes reactions to substances such as poison ivy or latex. Nickel allergies are also common and tend to present where people come into contact with the metal (e.g., earlobes, waistline near blue jeans snaps).

Irritant contact dermatitis results from direct damage to the epidermis from the offending substance rather than an immune mediated response. Detergents are one of the most common causes of irritant dermatitis (so-called dishpan hands). Diaper rash is another prototypical example.

Histologically, both show features of spongiotic dermatitis. Clinically, there are frequent clues to the diagnosis. For example, in poison ivy, the eruption often has a linear arrangement corresponding to the edge of the offending leaf that brushed along the skin. Depending on the offending agent, there may be peculiar distributions such as with allergic reactions to latex gloves or nickel containing jewelry. A histological clue to the diagnosis of allergic contact dermatitis is the presence of Langerhans cell microabscesses within the epidermis (Fig. 2.5) (not to be confused with the Pautrier's microabscesses of mycosis fungoides which are composed of neoplastic lymphocytes). Langerhans cell microabscesses are not always present in allergic contact dermatitis, and they are not entirely specific. In irritant contact dermatitis,

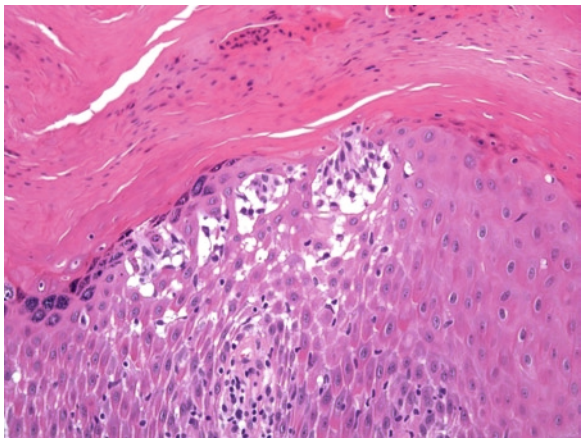

Fig. 2.5 *Langerhans cell microabscess*. Allergic contact dermatitis often has Langerhans cell microabscesses, characterized by collections of Langerhans cells within the spongiotic epidermis. Langerhans cells have reniform nuclei and relatively abundant pale eosinophilic cytoplasm

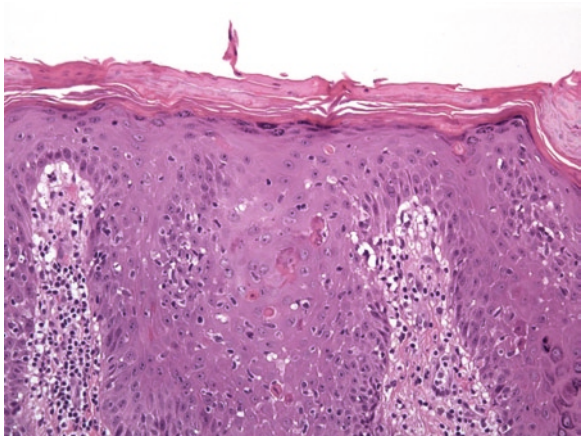

Fig. 2.6 *Irritant contact dermatitis*. Within the upper epidermis there are scattered dyskeratotic cells. This is a common but nonspecific finding in irritant contact dermatitis

the inflammatory infiltrate tends to be less intense and there may be ballooning degeneration of keratinocytes and/or occasional dyskeratotic keratinocytes in the epidermis, especially the upper half of the stratum spinosum (Fig. 2.6).

Nummular Dermatitis

This is one of the most common types of spongiotic dermatitis that is biopsied. Nummular dermatitis is characterized by round (coin-shaped) to oval patches variably composed of papules and vesicles usually on the extremities. As the eruption evolves, there may be central clearing, clinically resembling dermatophyte infection

(tinea). In patients with atopic dermatitis, they may have flares of their disease presenting as nummular dermatitis. Nummular dermatitis almost always has a component of epidermal acanthosis. Microscopically, it typically has the features of subacute or chronic spongiotic dermatitis. Clinically and histologically the differential diagnosis of nummular dermatitis is psoriasis vulgaris.

Dyshidrotic Eczema (Pompholyx or Palmoplantar Dermatitis)

Dyshidrotic eczema is characterized by a recurrent pruritic, often vesicular, eruption of the palms, soles, or digits. Clinically, the vesicles have a papular appearance. Over time, scaling and cracking can develop. In many patients, this is a manifestation of atopy. A significant proportion of dyshidrotic eczema is the result of an allergic contact dermatitis. Spongiotic vesicles are a very common histologic feature. It is important to always exclude dermatophyte infection, especially in eruptions from the feet. A PAS or GMS stain is recommended to exclude the possibility of an underlying fungal infection.

Id Reactions (Autoeczematization)

Id reactions are the development of an eczematous dermatitis in regions away from the primary inflammatory focus. Dermatophyte infections of the feet (tinea pedis) and stasis dermatitis are two of the most common inciting conditions for id reactions. The patient can develop eczematous dermatitis on the upper extremities, or trunk, far away from the triggering process. In the case of dermatophyte-triggered eczematous dermatitis, no fungi are detectable in the dermatitis representing the id reaction. The id reaction component is difficult to treat without addressing the underlying trigger.

Eczematous Drug Reactions

Drug reactions will be dealt with in more detail in a later section of the book. A minority of drug reactions may be histologically indistinguishable from other forms of eczematous dermatitis. Depending on what sources you read, eczematous drug eruptions can account for <5–10% of all new drug eruptions. In our personal experience, it is relatively uncommon, and the rate is <5%. Association with new medications can help correlation with the diagnosis. In the absence of clinical information implicating a medication, it is not possible to differentiate an eczematous drug reaction from other eczematous dermatitides.

Differential Diagnosis

Eczematous dermatitis is frequently secondarily impetiginized resulting in neutrophils in the stratum corneum. This is also a key feature of a dermatophyte infection. When neutrophils are present in the stratum corneum or upper epidermis, a PAS or GMS should be performed to exclude a possible fungal infection.

Nummular dermatitis and psoriasis may have significant clinical overlap and differentiating these entities is often a diagnostic problem. Nummular dermatitis has more edema fluid in the stratum corneum, less uniform hyperplasia, a retained or thickened granular layer and usually has eosinophils in the dermal infiltrate. These are not features of psoriasis (see Chap. 3).

A minority of cutaneous drug eruptions is eczematous (spongiotic) in nature. They can be indistinguishable from other forms of eczematous dermatitis. Diagnosis requires good correlation with medication history. Unfortunately, some drug eruptions commence months after initiation of a new medication. In that case it is ultimately up to the clinician to sort out the diagnosis; it is beyond the scope of histology in that situation.

Mycosis fungoides can figure into the differential diagnosis of eczematous dermatitis. A detailed discussion of mycosis fungoides is beyond the scope of this text, but references are provided at the end of this chapter. That being said, the differential diagnosis of mycosis fungoides vs. an eczematous dermatitis is relatively common. Lesions of mycosis fungoides have disproportionate amount of intraepidermal lymphocytes within a relatively non-spongiotic epidermis (Fig. 2.7). The intraepidermal lymphocytes have a halo artifact and frequently tag the basal layer of the epidermis. The neoplastic lymphocytes tend to have more irregular, cerebriform nuclei, but this is less helpful in actual practice. Immunostains and clonality studies can also be helpful. A shift in the ratio of CD4 to CD8 positive cells of >4–6:1 in the appropriate context favors mycosis fungoides over eczematous

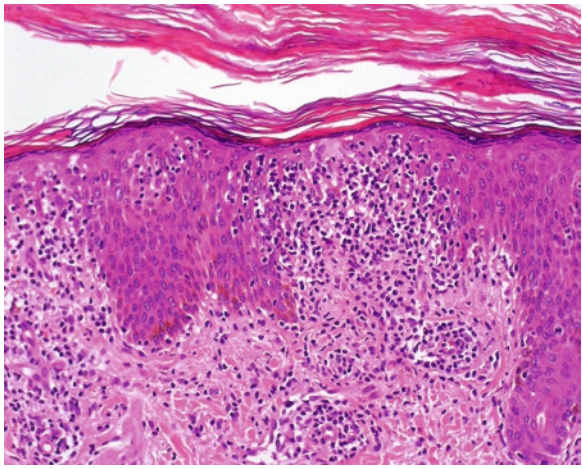

Fig. 2.7 *Mycosis fungoides* is characterized by epidermotropism of lymphocytes into the epidermis that is disproportionate to the amount of spongiosis

dermatitis. Immunostains for CD4 have to be correlated with immunostains for CD3, as Langerhans cells and histiocytes are also CD4 positive. One should not over interpret a collection of CD4-positive cells as a Pautrier's microabscess when in fact it is a Langerhans cell microabscess. Similarly, a monoclonal population of T-cells can be supportive, but is by no means diagnostic of mycosis fungoides. Eczematous processes can have clonal populations of T-cells. If mycosis fungoides is a strong possibility, assessing clonality from two different biopsies from different locations is useful; identical clones in different locations are supportive of mycosis fungoides. Clinical history can be helpful. A clinical history of long-standing (i.e., years) disease in non-sun-exposed areas on older adults is an important parameter that would also favor mycosis fungoides. Diagnosis of mycosis fungoides often takes many biopsies over time before a diagnosis can be made. Fortunately, it is an indolent disease and so it is best to be cautious and not push too much when confronted with this diagnostic question. See Table 2.4.

Table 2.4 Practical tips: eczematous dermatitis

- The clinical variants of eczematous dermatitis have essentially the same histologic features
- Acute, subacute and chronic spongiotic dermatitis represent a continuum. It is not important to sub-classify spongiotic dermatitis in the line diagnosis
- Use a descriptive diagnosis of "spongiotic dermatitis" (see sample reports at end of chapter)
- Langerhans cell microabscesses are suggestive of allergic contact dermatitis
- Eliminate where possible more specific entities
- If neutrophils are the in stratum corneum or epidermis, exclude dermatophytosis or psoriasis
- Eczematous dermatitis is more spongiotic than mycosis fungoides

Other Forms of Spongiotic Dermatitis

Stasis dermatitis and pityriasis rosea are also in the differential diagnosis. See below for discussion of these entities.

Stasis Dermatitis

Clinical Features

Stasis dermatitis typically presents on the medial aspect of the lower extremities in association with evidence of venous insufficiency. It usually presents in older patients or obese patients. Usually, stasis dermatitis presents as pruritic, scaly plaques. Rarely it presents as a more circumscribed process clinically, and can be confused with a neoplasm. Acroangiodermatitis, a specific form of stasis dermatitis, presents as violaceous macules, nodules or plaques on the dorsal feet. It can be clinically and histologically confused with Kaposi's sarcoma.

Microscopic Features

The epidermis shows features of subacute or chronic spongiotic dermatitis as described above. The key differentiating features are found in the dermis. Within the papillary dermis, there is a lobular proliferation of relatively thick-walled vessels (Fig. 2.8). There may be evidence of tissue edema or, in long-standing cases, fibrosis. There is extravasation of erythrocytes and associated perivascular siderophages to varying degrees. A perivascular lymphocytic infiltrate is present. The infiltrate is variable, but is usually less intense than the infiltrate of the eczematous dermatitides described above (Table 2.5).

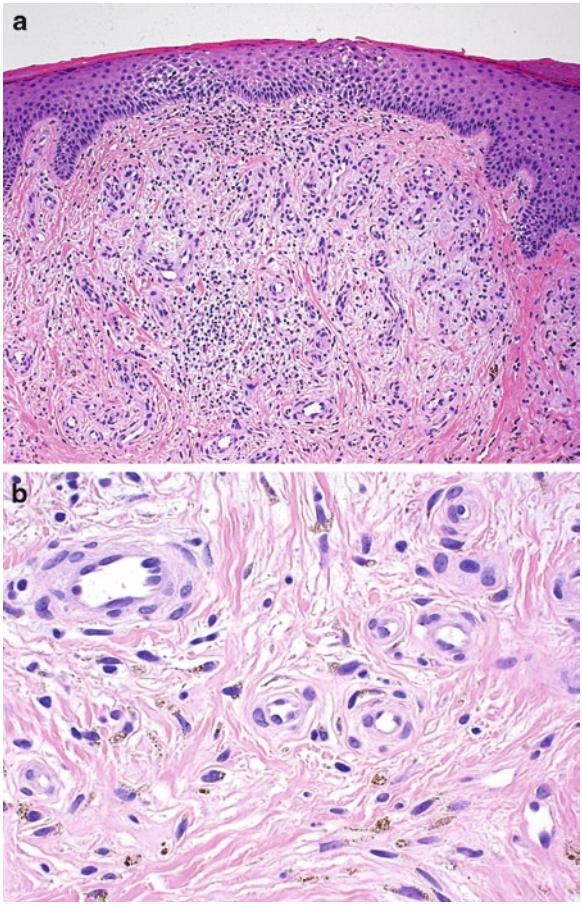

Fig. 2.8 *Stasis dermatitis*. (**a**) The epidermis shows variable spongiosis and acanthosis. Within the dermis there is a lobular proliferation of relatively thick-walled blood vessels and a perivascular lymphocytic infiltrate. (**b**) Higher power view of papillary dermal blood vessels with surrounding siderophages, a frequent finding in long-standing cases of stasis dermatitis

Table 2.5 Key microscopic findings: stasis dermatitis

- Variable acanthosis and spongiosis
- Lobular proliferation of relatively thick-walled vessels in superficial dermis
- Extravasation of erythrocytes and siderophages common

Differential Diagnosis

The differential diagnosis of most cases includes the forms of spongiotic dermatitis in the eczematous dermatitis group outlined above. In some cases, there may be a combination of eczematous dermatitis superimposed on underlying stasis change. In rare cases, the vascular proliferation is so prominent as to mimic a vascular neoplasm such as Kaposi's sarcoma. This form of stasis dermatitis is referred to as acroangiodermatitis (Fig. 2.9). Careful attention to histological features allows distinction. Acroangiodermatitis does not have the dense proliferation of spindled endothelial cells with slit-like vascular spaces, lacks the promontory sign of early Kaposi's sarcoma and does not express latent nuclear antigen of HHV-8. Recognition of more conventional areas of stasis change can be helpful (Table 2.6).

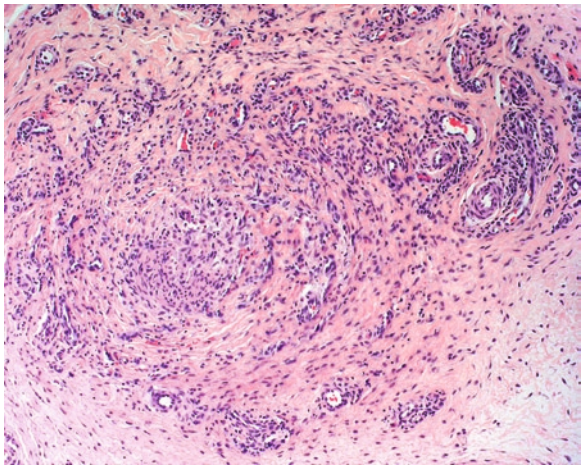

Fig. 2.9 *Acroangiodermatitis*. The reactive vascular proliferation due to stasis can sometimes be quite prominent and cause confusion with a vascular neoplasm

Table 2.6 Practical tips: stasis dermatitis

- Keep a high index of suspicion on biopsies from the lower legs
- The vascular changes are the most important feature
- Patients can have an eczematous dermatitis superimposed on underlying stasis change
- Occasionally stasis dermatitis can clinically mimic a neoplasm and the clinician may submit with a clinical diagnosis of squamous cell carcinoma

Pityriasis Rosea

Clinical Features

Pityriasis rosea usually presents in young adults, though a wide age range may be affected. The eruption starts as a salmon-colored herald patch that in the next 7–14 days is followed by a widespread, symmetric eruption of numerous small pink to red scaly plaques. The eruption usually starts on the trunk and then spread to the abdomen and proximal extremities.

Microscopic Features

The most characteristic feature of pityriasis rosea is the presence of discrete mounds of parakeratosis in the stratum corneum (Fig. 2.10). The epidermis shows mild spongiosis and mild acanthosis. Within the dermis, there is a superficial perivascular lymphocytic infiltrate. Eosinophils are rarely present. There may be extravasation of erythrocytes in the papillary dermis and exocytosis of erythrocytes into the overlying epidermis and, when present, is a helpful feature (Table 2.7).

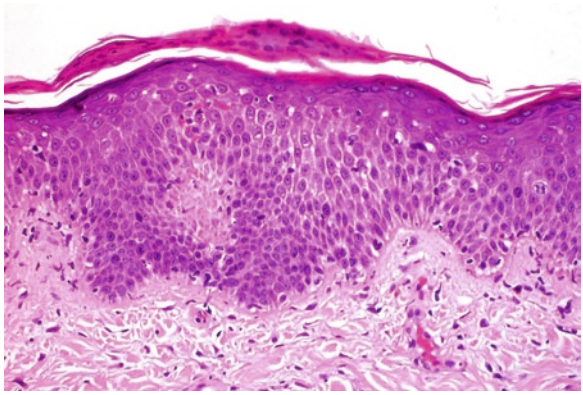

Fig. 2.10 *Pityriasis rosea*. In the stratum corneum, there are discrete mounds of parakeratosis. The epidermis is mildly spongiotic and acanthotic. The dermal infiltrate is predominately composed of lymphocytes. Extravasation of erythrocytes is commonly seen in the papillary dermis, and frequently there is exocytosis of erythrocytes into the epidermis

Table 2.7 Key microscopic findings: pityriasis rosea

- Discrete mounds of parakeratosis
- Spongiosis
- Papillary dermal hemorrhage common
- Mild perivascular lymphocytic infiltrate

Differential Diagnosis

The differential diagnosis includes subacute spongiotic dermatitis and it is often not possible to distinguish without clinical history. Guttate psoriasis (see Chap. 3) also resembles pityriasis rosea. Classically, guttate psoriasis has mounds of parakeratosis

surmounted by collections of neutrophils. Neutrophils are not a feature of pityriasis rosea (Table 2.8).

Table 2.8 Practical tips: pityriasis rosea

- Discrete mounds of parakeratosis are the key histologic feature
- A specific diagnosis of pityriasis rosea is not possible without the appropriate clinical history
- In the absence of a sufficient history, the case should be signed out descriptively as "spongiotic dermatitis" (see sample reports at the end of the chapter)

Vesicular Dermatophytosis

Dermatophyte infections can sometimes present with prominent spongiosis. Usually, there are neutrophils in the stratum corneum and eosinophils are found as part of the dermal infiltrate. Dermatophyte infection will be discussed in more detail in Chaps. 3 and 12. As a general rule, a PAS or GMS stain should always be considered when examining a spongiotic dermatitis involving the feet.

Sample Reports: Spongiotic Dermatitis NOS (Eczematous Dermatitis)

Example 1:

Clinical history: Rule out psoriasis.

Diagnosis: Spongiotic dermatitis, see comment.

Comment: The epidermis shows parakeratosis with irregular acanthosis, a maintained granular layer and diffuse mild spongiosis. Within the dermis, there is a superficial perivascular mixed inflammatory infiltrate of lymphocytes and scattered eosinophils. The degree of spongiosis, intact granular layer, and presence of eosinophils in the infiltrate argue against the possibility of psoriasis. The histological features are most consistent with an eczematous dermatitis such as nummular dermatitis. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: Rule out dermatitis, drug eruption, etc.

Diagnosis: Spongiotic dermatitis, see comment.

Comment: The epidermis shows parakeratosis, some hyperkeratosis, spongiosis, and occasional Langerhans cell microabscesses. Within the dermis, there is a superficial predominantly perivascular mixed infiltrate of lymphocytes and eosinophils. The histological features are compatible with an eczematous dermatitis. The presence of Langerhans cell microabscesses in the epidermis

suggests the possibility of a contact dermatitis. Clinicopathologic correlation is recommended.

Example 3:
Clinical history: Rule out mycosis fungoides.
Diagnosis: Spongiotic dermatitis, see comment.
Comment: The biopsy demonstrates parakeratosis overlying an epidermis with irregular acanthosis, and spongiosis. There is some exocytosis of lymphocytes, but no Pautrier's microabscesses. The histological features are most compatible with an eczematous dermatitis. The degree of spongiosis argues against the diagnosis of mycosis fungoides. That being said, if this eruption persists or progresses, additional biopsies over time may be indicated to evaluate for the possibility of mycosis fungoides. Clinicopathologic correlation is recommended.

Sample Report: Stasis Dermatitis

Clinical history: Rash on legs.
Diagnosis: Spongiotic dermatitis, see comment.
Comment: The epidermis is spongiotic with hyperkeratosis and parakeratosis. Within the dermis there is a lobular proliferation of relatively thick blood vessels in association with a mild perivascular lymphocytic infiltrate, and some dermal hemorrhage. The histologic features are consistent with stasis dermatitis. Clinicopathologic correlation is recommended.

Sample Report: Pityriasis Rosea

Clinical history: Rash on trunk.
Diagnosis: Spongiotic dermatitis, see comment.
Comment: There are focal mounds of parakeratosis overlying a mildly spongiotic epidermis. Within the dermis, there is a mild superficial perivascular lymphocytic infiltrate with focal extravasation of erythrocytes. Given the pattern of parakeratosis, pityriasis rosea should be considered. An eczematous dermatitis could also be considered. Clinicopathologic correlation is recommended.

General Comment: Spongiotic Versus Psoriasiform

As mentioned previously, the epidermis may have significant acanthosis in many of the forms of spongiotic dermatitis. Therefore, most of the above examples could have "psoriasiform dermatitis" as the diagnosis. However, the comment would remain essentially the same. This underscores the fact that the comment is more important in many ways than the top line diagnosis.

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Chapter 3
Psoriasiform Dermatitis

Keywords Psoriasiform dermatitis • Psoriasis • Psoriasis vulgaris • Guttate psoriasis • Pustular psoriasis • Pityriasis rubra pilaris • Lichen simplex chronicus • Prurigo nodularis

The psoriasiform pattern is characterized by acanthosis (epidermal hyperplasia) (Fig. 3.1). As mentioned in the previous chapter, acanthosis and spongiosis often coexist, and the classification of a dermatitis as spongiotic or psoriasiform can be somewhat arbitrary. This chapter will focus on entities in which spongiosis is not typically a prominent feature.

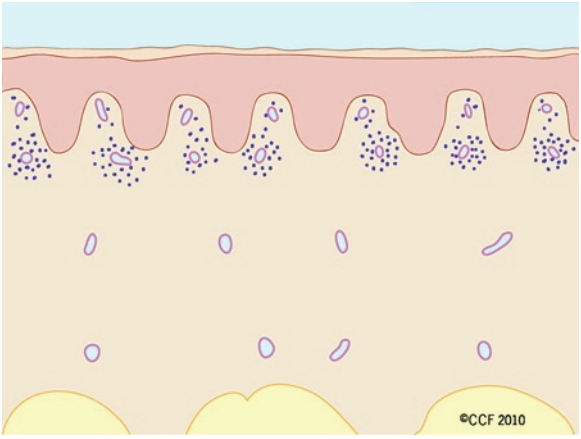

Fig. 3.1 *Schematic representation of psoriasiform dermatitis*. The psoriasiform pattern is typified by epidermal acanthosis with relatively little spongiosis. There is usually a superficial perivascular inflammatory infiltrate

Psoriasis

Psoriasis exists in three common clinical subtypes: psoriasis vulgaris (often referred to as just psoriasis), guttate psoriasis, and pustular psoriasis. Psoriasis vulgaris is the prototypical psoriasiform dermatitis.

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Psoriasis Vulgaris

Clinical Features

The common form of psoriasis usually presents in the second or third decade, but can present at any age. It presents as erythematous plaques with silvery scale. It commonly affects the extensor surfaces, scalp, gluteal cleft, and glans penis. Intertriginous areas can also be involved; this has been termed inverse psoriasis. Nail changes consisting of small pits and areas of yellow discoloration are frequently present. Psoriatic arthritis is seen in 1–5% of patients and its presence usually correlates with a more severe skin disease.

Microscopic Features

Classic psoriasis vulgaris shows prominent, often confluent, parakeratosis overlying the epidermis. The epidermis shows uniform acanthosis with suprapapillary plate thinning, and a diminished-to-absent granular layer (Fig. 3.2). Within the stratum corneum and/or epidermis there are collections of neutrophils and the scale has a "dry" appearance (Fig. 3.3). It is important to keep in mind that neutrophils in the stratum corneum do not have the classic appearance of neutrophils with multilobed nuclei and eosinophilic cytoplasm. Rather they have the appearance of hyperchromatic, somewhat squiggly nuclei. The papillary dermal blood vessels are dilated and tortuous (Fig. 3.4). Within the dermis, there is a superficial perivascular lymphocytic infiltrate. Some neutrophils may be present, but eosinophils are typically absent. Unfortunately, not all cases of psoriasis vulgaris have all of the classic features. Patients may have already had some therapy or self-treatment, thereby altering some of the histological features (Fig. 3.5). Some patients may have excoriated their skin lesions resulting in retention or even thickening of the granular cell

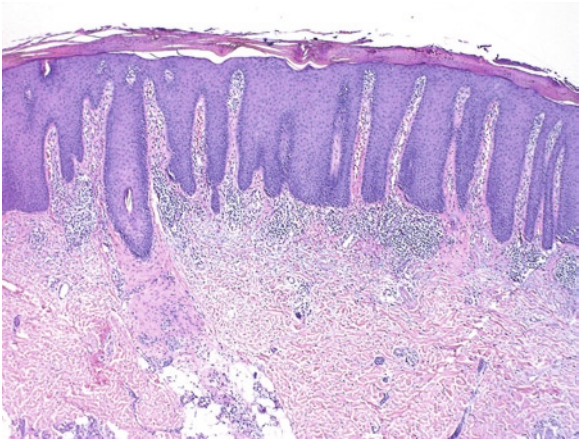

Fig. 3.2 *Psoriasis vulgaris* is characterized by confluent parakeratosis, a diminished granular layer and uniform acanthosis

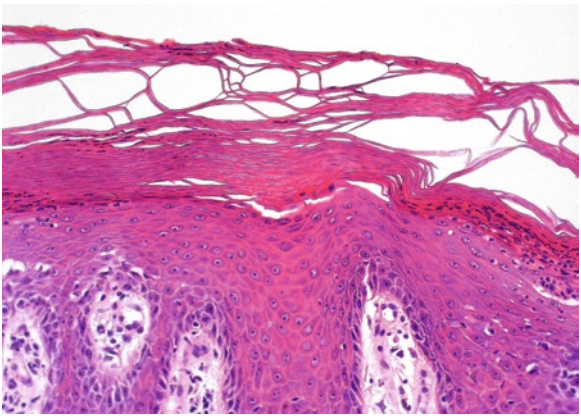

Fig. 3.3 *Psoriasis vulgaris*. The neutrophils in the stratum corneum and epidermis of psoriasis have dark, somewhat squiggly nuclei. The scale overlying the epidermis has a dry appearance without serum

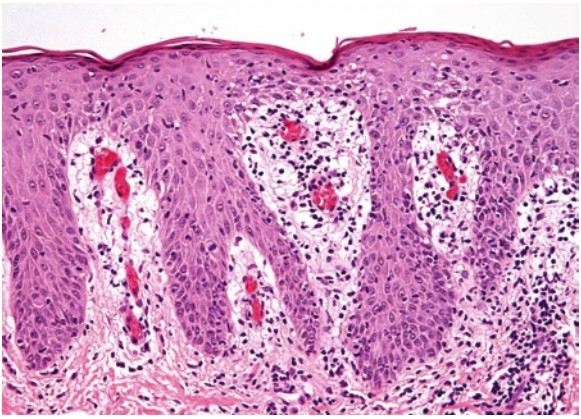

Fig. 3.4 *Psoriasis vulgaris*. This image demonstrates the suprapapillary plate thinning and dilated, tortuous papillary dermal blood vessels

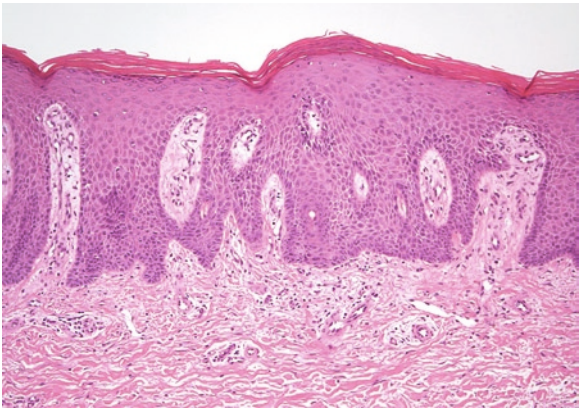

Fig. 3.5 *Partially treated psoriasis vulgaris*. In this case of psoriasis from a patient who has used some topical steroids prior to the biopsy, the epidermis had a partially recovered/retained granular layer and no collections of neutrophils were evident

Table 3.1 Key microscopic features: psoriasis vulgaris

- Parakeratosis
- Neutrophils in stratum corneum or epidermis
- Diminished or absent granular layer
- Uniform epidermal hyperplasia
- Suprapapillary plate thinning
- Dilated and tortuous papillary dermal blood vessels

layer. In such cases, a specific diagnosis may not be possible. Strategies to deal with this situation are outlined in the sample reports at the end of the chapter. See Table 3.1 for summary of microscopic features.

Differential Diagnosis

Eczematous dermatitis with the morphology of subacute or chronic spongiotic dermatitis can have overlapping features with psoriasis. Of the eczematous dermatitides, nummular dermatitis is more likely the clinical simulant in the eczematous dermatitis family, but other forms of eczema can also clinically mimic psoriasis. In eczematous dermatitis, eosinophils are often present in the inflammatory infiltrate; eosinophils are not a feature of psoriasis except in exceptional circumstances. The scale present in spongiotic dermatitis has a "wet" appearance with serum as opposed to the dry appearance in psoriasis. Furthermore, subacute and chronic spongiotic dermatitis lacks the suprapapillary plate thinning and the acanthosis is more irregular, and a retained granular layer is often present. The presence of neutrophils can help distinguish psoriasis, but secondary impetiginization can result in neutrophils in the stratum corneum of eczematous dermatitis. In such cases, the neutrophils are usually in association with serous fluid and bacterial organisms may be present. Interestingly, psoriasis rarely shows secondary impetiginization and the presence of bacteria in the stratum corneum would argue against the possibility of psoriasis. Langerhans cell microabscesses are a feature often present in contact dermatitis but not seen in psoriasis.

Dermatophyte infections of the skin have collections of neutrophils in the stratum corneum like psoriasis (Fig. 3.6) but the acanthosis is more irregular and there are usually eosinophils in the infiltrate. Dermatophytosis lacks the suprapapillary plate thinning and may be more spongiotic. Special stains such as PAS or GMS will identify the fungal hyphae (Fig. 3.6). See also Chap. 12.

Seborrheic dermatitis has histologic similarities. Seborrheic dermatitis has psoriasiform hyperplasia and prominent parakeratosis that often contains neutrophils. The neutrophils and parakeratosis tend to be most prominent at follicular ostia (Fig. 3.7). Seborrheic dermatitis has a more restricted clinical presentation on the scalp, central face and central chest. In some cases, the clinical and histological overlap is such that the disease could be classified as a combination of psoriasis and seborrheic dermatitis, so-called sebo-psoriasis.

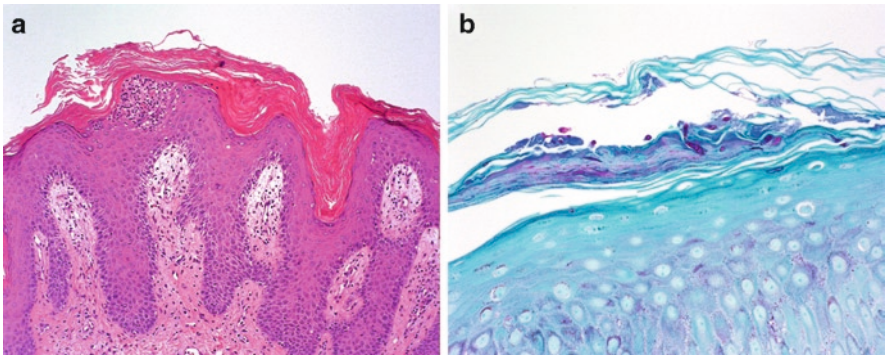

Fig. 3.6 *Dermatophyte infection resembling psoriasis*. (**a**) Similar to psoriasis, dermatophyte infections frequently have collections of neutrophils in the stratum corneum and psoriasiform hyperplasia. The granular layer is often intact and the dermis usually has some eosinophils as part of the infiltrate. (**b**) Fungal hyphae in the strum corneum highlighted by PAS stain

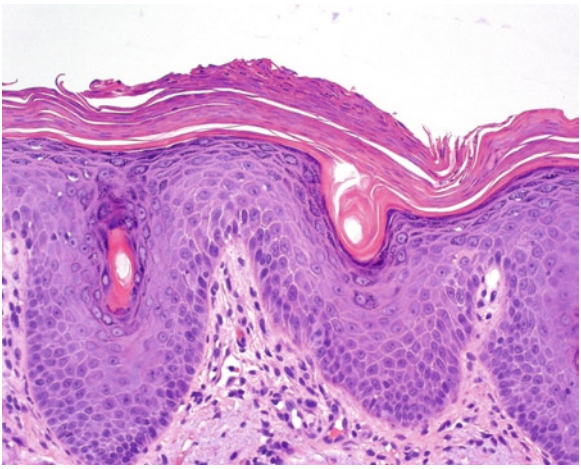

Fig. 3.7 *Seborrheic dermatitis*. There is psoriasiform hyperplasia and parakeratosis most conspicuous at follicular ostia

Pityriasis rubra pilaris (PRP) shares many similarities with psoriasis. Importantly, PRP lacks neutrophils and has alternating patterns of parakeratosis and hyperkeratosis. PRP is discussed in detail below.

Psoriasiform keratosis is a solitary benign cutaneous neoplasm that usually presents on the lower extremity of middle aged to older patients, but may present elsewhere. There is significant histological overlap such that it may be indistinguishable from psoriasis. Clinical presentation as a solitary neoplasm allows distinction.

The new class of biologic treatments (e.g., TNF-alpha inhibitors) can result in drug eruptions that histologically closely resembles psoriasis with confluent parakeratosis with neutrophils and uniform psoriasiform acanthosis. The presence of eosinophils in the dermis and knowledge of the clinical history help in the distinction (Table 3.2).

Table 3.2 Practical tips: psoriasis vulgaris

- Confluent parakeratosis is an important clue to the diagnosis of psoriasis vulgaris
- The "dry" nature of the parakeratotic scale is a clue to psoriasis
- Neutrophils in the stratum corneum should always prompt consideration of psoriasis or a dermatophyte infection (consider fungal stains)
- Psoriasis does not have eosinophils in the dermal infiltrate
- In excoriated/partially treated psoriasis vulgaris, the granular layer may be retained
- In psoriasis involving acral surfaces, the granular layer is almost always partially retained
- In cases where the diagnosis of psoriasis is suspected but the histologic features are insufficient for an unequivocal diagnosis, sign the case out descriptively as "psoriasiform dermatitis, see note" (see sample reports at the end of the chapter)

Psoriasis Variants

There are two important variants of psoriasis, guttate and pustular psoriasis. Although they are variants of psoriasis, they tend not to have significant psoriasiform hyperplasia because of their rapid onset.

Guttate Psoriasis

Clinical Features

Guttate psoriasis is characterized by a rapid onset of numerous small plaques. There is often a history of antecedent (streptococcal) pharyngitis.

Microscopic Features

Guttate psoriasis is characterized by discrete mounds of parakeratosis with associated collections of neutrophils overlying the epidermis (Fig. 3.8). In some cases, neutrophils may not be conspicuous. The epidermis typically does not have pronounced acanthosis, owing to the rapid onset of disease. The papillary dermal blood vessels are often dilated similar to the vulgaris variant. Again, eosinophils are not a feature (Table 3.3).

Differential Diagnosis

The closest histologic mimic of guttate psoriasis is pityriasis rosea. Collections of neutrophils on the mounds of parakeratosis allow for distinction of guttate psoriasis. If neutrophils are not present, a specific diagnosis may not be possible, but the clinician can be guided by the comment in your report (see sample reports at the end of the

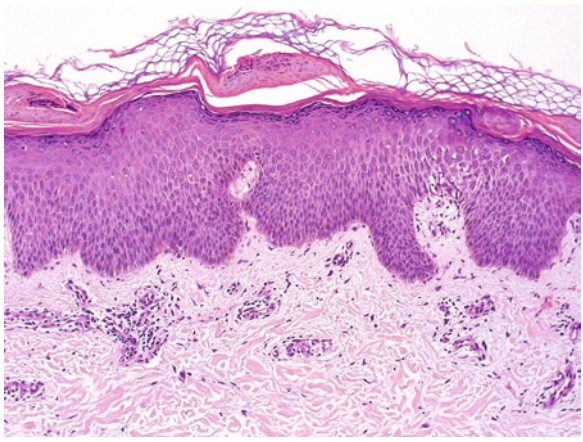

Fig. 3.8 *Guttate psoriasis* is characterized by mounds of parakeratosis with collections of neutrophils. The epidermis may be mildly spongiotic or relatively unremarkable

Table 3.3 Key microscopic features: guttate psoriasis

- Discrete mounds of parakeratosis with collections of neutrophils
- Epidermal changes less pronounced than psoriasis vulgaris

chapter). An eczematous dermatitis could also be considered in the histologic differential diagnosis. The same comments regarding eczematous dermatitis as discussed in the section on psoriasis vulgaris apply. See Table 3.4.

Table 3.4 Practical tips: guttate psoriasis

- Mounds of parakeratosis with neutrophils should prompt consideration of guttate psoriasis
- Neutrophils not always present; when absent also consider pityriasis rosea
- Clinical history of antecedent pharyngitis helpful (likely will require phone call)

Pustular Psoriasis

Clinical Features

Pustular psoriasis is characterized by a widespread rapid onset of numerous pustules. It can be associated with pregnancy or discontinuation of systemic steroids in patients with psoriasis.

Microscopic Features

This variant is typified by large collections of neutrophils in the epidermis and/or stratum corneum (Fig. 3.9). Because of the rapid onset, there is often no significant acanthosis and the granular layer is only partially diminished or normal (Table 3.5).

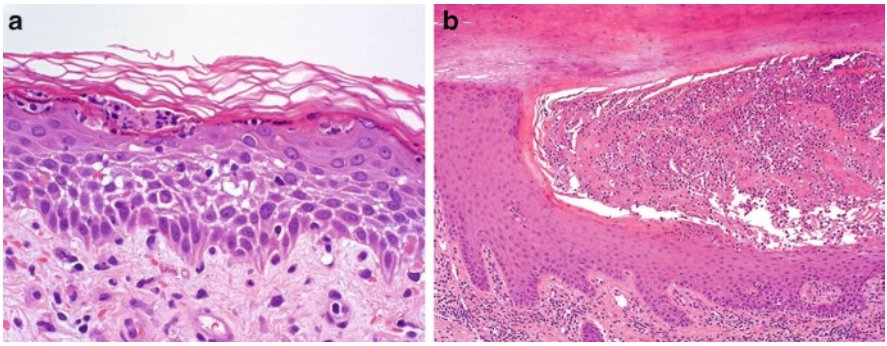

Fig. 3.9 *Pustular psoriasis*. (**a**) Early lesions may show small intraepidermal pustules with little epidermal change. (**b**) In more established lesions, the pustules are characterized by large collections of subcorneal/intraepidermal neutrophils. In more established lesions, the epidermis still often lacks changes seen in psoriasis vulgaris

Table 3.5 Key microscopic features: pustular psoriasis

- Large collections of neutrophils in stratum corneum or epidermis
- Less epidermal change than psoriasis vulgaris
- No eosinophils

Differential Diagnosis

Infections, such as dermatophytosis and candidiasis are in the differential diagnosis because of the collections of neutrophils. PAS or GMS stains can help resolve this question. Both dermatophyte and yeast infections usually have some eosinophils in the differential diagnosis.

Acute generalized exanthematous pustulosis (AGEP) is a peculiar form of drug eruption and can show striking resemblance to pustular psoriasis, but the presence of eosinophils (Fig. 3.10) and the history of new medications (e.g., vancomycin) can help distinguish it from pustular psoriasis (Table 3.6).

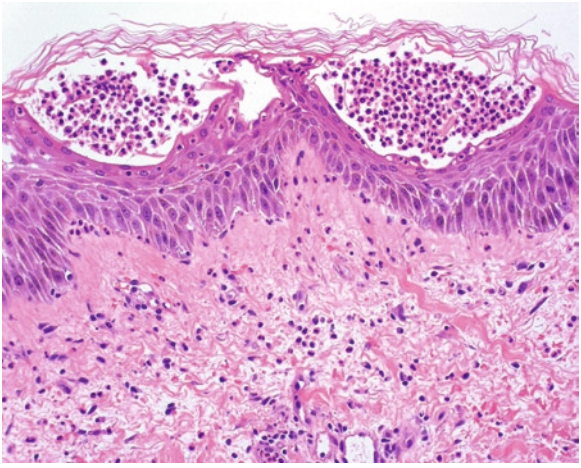

Fig. 3.10 *Acute generalized exanthematous pustular dermatosis (AGEP).* Within the epidermis there are large pustules consisting of collections of neutrophils. The inflammatory infiltrate in the dermis contains neutrophils, lymphocytes and eosinophils

Table 3.6 Practical tips: pustular psoriasis

- Rule out a fungal infection with PAS or GMS stains
- Eosinophils are not a feature of pustular psoriasis; if present consider fungal infection or AGEP/pustular drug eruption
- Patients often have history of psoriasis

Pityriasis Rubra Pilaris

Clinical Features

The most common form, or classical PRP, presents in adults and is characterized by small follicular papules, confluent perifollicular erythema with islands of spared skin, and palmoplantar keratoderma. Patients may also have yellow discoloration of nails.

Microscopic Features

The epidermis shows psoriasiform hyperplasia with a maintained to thickened granular layer and follicular plugging (Fig. 3.11). There is prominent hyperkeratosis and parakeratosis that is characterized by the so-called "checkerboard" pattern in which the parakeratosis alternates with zones of hyperkeratosis, both vertically and horizontally (Fig. 3.10). There are no collections of neutrophils in the epidermis. Within the dermis, there is frequently a mild, superficial, perivascular lymphocytic infiltrate that may rarely include eosinophils (Table 3.7).

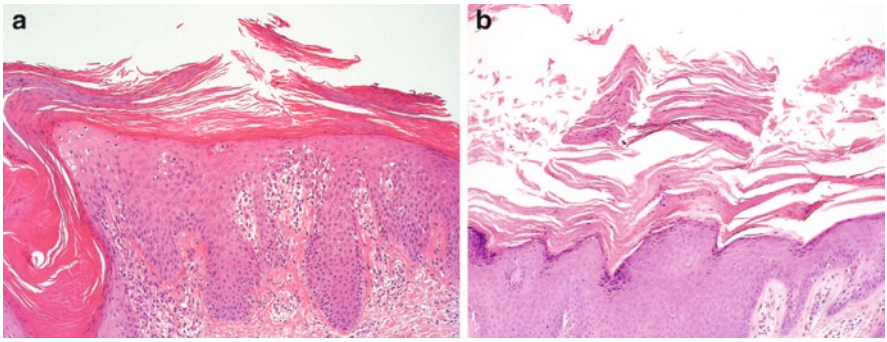

Fig. 3.11 *Pityriasis rubra pilaris (PRP)*. (**a**) Similar to psoriasis, there is uniform psoriasiform hyperplasia with hyperkeratosis and parakeratosis. Note the follicular plugging on the left side of the image. (**b**) The checkerboard pattern in the stratum corneum is characterized by zones of compact hyperkeratosis and parakeratosis that alternates vertically and horizontally

Table 3.7 Key microscopic features: pityriasis rubra pilaris (PRP)

- Psoriasiform hyperplasia but normal or thickened granular layer
- Follicular plugging
- Checkerboard pattern of hyperkeratosis and parakeratosis

Differential Diagnosis

Unlike psoriasis, PRP lacks the neutrophils in the epidermis or stratum corneum, and does not have suprapapillary plate thinning or a diminished granular layer. Chronic spongiotic dermatitis may show overlap, but it lacks the checkerboard pattern of parakeratosis. Follicular plugging can help distinguish PRP form psoriasis and chronic spongiotic dermatitis. Seborrheic dermatitis has follicular plugging, but often has neutrophils and a very different clinical presentation (Table 3.8).

Table 3.8 Practical tips: pityriasis rubra pilaris (PRP)

- Biopsies of early lesions of PRP may be inconclusive. If there is a clinical suspicion of PRP, and the biopsy specimens do not show characteristic morphology, a comment stating that a repeat biopsy from the most developed area of the eruption may help establish a diagnosis.
- Biopsies from the follicular papules are often relatively non-specific. The presence of follicular plugging even in the absence of a checkerboard pattern is suggestive in the appropriate clinical context.
- The checkerboard pattern of parakeratosis is often subtle.

Lichen Simplex Chronicus and Prurigo Nodularis

Clinical Features

Lichen simplex chronicus and prurigo nodularis are related entities that are the result of persistent scratching or rubbing. Lichen simplex chronicus presents as pruritic, scaly plaques and prurigo nodularis as pruritic nodules. The lesions may be ulcerated secondary to excoriation. As both are related to excoriation, it is important to remember that these lesions are only seen where the patient can reach. Common locations include nape of the neck, scalp (especially prurigo nodularis), shin, forearms, dorsal feet, and perianal/genital areas.

Microscopic Features

In lichen simplex chronicus, the epidermis shows prominent hyperkeratosis, with or without focal parakeratosis, hypergranulosis, and psoriasiform hyperplasia (Fig. 3.12). Within the dermis, there is fibrosis of the papillary dermis that is characterized by vertically oriented thick collagen fibers (so-called "vertical streaking"). Prurigo nodularis shows similar histologic features, but the epidermis may have a more pseudoepitheliomatous appearance or psoriasiform hyperplasia (Fig. 3.13). The dermal inflammatory infiltrate in both is typically sparse (Table 3.9).

Differential Diagnosis

Chronic spongiotic dermatitis shows less prominent psoriasiform hyperplasia and does not have the vertical streaking of the papillary dermal collagen. Eosinophils

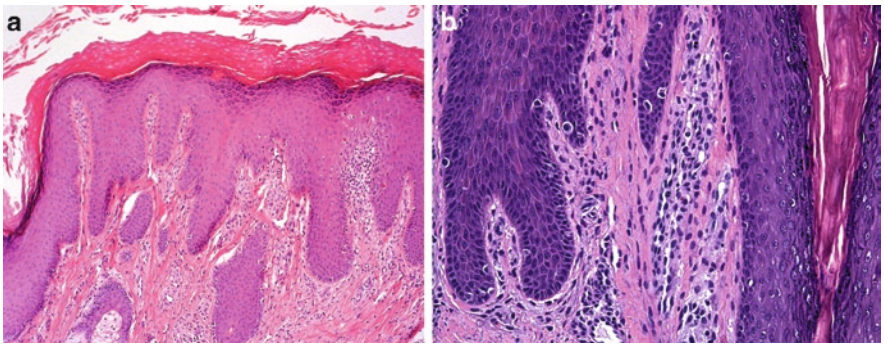

Fig. 3.12 *Lichen simplex chronicus*. (**a**) The epidermis resembles acral skin with compact hyperkeratosis, a thickened granular layer and acanthosis. The inflammatory infiltrate is typically sparse. (**b**) The papillary dermis is fibrotic with characteristic thick, vertically oriented collagen bundles

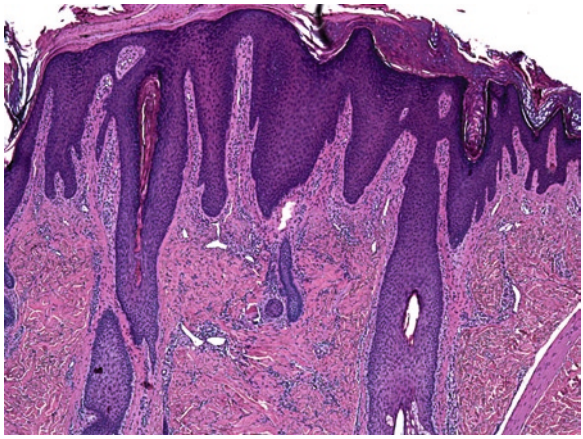

Fig. 3.13 *Prurigo nodularis* has significant histologic overlap with lichen simplex chronicus. The epidermis often, but not always, has a pseudoepitheliomatous growth pattern

Table 3.9 Key microscopic features: lichen simplex chronicus/prurigo nodularis

- Compact hyperkeratosis
- Acanthosis with thickened granular layer
- Vertically oriented, thickened collagen bundles in superficial dermis
- Sparse inflammatory infiltrate

are also a typical component of the inflammatory infiltrate. As a caveat, lichen simplex chronicus may be superimposed on a pre-existing chronic spongiotic dermatitis such as a long standing contact dermatitis or atopic dermatitis (Fig. 3.14).

The psoriasiform hyperplasia seen in lichen simplex chronicus can cause confusion with psoriasis. The confluent parakeratosis and diminished granular layer of psoriasis vulgaris distinguish it from lichen simplex chronicus and prurigo nodularis.

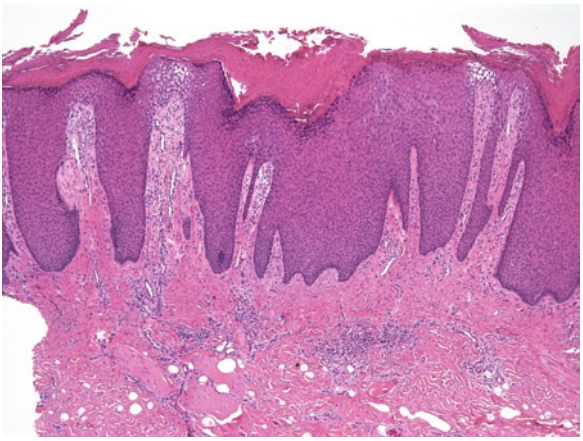

Fig. 3.14 *Spongiotic dermatitis with superimposed features of lichen simplex chronicus*. In long standing cases of eczematous dermatitis (e.g., atopic dermatitis), there may be coexisting features of a spongiotic dermatitis and lichen simplex chronicus/prurigo nodularis secondary to persistent excoriation. Although the architecture of this lesion is reminiscent of lichen simplex chronicus, the spongiosis and degree of inflammatory infiltrate is more in line with a spongiotic dermatitis

For prurigo nodularis, the differential diagnosis can include squamous cell carcinoma. Prurigo nodularis can show reactive atypia, but lacks atypical mitotic figures or pleomorphism and often presents as multiple lesions. The vertical fibrosis of prurigo nodularis helps identify this diagnosis. Squamous cell carcinoma will have a desmoplastic stromal response not seen in prurigo nodularis, and does not have the vertical collagen bundles of prurigo nodularis (Table 3.10).

Table 3.10 Practical tips: lichen simplex chronicus/prurigo nodularis

- "Hairy palm sign": The epidermal changes of both these entities resemble acral skin because of the prominent hyperkeratosis and hypergranulosis. However, lichen simplex chronicus and prurigo nodularis typically present on hair bearing skin. The presence of follicles in what otherwise looks like acral skin is a clue to the diagnosis of lichen simplex chronicus or prurigo nodularis.
- Lichen simplex chronicus and prurigo nodularis have overlapping features. Sometimes it may not be possible to distinguish them. In this situation the clinical presentation as a plaque or nodule should guide the diagnosis.
- In lesions with a prominent inflammatory infiltrate, biopsies with features of lichen simplex chronicus/prurigo nodularis may be superimposed upon other inflammatory conditions such as atopic or contact dermatitis. A significant inflammatory infiltrate or eosinophils suggest the possibility of an underlying dermatitis with superimposed lichen simplex chronicus.
- Prurigo nodularis vs. squamous cell carcinoma
  - Vertically oriented collagen bundles favor prurigo nodularis.
  - Squamous cell carcinoma is not itchy. A call to the clinician to get some clinical history can help.
  - Multiple lesions favor prurigo nodularis (note: some lesions of prurigo nodularis may be solitary).

Sample Reports: Psoriasis

Example 1:

Clinical history: Rule out psoriasis.
Diagnosis: Psoriasis, see comment.
Comment: There is confluent parakeratosis with collections of neutrophils overlying, and epidermis with a diminished granular layer, uniform psoriasiform hyperplasia, and a superficial perivascular lymphocytic infiltrate. The papillary dermal blood vessels are dilated and tortuous.
Note to reader: This is for a classic case of psoriasis. If the features are not clear-cut, a descriptive diagnosis can be used (see below).

Example 2:

Clinical history: Rule out psoriasis, nummular dermatitis.
Diagnosis: Psoriasiform dermatitis, see comment.
Comment: There is parakeratosis with focal collections of neutrophils and hyperkeratosis overlying an epidermis that has psoriasiform hyperplasia. The granular layer is largely intact. Within the dermis, the papillary dermal blood vessels are dilated and there is a superficial perivascular infiltrate of lymphocytes. No eosinophils are seen. The differential diagnosis includes psoriasis and nummular dermatitis. Given the presence of neutrophils in the stratum corneum, the uniform psoriasiform hyperplasia, the dilated dermal blood vessels, and absence of eosinophils, I believe this is most consistent with partially treated or excoriated psoriasis.

Sample Report: Nummular Dermatitis

Clinical history: Rule out psoriasis, nummular dermatitis.
Diagnosis: Psoriasiform dermatitis, see comment.
Comment: There is parakeratosis with focal neutrophils overlying an epidermis with irregular psoriasiform hyperplasia and some spongiosis. The granular layer is thickened. Within the dermis, there is a perivascular infiltrate of lymphocytes with focal eosinophils. A PAS stain is negative for fungi. The differential diagnosis includes psoriasis vs. nummular dermatitis. The histologic features are most consistent with an eczematous dermatitis such as nummular dermatitis. The thickened granular layer and eosinophils argue against the possibility of psoriasis. Clinicopathologic correlation is recommended.
Note to reader: In this case, it would be acceptable to top line the diagnosis as either a spongiotic dermatitis or psoriasiform dermatitis.

Sample Reports: Prurigo Nodularis/Lichen Simplex Chronicus

Example 1:

Clinical history: Lesion, rule out SCC.

Diagnosis: Psoriasiform dermatitis, see comment.

Comment: There is thick compact hyperkeratosis overlying an epidermis with a thickened granular layer and irregular psoriasiform hyperplasia. Within the dermis there is a scant perivascular infiltrate and thickened, vertically oriented collagen bundles in the papillary dermis. The histologic features are most consistent with prurigo nodularis.

Example 2:

Clinical history: Rule out dermatitis.

Diagnosis: Psoriasiform dermatitis consistent with lichen simplex chronicus, see comment.

Comment: There is thick, compact hyperkeratosis overlying an epidermis with psoriasiform hyperplasia and a thickened granular layer. There is vertical fibrosis of the collagen bundles of the papillary dermis. Within the dermis, there is a mild perivascular lymphocytic infiltrate. The histologic features are consistent with lichen simplex chronicus.

Example 3:

Clinical history: Dermatitis, rule out eczema.

Diagnosis: Psoriasiform dermatitis with superimposed features of lichen simplex chronicus, see comment.

Comment: There is a thick, compact hyperkeratosis overlying an epidermis with psoriasiform hyperplasia and a thickened granular layer. There is vertical fibrosis of the collagen bundles and a moderately dense perivascular inflammatory infiltrate with lymphocytes and scattered eosinophils. The histologic features are most consistent with a chronic eczematous dermatitis with superimposed features of lichen simplex chronicus.

Note to reader: This report is from a case of an eczematous dermatitis that was persistently excoriated. Therefore there were features of both a chronic spongiotic dermatitis and lichen simplex chronicus.

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Chapter 4
Interface Dermatitis

Keywords Interface dermatitis • Lichen planus • Lichenoid drug eruption • Fixed drug eruption • Morbilliform drug eruption • Erythema multiforme • Stevens–Johnson syndrome • Toxic epidermal necrolysis • Lupus erythematosus • Dermatomyositis • Graft vs. host disease • Pityriasis lichenoides • PLEVA

Interface dermatitis is characterized by damage to the epidermis from the inflammatory infiltrate. Microscopically, this is characterized by basal vacuolization with or without necrotic keratinocytes. Interface dermatitis can be broadly grouped into two subgroups based on the pattern of the inflammatory infiltrate: (1) lichenoid, or band-like, in which, the infiltrate forms a dense layer parallel to the overlying epidermis (Fig. 4.1) and (2) perivascular, in which the infiltrate is concentrated around blood vessels in either a superficial or superficial and deep distribution (Fig. 4.2).

Interface Dermatitis with Lichenoid Infiltrate

Lichen Planus

Clinical Features

Lichen Planus is the prototypical lichenoid interface dermatitis. Lichen planus usually presents in adults as pruritic, polygonal violaceous papules. There is a predilection for extensor surfaces of the wrists and ankles, but the eruption may be widespread. Lichen planus involves the oral mucosa, especially the buccal mucosa, in about 60% of patients. In the oral cavity, lichen planus has as a reticulated, lace-like appearance; erosions and ulceration can also occur.

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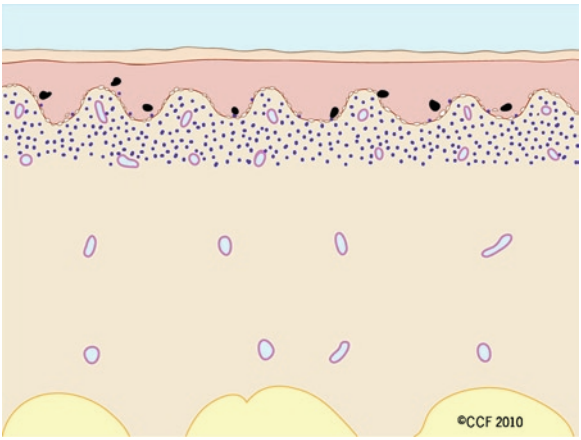

Fig. 4.1 *Schematic representation of interface dermatitis with lichenoid pattern*. This pattern of interface dermatitis is characterized by basal vacuolization with scattered dyskeratotic keratinocytes and a band-like, or lichenoid, inflammatory infiltrate

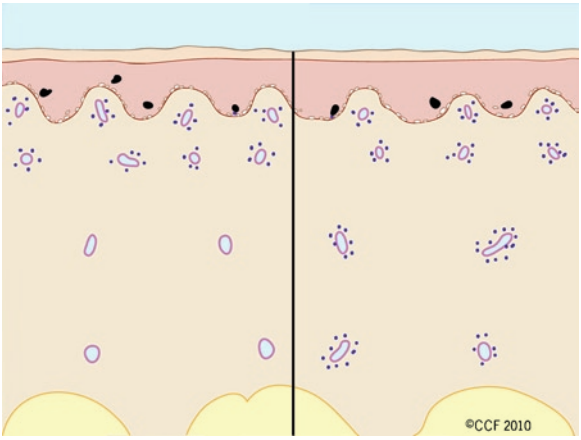

Fig. 4.2 *Schematic representation of interface dermatitis with a perivascular pattern of inflammation*. This pattern can be roughly divided into those that have a predominantly superficial or superficial and deep infiltrate in addition to the interface change

Microscopic Features

In cutaneous lichen planus, the stratum corneum shows compact hyperkeratosis, but not parakeratosis. The granular layer is thickened, often with a wedge-shaped pattern. The epidermis may show mild acanthosis. Within the dermis, there is a dense band-like pattern of mononuclear cells predominantly composed of lymphocytes (Fig. 4.3). Some admixed histiocytes may be present, but eosinophils are typically not seen. There is interface change manifested by basal vacuolization, exocytosis of lymphocytes and necrotic keratinocytes. These dyskeratotic cells may have lymphocytes "tagging" the keratinocytes, so-called satellite cell necrosis (Fig. 4.4). There may also be eosinophilic globules in the superficial dermis representing keratinocytes that have "dropped out" of the epidermis that are also referred to as Civatte bodies. As the epidermal damage evolves, the rete pegs lose their normal undulating pattern and take on a saw-tooth configuration (Table 4.1).

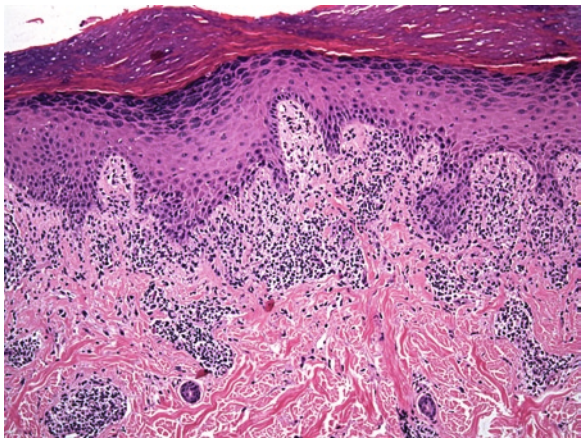

Fig. 4.3 *Lichen planus* is characterized by compact hyperkeratosis without parakeratosis, a thickened granular layer and variable acanthosis. The rete pegs have an irregular sawtooth configuration and there is a dense lichenoid lymphocytic infiltrate with basal vacuolization and dyskeratotic cells

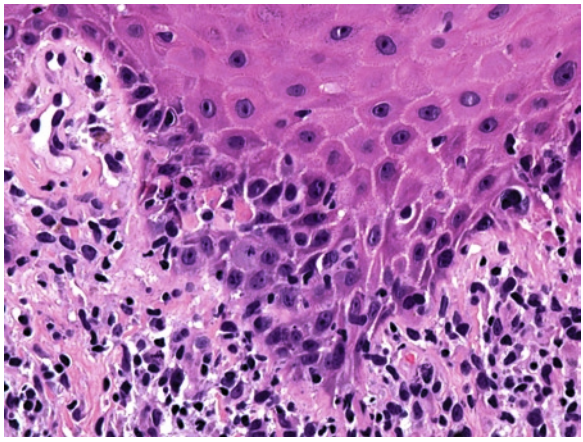

Fig. 4.4 *Lichen planus*. This high power image of the interface change demonstrates the lymphocytic infiltrate and the scattered dyskeratotic keratinocytes in the epidermis

Table 4.1 Key microscopic features: lichen planus

- Compact hyperkeratosis without parakeratosis
- Thickened granular layer
- Lichenoid infiltrate
- Interface change with basal vacuolization, dyskeratotic keratinocytes and saw-tooth pattern of dermoepidermal junction
- Typically no eosinophils

There are two histologic variants of cutaneous lichen planus to be aware of: hypertrophic and atrophic. In hypertrophic lichen planus, there is significant epidermal acanthosis in conjunction with other histologic findings of lichen planus (Fig. 4.5). In part, the epidermal hyperplasia may be the result of persistent excoriation as seen in lichen simplex chronicus and prurigo nodularis. Unlike typical lichen planus, eosinophils can be seen occasionally in hypertrophic lichen planus, but they should

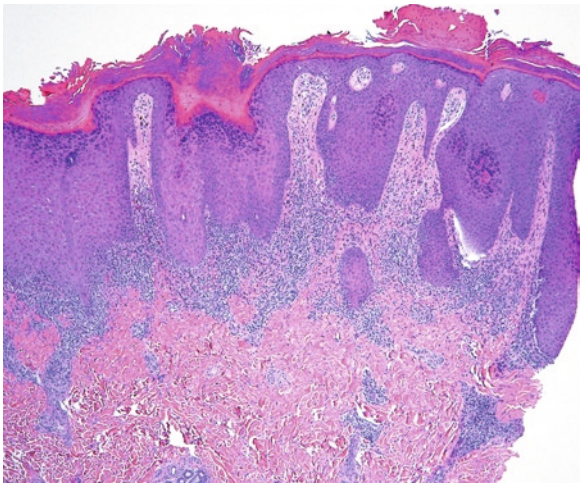

Fig. 4.5 *Hypertrophic lichen planus*. This variant of lichen planus resembles conventional lichen planus but with marked acanthosis

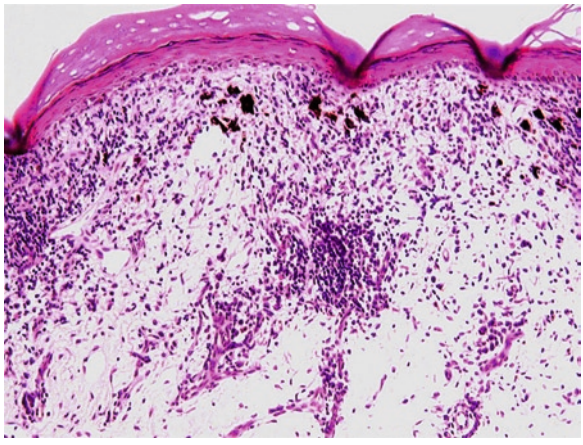

Fig. 4.6 *Atrophic lichen planus*. In atrophic lichen planus the epidermis in thinner than normal, and the interface change is subtler. Melanophages are frequently present in the dermis reflecting chronic damage to the epidermis

be sparse in number. In atrophic lichen planus, the epidermis is thinned and there is less pronounced hyperkeratosis and hypergranulosis (Fig. 4.6). Within the dermis, the infiltrate is frequently less intense, and there may be scattered melanophages. Atrophic lichen planus, in many cases, represent a burned out or resolving lesion of lichen planus.

In oral lichen planus, the findings are often more subtle. There is less hyperkeratosis, and, in contrast to cutaneous lichen planus, there may be some parakeratosis (Fig. 4.7). Frequently there is a subtle hypergranulosis characterized by a few keratohyaline granules in the superficial epidermis. Recognition of the granular layer may require examination at high power. Within the subepithelial stroma, there is a band-like infiltrate of lymphocytes admixed with plasma cells. Rare eosinophils may also be seen. Prominent saw-toothing is usually not present, and the degree of interface change may be milder in nature.

In lichen planus, there are characteristic, if not entirely specific, direct immunofluorescence findings. The most characteristic finding is shaggy deposition of

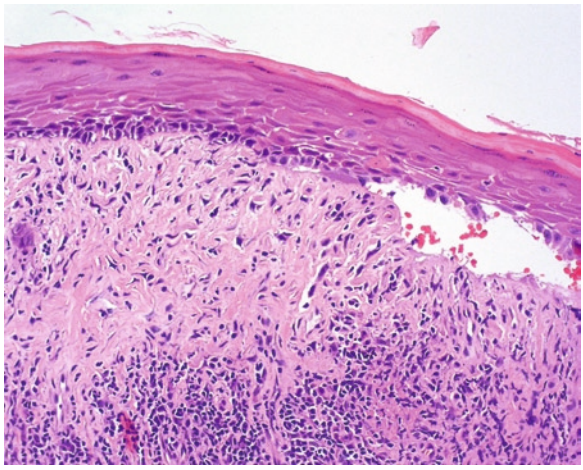

Fig. 4.7 *Oral lichen planus*. The epithelial changes are more subtle than in conventional lichen planus. There is hyperkeratosis and subtle evidence of formation of a granular layer characterized by focal coarse keratohyaline granules in the upper part of the epithelium. Some cases may show parakeratosis unlike typical lichen planus. The epithelium has interface damage but usually dose not show the sawtooth pattern

fibrinogen along the dermoepidermal junction. There is usually some complement deposition, and there is variable IgM deposition. If necrotic keratinocytes are present in the dermis, they can non-specifically take up immunoglobulins, especially IgM, but IgG or IgA staining may also be present. It is important to point out that DIF findings are only supportive and not diagnostic without appropriate histologic findings.

Differential Diagnosis

A common entity in the differential diagnosis is a benign lichenoid keratosis, also called lichen planus-like keratosis or lichenoid benign keratosis, depending on your preference. In some cases the histologic features may be indistinguishable. In other cases, they resemble a seborrheic keratosis that also has prominent interface change. Sometimes a recognizable component of solar lentigo is seen at the edges of the biopsy specimen. The clinical presentation is quite different. Benign lichenoid keratosis is a solitary lesion that usually presents on the trunk. Clinically, it mimics basal cell carcinoma, and the possibility of basal cell carcinoma is frequently suggested by the clinician. That can be a clue to the diagnosis.

Lichenoid drug eruption and a fixed drug can be confused with lichen planus. Lichenoid drug eruption may closely mimic lichen planus, but in addition to features resembling lichen planus there are eosinophils in the inflammatory infiltrate and usually some parakeratosis in the stratum corneum. Fixed drug eruptions lack the prominent epidermal changes and also have eosinophils in the infiltrate. The clinical history of fixed drug eruption is also distinctive as discussed below. Practical tips are summarized in Table 4.2.

Table 4.2 Practical tips: lichen planus

- If the clinical history is a solitary lesion, think benign lichenoid keratosis
- Eosinophils are not a typical feature of lichen planus with perhaps the exception of hypertrophic lichen planus. If present, consider lichenoid drug eruption
- Parakeratosis is not typical a feature of lichen planus. If present, the possibility of a lichenoid drug eruption should be considered
- Oral/mucosal lichen planus is more subtle
  - Mucosal epithelium does not normally have a granular layer, so there is not prominent hypergranulosis
  - The presence of a subtle granular layer is a diagnostic clue
  - Parakeratosis is often present in mucosal lichen planus
- In cases where the histologic features or clinical history are not clear cut, use a descriptive diagnosis of "lichenoid interface dermatitis, see comment". Refer to sample reports

Lichenoid Drug Eruption

Clinical Features

The lesions of lichenoid drug eruptions can clinically resemble lichen planus. However, they tend to be larger and are more frequently distributed on the trunk; lesions on the extremities are not limited to the flexural surfaces. Oral mucosa involvement is usually absent. Some of the more common agents that can result in a lichenoid drug eruption include beta blockers, captopril, thiazides, and Lasix.

Microscopic Features

Lichenoid drug eruptions, like lichen planus, are characterized by a band-like infiltrate with interface change, with evidence of epidermal damage including dyskeratotic keratinocytes and vacuolar change along the dermal-epidermal junction. There may also be acanthosis and hyperkeratosis. The histologic findings are essentially the same as lichen planus with some key exceptions (Fig. 4.8). There is often patchy parakeratosis, a feature not seen in lichen planus. Eosinophils are usually conspicuous, a feature that essentially excludes most cases of lichen planus. Thickening of the granular cell layer is usually, but not always present and is usually less prominent than in lichen planus (Table 4.3).

Differential Diagnosis

As outlined above, the differential diagnosis is primarily lichen planus and a fixed drug eruption. Differentiating lichen planus from lichenoid drug requires identification of features not seen in lichen planus such as parakeratosis and conspicuous eosinophils.

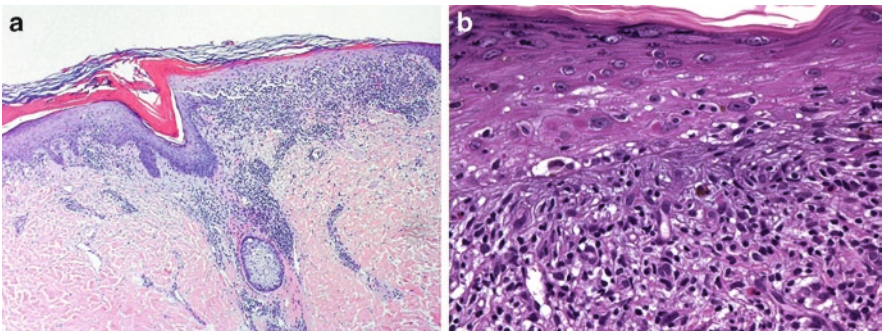

Fig. 4.8 *Lichenoid drug reaction*. (**a**). in this lower power image, the lesion resembles lichen planus but there is conspicuous parakeratosis. (**b**). The higher power image demonstrates the interface change with a lichenoid infiltrate that contains conspicuous eosinophils

Table 4.3 Key microscopic features: lichenoid drug eruption

- Compact hyperkeratosis and parakeratosis
- Lichenoid infiltrate of lymphocytes and eosinophils
- Interface change

Fixed drug eruptions tend to be localized (see below) and show less epidermal change. While still having the interface change and lichenoid infiltrate, they lack hyperkeratosis or granular layer thickening. See Table 4.4.

Table 4.4 Practical tips: lichenoid drug eruption

- Parakeratosis is a frequent feature of lichenoid drug eruptions. Its presence argues for lichenoid drug eruption rather than lichen planus.
- Eosinophils are conspicuous in the great majority of lichenoid drug eruptions. If you can pick up the presence of eosinophils on medium power (10× objective), it favors lichenoid drug eruption over lichen planus.
- Lichenoid drug eruptions are typically more widespread than lichen planus.
- Oral mucosa involvement is uncommon in lichenoid drug eruptions.

Fixed Drug Eruption

Clinical Features

Fixed drug eruptions present as one or more violaceous plaques usually on the extremities or genitalia. On re-exposure to the drug the eruption recurs in the same locations. Common sensitizing agents include barbiturates, ibuprofen, and sulfa drugs.

Microscopic Features

The stratum corneum of the epidermis varies from a normal basket weave pattern to having patchy parakeratosis. The epidermis may show ballooning degeneration of keratinocytes. Within the dermis, there is a lichenoid infiltrate composed of lymphocytes and eosinophils with interface damage to the overlying epidermis (Fig. 4.9). Melanophages are present as the lesion evolves (Table 4.5).

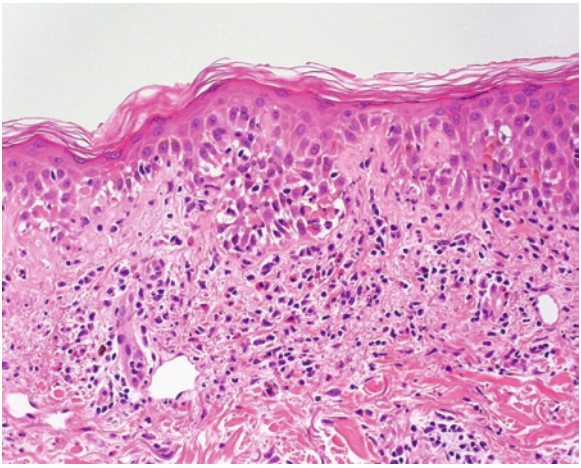

Fig. 4.9 *Fixed drug eruption*. The epidermis has a normal basket weave stratum corneum. There is a lichenoid infiltrate with prominent interface change and frequent eosinophils. Scattered melanophages are present

Table 4.5 Key microscopic features: fixed drug eruption

- Normal basket weave stratum corneum or parakeratosis; no hyperkeratosis
- Lichenoid infiltrate of lymphocytes and eosinophils
- Scattered melanophages
- Interface change

Differential Diagnosis

The differential diagnosis includes lichen planus and a lichenoid drug eruption (see above). Unlike both lichen planus and lichenoid drug eruptions, fixed drug eruptions have a more limited distribution. The plaques of fixed drug eruption are larger than the papular lesions of lichen planus and lichenoid drug eruptions. Histologically, fixed drug eruption has less epidermal change. While having a similar degree of interface change, fixed drug eruptions do not have hyperkeratosis or hypergranulosis. Frequently, fixed drug eruptions have a normal basket weave pattern to the stratum corneum. A morbilliform drug eruption could also be considered. Morbilliform drug

eruptions are more widespread, and have a perivascular rather than lichenoid pattern. The degree of epidermal damage is less in morbilliform drug eruptions. Erythema multiforme (EM) and graft vs. host disease (GVHD) could also be considered. Again, these conditions have a less prominent infiltrate than seen in fixed drug eruption. These conditions are discussed in more detail below. See Table 4.6.

Table 4.6 Practical tips: fixed drug eruption

- Clinically localized, not widespread
- Epidermal change limited
  - Patchy keratosis to normal stratum corneum
  - Granular layer not thickened
- Only make a diagnosis of fixed drug eruption with a solid clinical history. A phone call to the clinician is helpful in cases with inadequate history
- Melanophages can be a clue to an evolving or recurrent fixed drug eruption
- Fixed drug eruptions have more prominent interface change than morbilliform drug eruptions

Interface Dermatitis with Perivascular Infiltrate

In this section, the entities have a predominantly perivascular pattern of inflammation rather than lichenoid pattern.

Morbilliform Drug Eruption

Clinical Features

Morbilliform drug eruptions present as widespread erythematous, blanchable macules or papules. They can present shortly after initiation of the offending medication or it can take several months for the hypersensitivity reaction to develop.

Microscopic Features

The epidermis typically shows little change except for some mild basal vacuolization. Parakeratosis, acanthosis and spongiosis are not a typical feature except in rare eczematous drug eruptions (see Chap. 2). Occasional necrotic keratinocytes may be present, but this is not an invariable feature. Within the dermis, there is a mild superficial perivascular mixed inflammatory infiltrate of lymphocytes and eosinophils (Fig. 4.10). In many cases, there is no interface damage to the epidermis and the predominant finding is a superficial perivascular infiltrate (see Chap. 5) (Table 4.7).

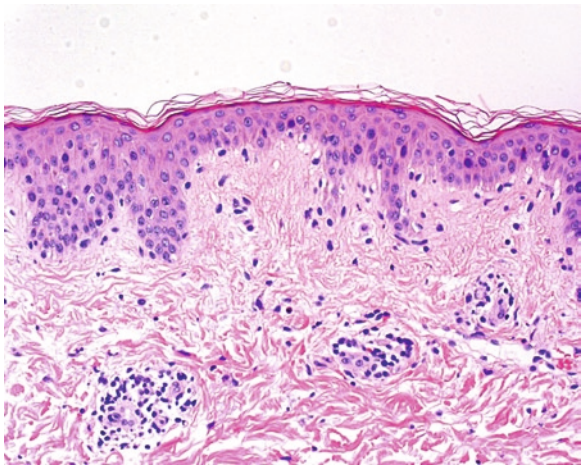

Fig. 4.10 *Morbilliform drug eruption*. The epidermis appears relatively normal except for mild vacuolar change. With the dermis there is a mild superficial perivascular infiltrate of lymphocytes and eosinophils

Table 4.7 Key microscopic features: morbilliform drug eruption

- Mild basal vacuolization or no epidermal change
- Superficial perivascular infiltrate of lymphocytes admixed with eosinophils

Differential Diagnosis

In cases with interface damage, the differential diagnosis of morbilliform drug eruption includes acute GVHD, fixed drug eruption, lupus erythematosus, dermatomyositis, and viral exanthem. Acute GVHD typically occurs in the setting of bone marrow transplantations and rarely in solid organ transplants. It usually occurs relatively soon after the transplant, and in most cases, but by no means all, lack eosinophils. Connective tissue disease such as lupus erythematosus and dermatomyositis are characterized by interface change. However, they lack eosinophils and typically have increased dermal mucin. Viral exanthems usually lack eosinophils and are rarely biopsied.

In drug eruptions without interface change, the differential diagnosis includes dermal hypersensitivity reactions such as urticaria. Histologically, these entities are essentially indistinguishable and require clinical information (see Chap. 5). So-called papular dermatitis, also known as itchy red bump disease or papular eczema, has a similar pattern of perivascular infiltrate, but usually has reactive epidermal changes related to excoriation. See Table 4.8.

Table 4.8 Practical tips: morbilliform drug eruption

- The interface change in most morbilliform drug eruptions is mild in nature. If numerous dyskeratotic keratinocytes are present, other entities should be considered.
- Interface change is not always present
- The dermal infiltrate is typically mild in nature and is composed of lymphocytes and eosinophils
- Eosinophils are not necessarily prominent
- Without a good history, it is best to give a descriptive diagnosis and suggest the possibility of a drug eruption in the report comment. See example reports.
- A phone call to the clinician can be helpful if a good history is not available

Erythema Multiforme, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

These entities are viewed by some as a spectrum of the same disease process and by others as distinct entities. Histologically, they are similar to identical and will be dealt with as a group.

Clinical Features

In classic erythema multiforme (EM), the patient presents with episodic eruptions of macules, papules, or targetoid lesions on the extensor surfaces, palms, soles, and/or oral mucosa. If there is extensive mucosal involvement, the eruption can qualify for the designation of Stevens–Johnson syndrome (SJS). The eruption can be associated with herpes simplex virus infections (especially EM), mycoplasma infections, and drugs. SJS is typically associated with medications, with sulfa drugs being one of the most common triggers.

Toxic epidermal necrolysis (TEN) presents with widespread tender macular eruption with vesicles and bullae. Application of pressure to the skin can cause detachment of the epidermis (Nikolsky's sign). TEN is a medical emergency necessitating admission to a burn unit. The mortality ranges from 25 to 50%.

Microscopic Features

All of the entities in this group have essentially the same histologic features. The epidermis is relatively normal with a basket weave stratum corneum lacking parakeratosis or hyperkeratosis. There is vacuolar interface damage with necrosis of keratinocytes, often at all levels of the epidermis, in association with a mild superficial perivascular lymphocytic infiltrate (Fig. 4.11). Eosinophils are sometimes present, especially in cases related to medications. In TEN, there is often full-thickness necrosis, but this is not a specific finding for this entity (Fig. 4.12) (Table 4.9).

Differential Diagnosis

The histologic differential diagnosis can include morbilliform drug eruption, graft versus host disease (GVHD) and connective tissue disease such as lupus erythematosus or dermatomyositis. The pronounced epidermal damage helps exclude a typical drug eruption. GVHD has the appropriate clinical history. In connective tissue disease, there are epidermal changes (e.g., parakeratosis, thickened basement

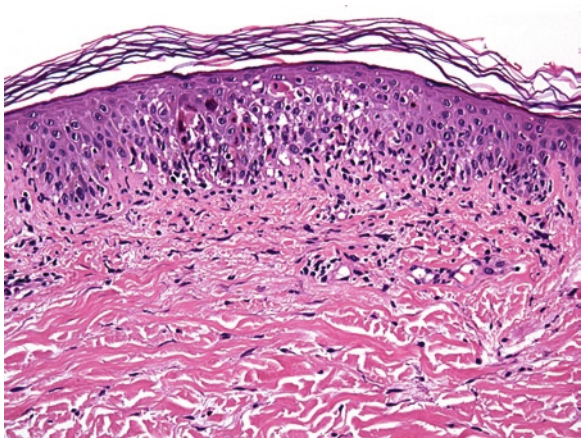

Fig. 4.11 *Erythema multiforme*. The epidermis has a normal stratum corneum. There is prominent epidermal damage characterized by dyskeratotic keratinocytes at all levels of the epidermis. Note the disproportionately sparse superficial lymphocytic infiltrate in comparison to the degree of epidermal damage

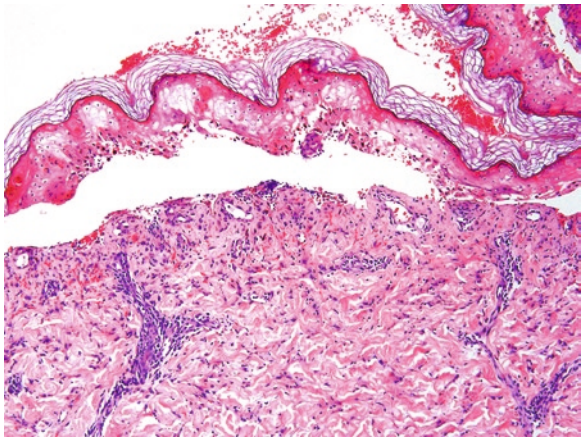

Fig. 4.12 *Toxic epidermal necrolysis*. In this case there is full thickness acute necrosis of the epidermis and a sparse superficial perivascular lymphocytic infiltrate

Table 4.9 Key microscopic features: erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis

- Normal basket-weave stratum corneum
- Mild perivascular lymphocytic infiltrate (with or without scattered eosinophils)
- Basal vacuolization with dyskeratotic keratinocytes at all levels of the epidermis
- May have full thickness necrosis of epidermis

membrane) that are not seen in the EM/SJS/TEN spectrum. Clinically, TEN and staphylococcal scalded skin syndrome (SSSS) can look alike. This clinical difference can be the source of a middle of the night frozen section, and so familiarity with this differential diagnosis is important. In SSSS a bacterial toxin causes a split between the stratum corneum and underlying epidermis. There is no dyskeratosis or interface change (Fig. 4.13). Practical tips are summarized in Table 4.10.

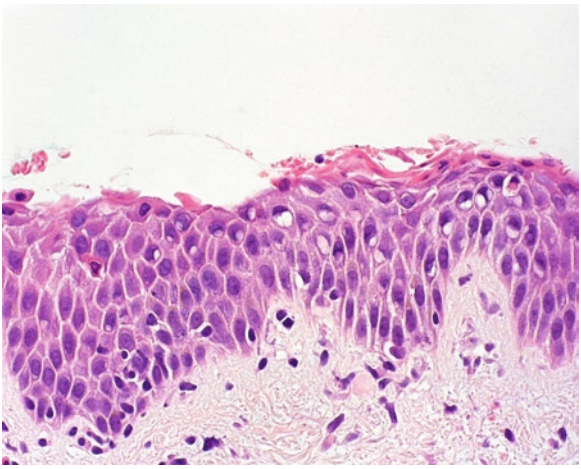

Fig. 4.13 *Staphylococcal scalded skin syndrome (SSSS).* SSSS is characterized by a split between the stratum spinosum and stratum corneum. It does not have interface change or prominent keratinocyte necrosis in contrast to toxic epidermal necrolysis

Table 4.10 Practical tips: erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis

- Degree of epidermal damage is disproportionate to the density of the infiltrate
- Because this group has an acute onset, the epidermis retains its normal basket-weave pattern in the stratum corneum
- If there are large areas of full thickness necrosis, SJS or TEN is more likely

Lupus Erythematosus

Clinical Features

Cutaneous lupus erythematosus can be subdivided into chronic (discoid), subacute, and systemic (acute) forms. There is a clinical overlap, and patients with discoid or subacute lupus erythematosus can progress to systemic disease, though it is less common in discoid lupus erythematosus.

Chronic, or discoid, lupus erythematosus is characterized by sharply demarcated erythematous scaly plaques usually involving the head and neck, often involving the face in a butterfly pattern. Lesions on the scalp can result in scarring alopecia. A variant of discoid lupus erythematosus called tumid lupus presents as juicy papules and plaques on the upper trunk, and head, and neck. The tumid variant has less scale. Chronic forms of lupus erythematosus are usually not associated with underlying systemic disease. Progression to systemic disease is seen in roughly 5–10% of cases. Antinuclear antibody (ANA) titers are positive in approximately 70% of the cases.

The cutaneous lesions of subacute lupus erythematosus manifest as annular lesions or plaques in photodistributed areas on the head and neck, upper trunk, and upper extremities. The patients often have mild musculoskeletal symptoms. Central nervous system involvement is usually absent and renal involvement is variable. Traditionally renal involvement was not considered common, but some reports have

refuted this finding. Positive ANA titers are seen in about 50% of cases. Patients may develop lesions of discoid lupus erythematosus or progress to fully developed systemic lupus erythematosus.

Cutaneous lesions are present in about 80% of patients with systemic lupus erythematosus. The cutaneous lesions are less well defined as in the other forms of cutaneous lupus erythematosus. They present as erythematous patches with little scale. As in other forms of cutaneous lupus erythematosus, the cutaneous lesions are in photodistributed areas, especially the malar face. Positive ANA titers are seen in approximately 90% of cases and >50% have anti-double stranded DNA antibodies.

Microscopic Features

Similar to the clinical manifestations, there is significant histologic overlap in the different clinical subtypes of cutaneous lupus erythematosus. From a practical standpoint, the overlap may preclude subclassification based on histologic features alone. All are a characterized by interface change of basal vacuolization and a perivascular lymphocytic infiltrate with increased dermal mucin (Fig. 4.14). Dermal mucin appears as stringy blue–gray material between the dermal collagen of the reticular dermis. It is not to be confused with solar elastosis; solar elastosis does not have the delicate appearance of dermal mucin, but resembles the structure of collagen fibers. Dermal mucin may be variably identifiable on routine H&E stained sections; it depends on the slide preparation technique of individual laboratories. Colloidal iron stains can be helpful in highlighting dermal mucin when it is not evident on routine H&E stains, but in most cases, it is not necessary (Table 4.11).

In discoid lupus erythematosus, the epidermis shows hyperkeratosis, variable epidermal atrophy alternating with acanthosis and follicular plugging (Fig. 4.15). The basement membrane is often thickened. The inflammatory infiltrate has a superficial and deep pattern, and frequently involves adnexal structures. In older "burned out" lesions, there may be less active interface change. In such cases, the evidence of epidermal change includes the thickened basement membrane, epidermal atrophy and melanophages

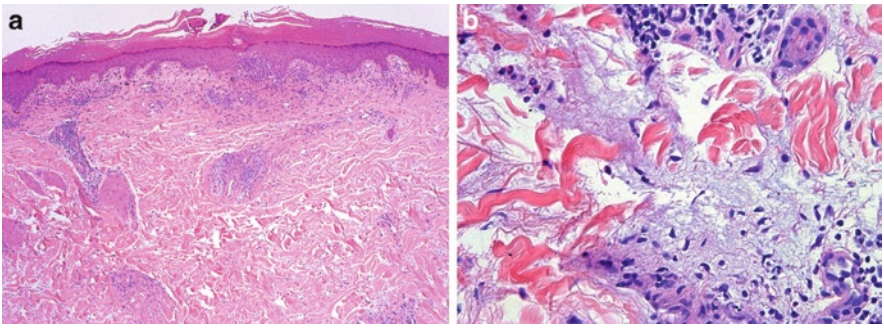

Fig. 4.14 *Lupus erythematosus*. (**a**). There is interface change and a superficial and deep perivascular lymphocytic infiltrate. (**b**). Between the collagen bundles there is deposition of dermal mucin characterized by blue-gray, somewhat delicate, stringy material

Table 4.11 Key microscopic features: lupus erythematosus

- Variable hyperkeratosis and parakeratosis
- Interface change with basal vacuolization
- Epidermal basement membrane often thickened
- Superficial or superficial and deep perivascular or perivascular and periadnexal lymphocytic infiltrate
- Increased dermal mucin

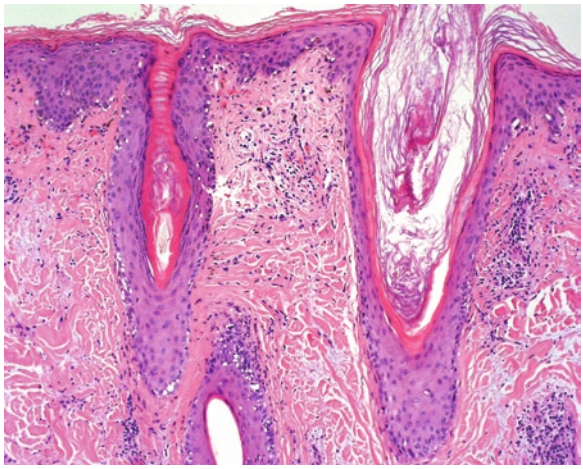

Fig. 4.15 *Lupus erythematosus*. In lupus erythematosus, especially discoid forms, the epidermis demonstrates follicular plugging and alternating acanthosis and atrophy in addition to the interface change. Note the blue-gray dermal mucin between the collagen bundles

in the upper dermis. In the tumid form, significant interface change is typically absent; the combination of a superficial and deep infiltrate with increased dermal mucin is an important clue (Fig. 4.16). Subacute lupus erythematosus differs from the discoid form only slightly. There is usually a less intense inflammatory infiltrate and more prominent atrophy. In systemic lupus erythematosus, there is prominent basal vacuolization but necrotic keratinocytes are rare. The infiltrate is typically less intense and usually in a superficial perivascular distribution.

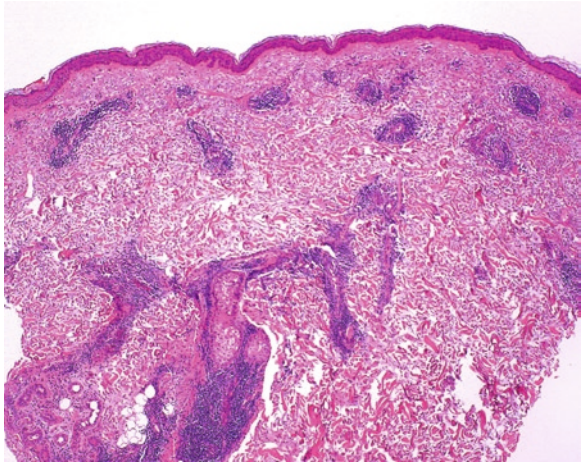

Fig. 4.16 *Tumid lupus erythematosus*. In the tumid form of lupus erythematosus, interface change is focal or absent. The key features are the superficial and deep lymphocytic infiltrate and dermal mucin deposition

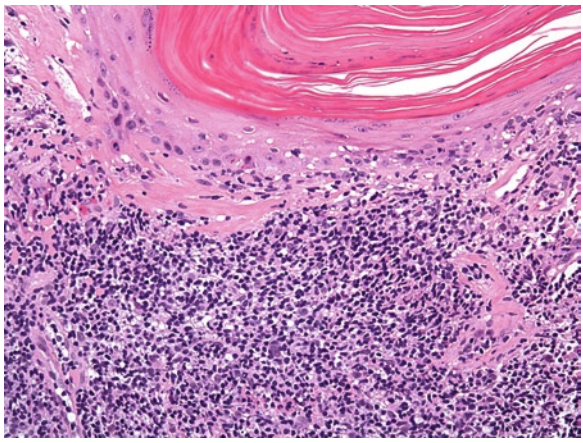

Fig. 4.17 *Reactive epidermal atypia in lupus erythematosus*. In some cases of lupus erythematosus, the interface change can result in reactive atypia of the epidermis

Differential Diagnosis

In cases with relatively numerous necrotic keratinocytes, the differential diagnosis includes EM. However, EM is an acute process and does not show the other epidermal changes of lupus erythematosus such as hyperkeratosis, atrophy, or basement membrane thickening. In cases with a dense inflammatory infiltrate, lichen planus could be considered, but the presence of dermal mucin and a deep inflammatory component are against lichen planus. In both instances, clinical history is also helpful. Dermatomyositis can be remarkably similar to lupus erythematosus (see below). It also shows interface dermatitis with increased dermal mucin. The inflammatory infiltrate in dermatomyositis is generally mild and restricted to the superficial dermis. In some cases, it may not be possible to distinguish between these entities except by clinical history. Some cases of lupus erythematosus, especially discoid lupus erythematosus, show reactive atypia in the keratinocytes of the epidermis (Fig. 4.17). The reactive epithelial atypia can mimic the dysplasia of actinic keratosis or even squamous cell carcinoma. Confusion with an actinic keratosis is usually more of a risk in superficial shave biopsies. The clinical history and the presence of other findings of lupus erythematosus will allow for distinction (Table 4.12).

Dermatomyositis

Clinical Features

Dermatomyositis is characterized by the combination of muscle weakness and characteristic cutaneous findings of erythematous to violaceous slightly scaly lesions. The face, shoulders and extensor surfaces of the extremities are most commonly

Table 4.12 Practical tips: lupus erythematosus

- Distribution is important: Lupus erythematosus is a photo-distributed disease
- Eosinophils are not a feature of lupus erythematosus except in the rare cases of drug-induced lupus erythematosus. The presence of eosinophils raises the possibility of dermal hypersensitivity reactions such as an arthropod bite reaction or drug eruption.
- The "actinic keratosis clue." Remember that some cases of lupus erythematous can superficially resemble actinic keratosis. If there is interface change and squamous atypia, consider the possibility of lupus erythematosus.
- Remember that biopsies from old lesions may not show active vacuolar interface change. Look for evidence of past interface damage such as atrophy, basement membrane thickening, and melanophages.
- Colloidal iron studies may help highlight the dermal mucin
- Some cases of dermatomyositis and lupus erythematosus are histologically indistinguishable
- Tumid lupus erythematosus lacks interface change

involved. Involvement of the face frequently takes the form of a periorbital heliotrope rash. Involvement of the shoulders is often diffuse causing the shawl sign. Periungual erythema and Gottron's papules are common findings on the hands. Muscle weakness, when present, involves proximal muscles. Cutaneous involvement can precede muscle involvement by months to years, and some patients never develop muscle weakness (so-called dermatomyositis sine myositis).

Microscopic Features

The histologic features are characterized by basal vacuolization, a minimal to mild superficial perivascular lymphocytic infiltrate and increased dermal mucin (Fig. 4.18). The basement membrane may be thickened, and melanophages may be seen in the upper dermis. Occasional neutrophils may be present. In some cases, interface change is not apparent on the biopsy specimen. In cases such as this, the prominent dermal mucin and scant to mild perivascular lymphocytic infiltrate should serve as a clue to the diagnosis (Table 4.13).

Differential Diagnosis

The primary differential diagnosis is lupus erythematosus. Unfortunately, it is not possible to unequivocally differentiate dermatomyositis from lupus erythematosus. (See also above section on lupus erythematosus). The same comments above on differentiating lupus erythematosus from other forms of interface dermatitis apply to dermatomyositis (see Table 4.14).

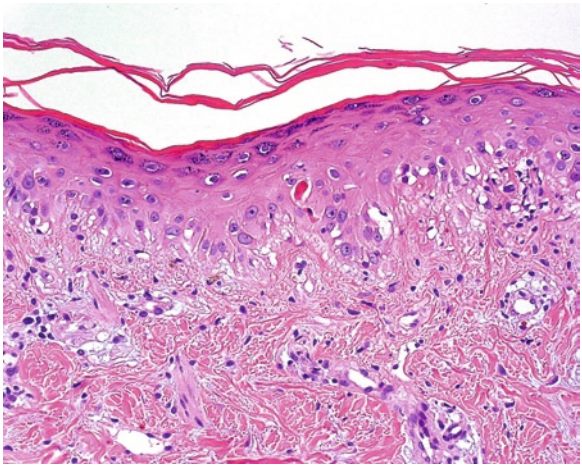

Fig. 4.18 *Dermatomyositis*. In dermatomyositis there is typically interface change with basal vacuolization, but the infiltrate is sparse or mild in nature. Dermal mucin deposition is present

Table 4.13 Dermatomyositis: key microscopic features

- Basal vacuolization
- Mild superficial perivascular lymphocytic infiltrate
- Increased dermal mucin

Table 4.14 Dermatomyositis: practical tips

- The infiltrate in dermatomyositis is usually mild and restricted to the superficial dermis. If there is a deep component, consider the diagnosis of lupus erythematosus.
- Eosinophils are not a feature of dermatomyositis. If present consider the diagnosis of a drug eruption.
- Colloidal iron stains may help highlight the dermal mucin.
- Dermatomyositis is pruritic; this clinical information can be a clue.

Graft Versus Host Disease

Clinical Features

Cutaneous graft versus host disease (GVHD) usually occurs in the setting of bone marrow transplant, but can sometimes occur in the setting of solid organ transplants. GVHD can be subdivided into acute GVHD and chronic GVHD. Acute GVHD typically occurs 2–4 weeks after transplantation, but it can be quite variable and may be several weeks to months after transplantation. Another variable that is increasingly seen is the practice of donor lymphocyte reinfusion. In this setting, acute GVHD can present many months after the original transplant. The reinfusion of donor lymphocytes essentially resets the GVHD clock. The eruption of acute GVHD is characterized by an erythematous macular to papular eruption involving the face, posterior neck, ears, hands and feet. The eruption often starts with facial erythema that subsequently involves other parts of the body with a maculopapular eruption. Co-existing diarrhea is often present, and may precede the cutaneous eruption. Laboratory tests frequently show elevated liver enzymes.

Chronic GVHD classically occurs greater than 6 months after transplantation. Chronic GVHD is subdivided into lichenoid and sclerodermoid forms. Classically, chronic GVHD first manifests with the lichenoid form, with the sclerodermoid form following. Some patients present with both forms simultaneously. Lichenoid chronic GVHD presents as polygonal violaceous papules reminiscent of lichen planus. Oral mucosal involvement is seen in approximately 90% of patients. Sclerodermoid GVHD presents as areas of dermal sclerosis similar to morphea/scleroderma (see Chap. 9).

Microscopic Features

Acute GVHD

In acute GVHD, the epidermis is relatively normal, but some keratinocyte atypia may be seen as a result of prior chemotherapy. Within the dermis, there is a sparse infiltrate of lymphocytes. Occasionally eosinophils may be part of the infiltrate. The interface change is manifested by basal vacuolization. As the eruption progresses, necrotic keratinocytes are seen often with lymphocyte satellitosis (Fig. 4.19). Severe cases can show cleft formation between the epidermis and dermis or even full thickness necrosis of the epidermis. Fortunately, this is rarely seen. Acute GVHD is graded by the following scheme:

Grade 0: Normal skin.
Grade 1: Basal vacuolization with a mild superficial perivascular lymphocytic infiltrate.
Grade 2: Same features as Grade 1 with scattered necrotic keratinocytes and satellite cell necrosis.
Grade 3: Same features as Grade 2 but with cleft formation between epidermis and dermis.
Grade 4: Same as features as Grade 2 or 3 with complete separation of the epidermis from the dermis.

Unlike acute GVHD, there is no grading scheme for chronic GVHD. Lichenoid chronic GVHD shows epidermal changes of hyperkeratosis and hypergranulosis in addition to interface change of basal vacuolization with necrotic keratinocytes and satellite cell necrosis (Fig. 4.20). The infiltrate in the dermis is usually mild, but is often more dense than seen with acute GVHD, and in some cases, there is a dense band-like infiltrate similar to lichen planus. Rarely some biopsies may show transitional forms with histologic features of acute GVHD and lichenoid chronic GVHD in the same biopsy or different concurrent biopsies from the same patient.

Sclerodermoid chronic GVHD resembles morphea or scleroderma (see below). There is epidermal atrophy with dermal sclerosis characterized by fibrosis with compaction of collagen fibers in the reticular dermis (Fig. 4.21). There is a loss of adnexal structures. Microscopic features are summarized in Table 4.15.

Table 4.15 Key microscopic features: graft vs. host disease (GVHD)

- Basal vacuolization
- Variable amount of dyskeratotic keratinocytes
- Satellite cell necrosis
- Mild superficial perivascular lymphocytic infiltrate
- Lichenoid chronic GVHD has a thickened granular layer and hyperkeratosis
- Sclerodermoid chronic GVHD has thickened and compacted dermal collagen bundles

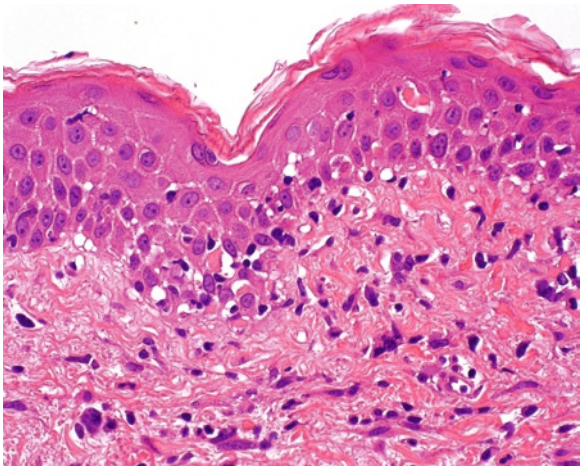

Fig. 4.19 *Acute graft vs. host disease*. In acute graft vs. host disease there is variable interface change with basal vacuolization and dyskeratotic keratinocytes. Satellite cell necrosis, characterized by lymphocytes tagging dyskeratotic cells, is commonly seen. The dermal infiltrate is usually mild in nature. This lesion would be considered grade 2

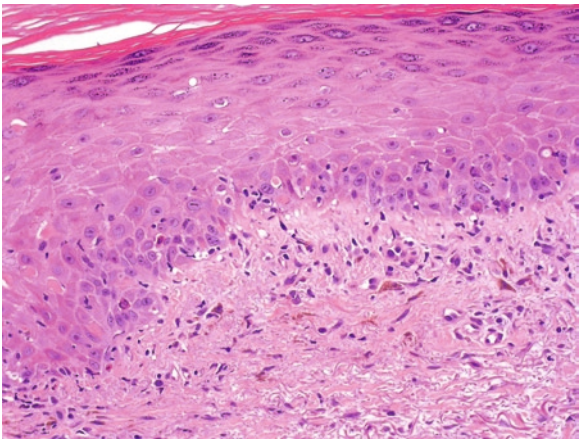

Fig. 4.20 *Lichenoid chronic graft vs. host disease*. This form of chronic graft vs. host disease has features that overlap with lichen planus, namely compact hyperkeratosis, a thickened granular layer and interface change. The infiltrate in lichenoid graft vs. host disease is milder in nature

Differential Diagnosis

In acute GVHD, the histologic and clinical differential diagnosis is usually a drug eruption. In most cases of acute GVHD, there are no eosinophils unlike typical drug eruptions. However, acute GVHD can sometimes have eosinophils as part of the infiltrate, and the presence of eosinophils is by no means diagnostic of a drug eruption in this setting as it was once believed. Satellite cell necrosis is more common in

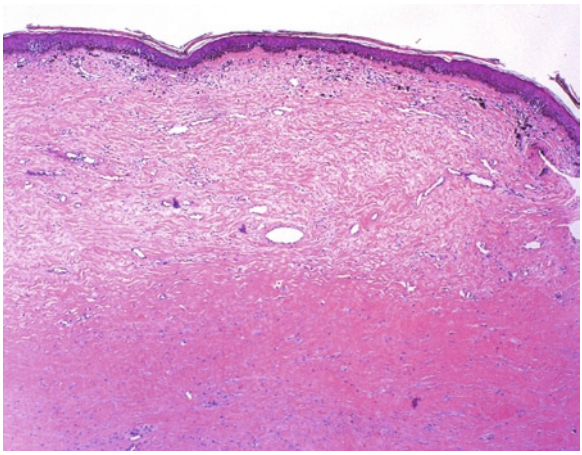

Fig. 4.21 *Sclerodermoid chronic graft vs. host disease*. This form of chronic graft vs. host disease resembles morphea/scleroderma. There is sclerosis of the dermis characterized by compactin of the collagen fibers with loss of the normal space between collagen fibers of the reticular dermis and loss of adnexal structures. Inflammation is absent to mild. There is often no active interface change

GVHD, but unequivocal distinction may not always be possible. From a practical perspective, most patients for whom acute GVHD is a diagnostic consideration do not have a sufficiently reconstituted immune system to mount a drug eruption and the bias should be toward the diagnosis of acute GVHD. EM could be considered from a histologic standpoint, but the clinical situation typically negates EM from consideration.

In lichenoid chronic GVHD, the primary differential diagnosis is lichen planus. Lichen planus typically has a denser infiltrate. Clinical history is also helpful. It is not possible to distinguish sclerodermoid chronic GVHD from morphea or scleroderma histologically; clinical information is essential. See Table 4.16.

Table 4.16 Practical tips: graft vs. host disease (GVHD)

- It is rare to see acute GVHD before 14 days after transplantation.
- The histologic features may lag the clinical presentation. In very early biopsies of GVHD, the skin may show no histologic abnormalities.
- Deeper levels or subsequent biopsies may show classic GVHD.
- Late onset acute GVHD (> 6 months after transplantation) may be seen in the setting of donor lymphocyte reinfusion, an increasingly common practice.
- Eosinophils may sometimes be seen in GVHD and does not exclude the diagnosis in the appropriate clinical setting. From a practical viewpoint, many of these patients may not have a sufficient immune system to mount a drug eruption. Our bias is that the eruption in this clinical setting is GVHD until proven otherwise.
- Additional clinical information (e.g., diarrhea or elevated liver enzymes) can help corroborate the diagnosis.

Pityriasis Lichenoides

Clinical Features

Pityriasis lichenoides is most common in young adult men and typically involves the extremities, trunk, and buttocks. Pityriasis lichenoides exists in two forms: pityriasis

lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC). PLEVA presents as recurrent crops of skin-colored papules that become hemorrhagic or crusted, ulcerate, and leave behind varioliform (smallpox-like) scars. PLC is less hemorrhagic consisting of red-brown, scaly macules to papules. In PLC, the lesions heal without scarring, but there may be post-inflammatory changes.

Microscopic Features

The microscopic features show significant overlap between the two entities. Both show epidermal changes of parakeratosis, basal vacuolization and necrotic keratinocytes. The epidermal change is more pronounced in PLEVA with more numerous necrotic keratinocytes and prominent exocytosis of lymphocytes and often erythrocytes (Fig. 4.22). In PLEVA, the infiltrate is superficial and deep and often has a wedge-shaped configuration. Extravasation of erythrocytes is commonly present, especially in PLEVA, but fibrinoid necrosis of blood vessels is absent. In late lesions of PLEVA the biopsy may show ulceration of the epidermis. The changes in PLC are subtler than in PLEVA (Fig. 4.23). There is often confluent parakeratosis, and scattered dyskeratotic keratinocytes in the epidermis. There may be variable acanthosis and the interface change consisting of basal vacuolization is usually subtle. The dermal inflammatory infiltrate is predominantly composed of lymphocytes and usually restricted to the superficial dermis (Table 4.17).

Differential Diagnosis

For PLEVA, the differential diagnosis includes lymphomatoid papulosis (LYP) (see Chap. 5). Both have similar clinical histories of recurrent crops of papules that can ulcerate and both can show a superficial and deep infiltrate with interface

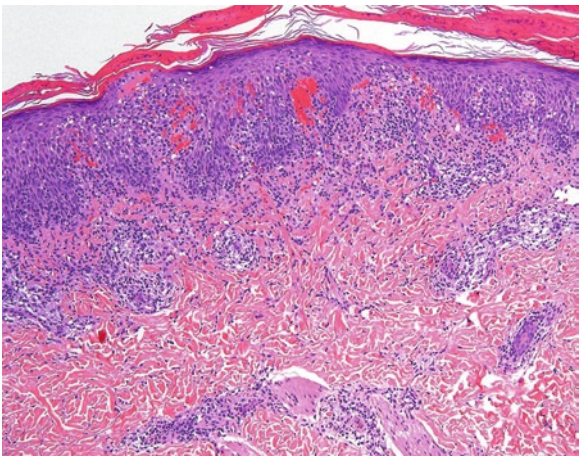

Fig. 4.22 *Pityriasis lichenoides et varioliformis acuta (PLEVA)*. The histologic features of PLEVA are variable depending on which stage the biopsy is taken. The most characteristic findings include parakeratosis and serum crust scale overlying the epidermis in association with interface change, a superficial and deep perivascular lymphocytic infiltrate, and prominent hemorrhage in the superficial dermis

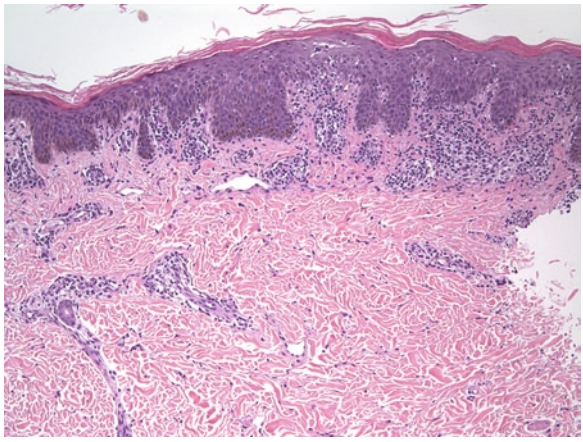

Fig. 4.23 *Pityriasis lichenoides chronica (PLC).* In PLC, there is parakeratosis overlying the epidermis. There is interface change and usually a mild to moderate lymphocytic infiltrate in the upper dermis

Table 4.17 Key microscopic features: pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC)

PLEVA
• Parakeratosis, spongiosis, and basal vacuolization
• Dyskeratotic keratinocytes
• Superficial and deep perivascular lymphocytic infiltrate
• Extravasation of erythrocytes in papillary dermis
PLC
• Parakeratosis
• Variable acanthosis
• Occasional dyskeratotic cells
• Mild basal vacuolization
• Superficial perivascular lymphocytic infiltrate

change. LYP usually has a population of large atypical CD30+ cells. Lupus erythematosus could be considered, but the clinical presentation is different, the degree of epidermal damage is more pronounced in PLEVA, and PLEVA does not have increased dermal mucin. EM is in the differential diagnosis, but PLEVA has more epidermal changes (e.g., parakeratosis) and a denser inflammatory infiltrate. For PLC, the differential diagnosis includes pityriasis rosea, spongiotic/eczematous dermatitis, and guttate psoriasis. Pityriasis rosea has more discrete mounds of parakeratosis and lacks interface change. Similarly, spongiotic dermatitis lacks interface change and has more pronounced spongiosis. Guttate psoriasis has mounds of parakeratosis that can have collections of neutrophils. Dyskeratotic cells or interface change are not features of guttate psoriasis.

Obviously with the overlapping histologic features, PLEVA and PLC can be confused, as these entities represent ends of a morphologic spectrum. Knowledge of the clinical presentation may be required to distinguish them. Classification of a given lesion as PLEVA or PLC may not be possible. In such a setting, the more generic term pityriasis lichenoides can be used. See Table 4.18.

Table 4.18 Practical tips: PLEVA and PLC

- Maintain a high index of suspicion
- The presence of interface change with hemorrhage is an important clue especially for PLEVA
- Knowledge of the clinical history is especially helpful for the diagnosis of PLEVA or PLC
  - PLEVA presents as hemorrhagic papules
  - PLC presents as papules or small plaques
- An ulcerated lesion of PLEVA has non-specific histologic features. Suggest re-biopsy of a more recent lesion

Sample Reports: Lichen Planus

Example 1:

Clinical history: Pruritic papules on wrist; rule-out lichen planus.
Diagnosis: Lichen planus, see comment.
Comment: Sections demonstrate an epidermis with compact hyperkeratosis and a thickened granular layer. Within the dermis, there is a lichenoid infiltrate of lymphocytes with prominent interface change with saw-toothing of the rete pegs and scattered dyskeratotic keratinocytes. The histologic features are consistent with lichen planus. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: Lesion on chest.
Diagnosis: Lichenoid interface dermatitis, see comment.
Comment: The biopsy demonstrates many features of lichen planus including compact hyperkeratosis, a thickened granular layer and a lichenoid infiltrate of lymphocytes with prominent interface change. If there are multiple lesions, this could be compatible with lichen planus. If this is a solitary lesion, a benign lichenoid keratosis is favored. Clinicopathologic correlation is recommended.

Example 3:

Clinical history: Leukoplakia, rule out malignancy.
Diagnosis: Lichenoid mucositis, see comment.
Comment: There is some parakeratosis and a subtle granular layer. Within the subepithelial stroma, there is a lichenoid infiltrate of lymphocytes with interface change characterized by basal vacuolization and scattered dyskeratotic cells. No atypia or dysplasia is seen. The histologic features are consistent with oral lichen planus. Clinicopathologic correlation is recommended.

Sample Reports: Lichenoid Drug Eruption

Example 1:

Clinical history: Rule out drug eruption.

Diagnosis: Lichenoid interface dermatitis consistent with lichenoid drug eruption, see comment.

Comment: There is compact hyperkeratosis and parakeratosis overlying the epidermis. Within the dermis, there is a lichenoid infiltrate of lymphocytes and eosinophils with prominent interface change. The histologic features are consistent with a lichenoid drug eruption. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: Rule out lichen planus.

Diagnosis: Lichenoid interface dermatitis, see comment.

Comment: There is focal parakeratosis and compact hyperkeratosis overlying an epidermis with a thickened granular layer. Within the dermis, there is a lichenoid infiltrate of lymphocytes admixed with eosinophils in association with interface change. The presence of parakeratosis and eosinophils favors a lichenoid drug eruption over lichen planus. Clinicopathologic correlation is recommended.

Sample Report: Fixed Drug Eruption

Example 1:

Clinical history: Recurrent lesion, rule out fixed drug eruption.

Diagnosis: Interface dermatitis consistent with fixed drug eruption, see comment.

Comment: There is normal basket-weave stratum corneum overlying the epidermis. Within the dermis, there is a lichenoid mixed infiltrate of lymphocytes and eosinophils with prominent interface change. Scattered melanophages are present in the dermis. The histologic features are consistent with the clinical impression of a fixed drug eruption.

Example 2:

Clinical history: Rule out drug eruption vs. other.

Diagnosis: Interface dermatitis, see comment.

Comment: The epidermis has focal parakeratosis. Within the dermis, there is a lichenoid infiltrate of lymphocytes and eosinophils in association with prominent interface change with basal vacuolization and dyskeratotic cells. Also within the dermis, there are

scattered melanophages. The histologic features are compatible with a dermal hypersensitivity reaction such as a drug eruption. The prominent interface change and melanophages could suggest the possibility of a fixed drug eruption in the appropriate clinical context. Clinicopathologic correlation is recommended.

Sample Reports: Morbilliform Drug Eruption

Example 1:

Clinical history: Connective tissue disease (code word for lupus erythematosus or dermatomyositis) vs. drug eruption.

Diagnosis: Mild interface dermatitis consistent with a drug eruption, see comment.

Comment: Within the dermis, there is a mild superficial perivascular mixed infiltrate of lymphocytes and scattered eosinophils. There is focal interface change characterized by basal vacuolization. The histologic features are consistent with a drug eruption. The presence of eosinophils argues against the diagnosis of connective tissue disease such as lupus erythematosus or dermatomyositis. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: Rule-out eczema.

Diagnosis: Skin, trunk, punch biopsy: Superficial perivascular mixed infiltrate with focal interface change, see comment.

Comment: The epidermis is relatively normal without significant spongiosis. Within the dermis, there is a superficial perivascular infiltrate of lymphocytes and scattered eosinophils in association with focal basal vacuolization. The histologic features are most consistent with a dermal hypersensitivity reaction such as a drug eruption. Papular eczema could be considered, but the absence of reactive epidermal change consistent with excoriation argues against this diagnosis. The absence of epidermal spongiosis is against the possibility of an eczematous dermatitis. Clinicopathologic correlation is recommended.

Sample Reports: Erythema Multiforme, Toxic Epidermal Necrolysis

Example 1:

Clinical history: Rule-out EM.

Diagnosis: Erythema multiforme, see comment.

Comment: There is a normal basket-weave stratum corneum overlying the epidermis. Within the dermis, there is a mild superficial perivascular infiltrate of lymphocytes. There is interface change with basal vacuolization and dyskeratotic keratinocytes scattered throughout all levels of the epidermis. The histologic features are those of Erythema multiforme. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: EM vs. drug eruption.

Diagnosis: Interface dermatitis, see comment.

Comment: There is a normal basket-weave stratum corneum overlying the epidermis. Within the dermis, there is a superficial perivascular infiltrate of lymphocytes with occasional eosinophils. There is prominent basal vacuolization with numerous dyskeratotic keratinocytes. Given the degree of epidermal damage, the biopsy findings are most consistent with Erythema multiforme rather than a typical drug eruption. Eosinophils may be seen in Erythema multiforme and do not exclude the diagnosis. Clinicopathologic correlation is recommended.

Example 3:

Clinical history: SSSS vs. TEN.

Diagnosis: Consistent with toxic epidermal necrolysis, see comment.

Comment: The stratum corneum is intact. Within the dermis, there is a sparse superficial perivascular lymphocytic infiltrate in association with basal vacuolization and numerous dyskeratotic keratinocytes. The histologic features are diagnostic of toxic epidermal necrolysis in the appropriate clinical context.

Sample Reports: Lupus Erythematosus

Example 1:

Clinical history: Lupus erythematosus vs. dermatomyositis.

Diagnosis: Interface dermatitis, see comment.

Comment: There is focal parakeratosis overlying the epidermis. Within the dermis, there is a superficial and deep perivascular lymphocytic infiltrate with increased dermal mucin. There is interface change characterized by basal vacuolization. The histologic features are consistent with connective tissue disease. The presence of a deep inflammatory component favors the diagnosis of lupus erythematosus over dermatomyositis. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: Plaque on scalp.

Diagnosis: Interface change consistent with lupus erythematosus, see comment.

Comment: There is parakeratosis and compact hyperkeratosis overlying the epidermis. Follicular plugging is noted. There is interface change characterized by basal vacuolization and basement membrane thickening. Within the dermis, there is a superficial and deep perivascular lymphocytic infiltrate with increased dermal mucin. The histologic features are characteristic of discoid lupus erythematosus. Clinicopathologic correlation is recommended.

Example 3:

Clinical history: Annular lesion.

Diagnosis: Skin, arm, punch biopsy: lupus erythematosus, see comment.

Comment: The epidermis shows some parakeratosis and hyperkeratosis. There is interface change characterized by basal vacuolization. Within the dermis, there is a superficial perivascular lymphocytic infiltrate and increased dermal mucin. The histologic features and clinical history of an annular lesion are characteristic of lupus erythematosus. Clinicopathologic correlation is recommended.

Sample Reports: Dermatomyositis (See Also Sample Reports for Lupus Erythematosus)

Example 1:

Clinical history: Rule out dermatomyositis.

Diagnosis: Skin, arm, punch biopsy: Interface dermatitis consistent with dermatomyositis, see comment.

Comment: There is interface change characterized by basal vacuolization in association with a mild superficial perivascular lymphocytic infiltrate and increased dermal mucin. The histologic features are consistent with the diagnosis of dermatomyositis in the appropriate clinical context. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: Dermatomyositis vs. lupus erythematosus.

Diagnosis: Skin, arm, punch biopsy: Interface dermatitis, see comment.

Comment: There is interface change characterized by basal vacuolization in association with a mild superficial perivascular lymphocytic infiltrate and increased dermal mucin. The mild nature of the inflammatory infiltrate could slightly favor dermatomyositis, but lupus erythematosus cannot be excluded. Clinicopathologic correlation is recommended.

Sample Reports: Graft Versus Host Disease

Example 1:

Clinical history: Bone marrow transplant 4 weeks ago now with new rash. Rule out GVHD vs. drug eruption.

Diagnosis: Skin, arm, punch biopsy: Acute graft versus host disease, grade 2 of 4, see comment.

Comment: The epidermis has a normal basket-weave stratum corneum. Within the dermis, there is a mild superficial perivascular infiltrate with interface change characterized by basal vacuolization and focal satellite cell necrosis. The histologic features are characteristic of acute graft versus host disease, grade 2 of 4. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: Drug eruption vs. GVHD.

Diagnosis: Skin, arm, punch biopsy: Interface dermatitis, see comment.

Comment: Sections demonstrate an interface dermatitis characterized by basal vacuolization with focal satellite cell necrosis. Within the dermis, there is a mild superficial perivascular lymphocytic infiltrate admixed with eosinophils. Given the clinical context of recent stem cell transplantation, the diagnosis of acute graft versus host disease, grade 2 of 4, is favored despite the presence of eosinophils. Clinicopathologic correlation is recommended.

Example 3:

Clinical history: Bone marrow transplantation 7 months ago; rule out GVHD.

Diagnosis: Skin, arm, biopsy: Lichenoid chronic graft versus host disease, see comment.

Comment: The epidermis shows compact hyperkeratosis and a thickened granular layer. Within the dermis there is a mild perivascular to lichenoid lymphocytic infiltrate with scattered melanophages in association with interface change characterized by basal vacuolization and scattered dyskeratotic cells. The histologic features are compatible with lichenoid chronic graft versus host disease.

PLEVA and PLC: Sample Reports

Example 1:

Clinical history: Rule-out LYP vs. PLEVA.

Diagnosis: Skin, buttock, punch biopsy: Pityriasis lichenoides et varioliformis acuta (PLEVA), see comment.

Comment: There is parakeratosis overlying the epidermis. Within the dermis, there is a superficial and deep perivascular lymphocytic infiltrate with prominent interface change and papillary dermal hemorrhage. Because of the clinical suspicion for possible lymphomatoid papulosis, an immunohistochemical stain for CD30 was performed and compared to appropriate controls. No significant immunoreactivity for CD30 was seen in the dermal infiltrate. In the appropriate clinical context, the histologic features are consistent with the diagnosis of PLEVA. Clinicopathologic correlation is recommended.

Example 2:

Clinical history: Rule erythema multiforme vs. PLEVA.

Diagnosis: Skin, arm, punch biopsy: Interface dermatitis consistent with Pityriasis lichenoides et varioliformis acuta (PLEVA), see comment.

Comment: There is parakeratosis overlying the epidermis. Within the dermis, there is a superficial and deep perivascular lymphocytic infiltrate associated with papillary dermal hemorrhage and interface change with numerous dyskeratotic cells. The histologic features are consistent with PLEVA. The presence of parakeratosis, papillary dermal hemorrhage and the density of the inflammatory infiltrate are against erythema multiforme (EM). Clinicopathologic correlation is recommended.

Example 3:

Clinical history: Pityriasis rosea vs. PLC.

Diagnosis: Skin, buttock, punch biopsy: Interface dermatitis consistent with pityriasis lichenoides chronica, see comment.

Comment: There is near confluent parakeratosis overlying a mildly acanthotic epidermis. Scattered dyskeratotic keratinocytes are present. Within the dermis, there is a superficial perivascular lymphocytic infiltrate associated with interface change characterized by focal basal vacuolization.

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Chapter 5
Perivascular Dermatitis

Keywords Perivascular dermatitis • Morbilliform drug eruption • Viral exanthem • Erythema annulare centrifugum • Figurate erythema • Pigmented purpuric dermatosis • Schamberg's disease • Urticaria • Mastocytosis • Lymphomatoid papulosis • Anaplastic large cell lymphoma • Arthropod bite reaction

Entities in this category are characterized by the absence of significant epidermal change and the presence of an inflammatory infiltrate that is largely restricted to the superficial, or superficial and deep dermis around blood vessels (Figs. 5.1 and 5.2). Not infrequently, there may be some overlap with the superficial, and superficial and deep perivascular patterns. To the consternation of many pathologists, initial perusal of a skin biopsy demonstrating a superficial or superficial and deep inflammatory infiltrate in the absence of spongiosis or other epidermal change may seem like an exercise in diagnostic futility. However, by paying close attention to the composition and distribution of the inflammatory infiltrate, one can apply an organized approach to this clinically diverse group of disorders (Tables 5.1 and 5.2). This chapter will cover most of the important and common diseases having the superficial and deep pattern of inflammation.

Morbilliform Drug Eruption

Clinical Features

Morbilliform (or exanthematous) drug reactions are characterized by a generalized eruption of pruritic erythematous macules and papules. Lesions usually develop within 1 day to 3 weeks after the inciting agent is administered.

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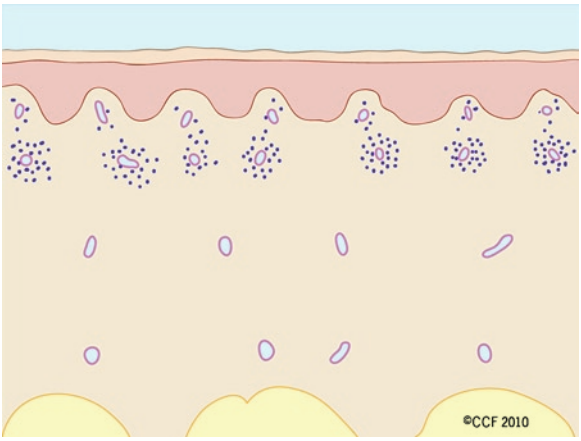

Fig. 5.1 *Schematic representation of superficial perivascular pattern*. The inflammatory infiltrate is concentrated around the vessels of the superficial vascular plexus. There is no significant epidermal change

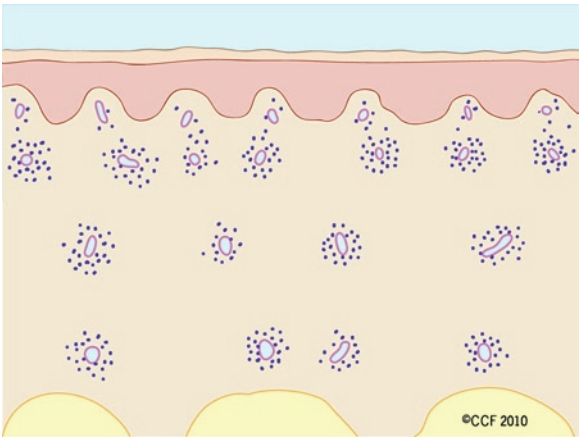

Fig. 5.2 *Schematic representation of superficial and deep perivascular pattern*. The inflammatory infiltrate is concentrated around the vessels of the superficial and deep vascular plexus There is no significant epidermal change

Table 5.1 Superficial perivascular dermatitis

Lymphocytes predominate
- Drug reactions (morbilliform)
- Viral exanthems
- Chronic urticaria
- Superficial annulare centrifugum (gyrate *erythema*)

Lymphocytes with extravasated erythrocytes and/or siderophages
- Schamberg's disease and other forms of pigmented purpuric dermatosis
- Stasis dermatitis (discussed in Chap. 2)

Eosinophils
- Urticaria
- Urticarial hypersensitivity reaction (arthropod bite or drug)
- Drug reactions (morbilliform)

Mast cells perivascular and interstitially
- Cutaneous mastocytosis (especially telangiectasia eruptiva macularis perstans or TMEP)

Table 5.2 Superficial and deep perivascular dermatitis

Lymphocytes predominate
- Deep annular erythema (gyrate erythema)
- Polymorphous light eruption
- Perniosis (chilblains)
- Lymphomatoid papulosis

Eosinophils
- Dermal hypersensitivity reaction (including arthropod bite reaction or drug)

Plasma cells
- Morphea (discussed in Chap. 9)

Microscopic Features

The epidermis is often unremarkable. Within the dermis, there is a mixed inflammatory infiltrate, usually predominantly composed of lymphocytes, admixed with some eosinophils surrounding the superficial vascular plexus (Fig. 5.3). Papillary dermal edema is often present. Mild interface change may also be present as discussed in Chap. 3. It should be kept in mind that in some cases, eosinophils are the predominant inflammatory cells and some cases may have a deep perivascular infiltrate as well (Table 5.3).

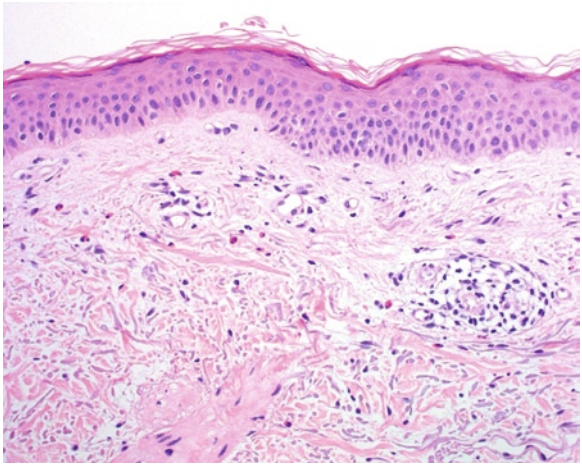

Fig. 5.3 *Morbilliform drug eruption*. There is a mixed inflammatory infiltrate composed of lymphocytes and eosinophils surrounding the superficial perivascular plexus. The epidermis in this case is unremarkable

Table 5.3 Key microscopic features: drug eruption

- Epidermis normal or with mild interface change
- Usually mild superficial perivascular infiltrate but may be deep
- Infiltrate may be predominantly composed of lymphocytes or eosinophils, but eosinophils are usually present

Differential Diagnosis

The histopathologic differential diagnosis includes other entities characterized by a mild superficial perivascular infiltrate, including viral exanthema and urticaria (discussed below). In general, viral exanthems do not have eosinophils. Urticaria is essentially indistinguishable. Differentiation requires knowledge of the clinical presentation. An arthropod bite reaction can be considered, but they typically have a denser infiltrate. Without a good clinical history, it is best to use a descriptive diagnosis (see sample reports) (Table 5.4).

Table 5.4 Practical tips: drug eruption

- Sparse infiltrate is a clue
- Usually widespread eruptions
- Clinical correlation is critical: call clinician and ask about new medications

Viral Exanthems

Clinical Features

Viral exanthems are acute, widespread self-limited eruptions of erythematous macules, papules, and vesicles that are often accompanied by fever.

Microscopic Features

Similar to morbilliform drug eruptions, most viral exanthems are characterized by a nonspecific superficial perivascular lymphocytic infiltrate. Eosinophils are usually not present. Focal basilar vacuolar alteration may be observed.

Differential Diagnosis

The primary differential diagnosis is a drug eruption. The degree of histologic overlap precludes unequivocal microscopic discrimination. Eosinophils favor a drug eruption. Clinical information is essential. Fortunately, viral exanthems are rarely biopsied.

Erythema Annulare Centrifugum

Clinical Features

Erythema annulare centrifugum, also known as gyrate erythema, is characterized by annular, scaly erythematous plaques involving the trunk and proximal extremities. There is trailing scale behind the advancing edge of the lesions. Initially, this disorder may present as small, pink papules that enlarge and form an arciform or semilunar pattern. Lesions do advance, and can disappear and recur. The pathogenesis is unknown; however, the condition has been associated with a number of infectious agents, malignant tumors, and drugs.

Microscopic Features

Both superficial and deep patterns may be observed. In the superficial variant, there is a moderately dense infiltrate of lymphocytes and rarely eosinophils involving the superficial vascular plexus. Superficial erythema annulare centrifugum may be accompanied by slight epidermal changes of spongiosis, especially in biopsies from the leading edge of a lesion. In the deep variant, the inflammatory infiltrate involves both the superficial and deep vascular plexuses in the absence of epidermal change. In both the superficial and deep patterns of erythema annulare centrifugum, the inflammatory infiltrate is tightly cuffed around the vessels in a so-called 'coat-sleeve' distribution (Fig. 5.4). This histologic feature is quite characteristic but not diagnostic of erythema annulare centrifugum (Table 5.5).

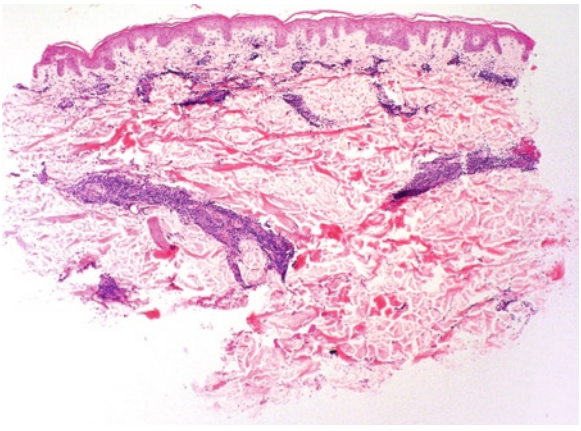

Fig. 5.4 *Erythema annulare centrifugum*. There is a superficial and deep perivascular lymphocytic infiltrate

Table 5.5 Key microscopic features: erythema annulare centrifugum/gyrate erythemas

- Superficial or superficial and deep perivascular pattern
- The superficial variant may show slight spongiosis and scale
- The deep variant generally lacks epidermal changes
- Coat-sleeve pattern of infiltrate

Differential Diagnosis

The differential diagnosis of superficial erythema annulare centrifugum includes pityriasis rosea (if spongiosis is evident) and arthropod bite or drug reaction (if eosinophils are observed). The differential diagnosis of deep erythema annulare centrifugum includes polymorphous light reaction, chronic urticaria, and drug reaction. These latter entities typically do not have the coat-sleeve pattern. However, recognition of erythema annulare centrifugum usually requires correlation with the clinical presentation, as the histologic features are somewhat nonspecific. See Table 5.6.

Table 5.6 Practical tips: erythema annulare centrifugum/gyrate erythemas (superficial and deep)

- In general, when the clinical description is that of an annular, scaly lesion, PAS stain is recommended to exclude a clinically unsuspected fungal infection
- The "coat-sleeve" or "cuffing" arrangement of lymphocytes around the vascular plexuses is characteristic of erythema annulare centrifugum but not entirely specific
- In general, obtaining levels may be quite helpful in examination of all lesions demonstrating a superficial perivascular lymphocytic infiltrate in the absence of epidermal change

Pigmented Purpuric Dermatosis (Schamberg's Disease)

Clinical Features

The pigmented purpuric dermatoses are a group of inflammatory skin diseases in which lymphocytic infiltrates around venules result in extravasated erythrocytes and hemosiderin deposition, manifesting clinically as purpuric macules, brown, or golden-brown patches. Depending on the color, size, and distribution of lesions, cases are classified into several types, including Schamberg's disease (the most common), purpura annulare telangiectoides or Majocchi's disease, lichenoid purpura of Gougerot and Blum, lichen aureus, and eczematoid-like purpura of Doucas and Kapetanakis. Schamberg's disease may occur in persons of any age, and clinically presents as irregular patches and plaques of orange-brown, cayenne pepper-like discoloration. The lesions are chronic and may persist for years. Gougerot and Blum mainly affects middle-aged men and is characterized by pigmented purpura with lichenoid change. Scaling and lichenification are also seen with eczematoid-like purpura. Lichen aureus and Majocchi's disease are usually seen in children or young adults. In lichen aureus, the eruption is usually a

solitary lesion or localized group of lesions that may affect any part of the body; the leg is most commonly involved. Majocchi's disease is characterized by small annular plaques of purpura that contain prominent telangiectasia.

Microscopic Features

The histologic differences between the clinical entities of the pigmented purpuric dermatoses lie in the number, pattern, and distribution of lymphocytes and number of siderophages. In Schamberg's disease and in purpura annulare telangiectoides or Majocchi's disease, there is usually a perivascular and interstitial lymphocytic infiltrate admixed with extravasated erythrocytes and/or siderophages (Fig. 5.5). There is no significant damage to the affected blood vessels that is evident on histologic examination (Fig. 5.6). The epidermis is usually unremarkable but may demonstrate slight spongiosis. In eczematoid-like purpura of Doucas and Kapetanakis, epidermal spongiosis is more extensive than in other variants. The infiltrate is band-like and heavy in lichen aureus (Fig. 5.7) and lichenoid purpura of Gougerot and Blum (Table 5.7 highlights key microscopic features of the pigmented purpuric dermatoses).

Differential Diagnosis

Because of the presence of hemorrhage, leukocytoclastic vasculitis is often considered in the differential diagnosis. However, in leukocytoclastic vasculitis, the inflammatory component is composed of neutrophils with associated leukocytoclasis and the vessels show fibrin deposition and sometimes frank necrosis (see Chap. 6). Stasis dermatitis may show evidence of hemorrhage, but the lobular proliferation of

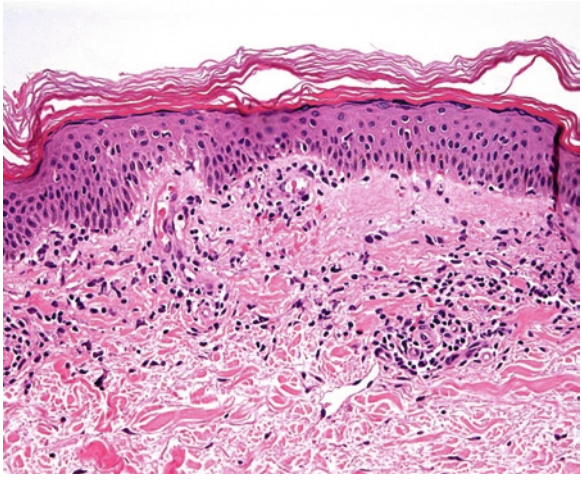

Fig. 5.5 *Schamberg's disease*. There is a superficial perivascular inflammatory infiltrate composed of lymphocytes and extravasated erythrocytes. The epidermis is unremarkable

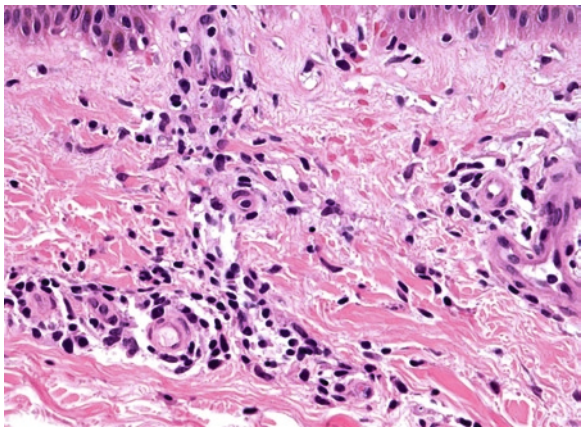

Fig. 5.6 *Schamberg's disease*. The infiltrate is composed of lymphocytes and extravasated erythrocytes. There is no overt vascular damage

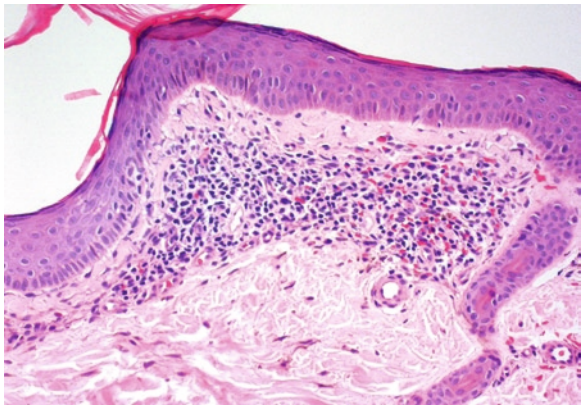

Fig. 5.7 *Lichen aureus*. In this form of pigmented purpuric dermatosis the infiltrate has a lichenoid pattern. Note the prominent erythrocyte extravasation

Table 5.7 Key microscopic features: pigmented purpuric dermatosis (Schamberg's disease)

- Superficial perivascular dermatitis with little epidermal change; occasionally may have some spongiosis
- Mild superficial lymphocytic infiltrate with extravasated erythrocytes and siderophages
- Occasionally may have a lichenoid infiltrate
- No fibrinoid necrosis

relatively thick-walled vessels in the superficial dermis distinguishes it from pigmented purpuric dermatosis (see Chap. 2). Lichenoid variants of pigmented purpuric dermatosis may show overlapping histologic features with purpuric mycosis fungoides. Both entities may demonstrate solitary lymphocytes in the lower half of the epidermis. However, edema of the papillary dermis and extravasated erythrocytes are more commonly found in the former. See Table 5.8.

Table 5.8 Practical tips: Schamberg's disease

- Early lesions of Schamberg's may demonstrate extravasated erythrocytes but no siderophages
- The absence of overt vascular damage helps distinguish pigmented purpuric dermatosis from leukocytoclastic vasculitis
- Epidermotropism of large, atypical lymphocytes and lack of extravasated erythrocytes favor mycosis fungoides over pigmented purpuric dermatosis

Urticaria

Clinical Features

Urticaria classically presents as transient (<24 h), erythematous plaques without scale (i.e., hives). In some cases, the lesions may be persistent.

Microscopic Features

The epidermis is unremarkable. The papillary dermis usually shows evidence of edema. The infiltrate may be primarily superficial or superficial and deep. In well-developed lesions, there is a mild perivascular and interstitial mixed infiltrate typically rich in eosinophils (Fig. 5.8). In contrast to arthropod bite reactions and Wells' syndrome, the infiltrate is typically sparse. As a result of the sparse nature of the infiltrate, the biopsy may superficially resemble normal skin on low power examination. Neutrophils and lymphocytes are often a component of the infiltrate (Fig. 5.8). Collections of neutrophils within vessel lumens may be a clue in some cases (Table 5.9). Chronic urticaria may be characterized by a nonspecific perivascular lymphocytic infiltrate.

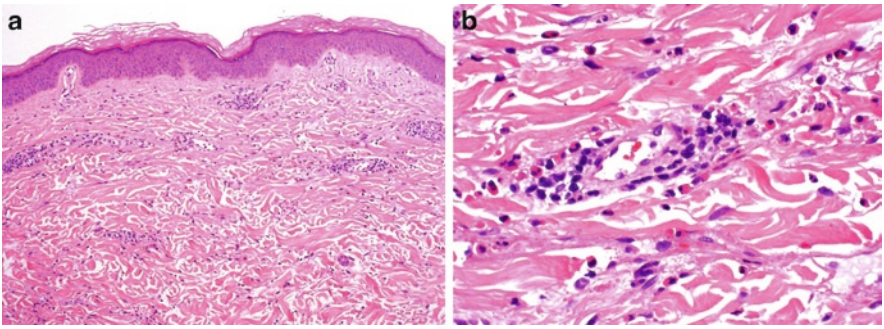

Fig. 5.8 *Urticaria*. (**a**) There is a slight superficial perivascular and interstitial inflammatory infiltrate with prominent eosinophils. Epidermal change is absent. (**b**) Eosinophils are typically conspicuous in urticaria, but admixed lymphocytes and neutrophils may also be present

Table 5.9 Key microscopic features: urticaria

- Epidermis is unremarkable
- Papillary dermal edema
- Infiltrate may be superficial, or superficial and deep
- In contrast to arthropod bite and Wells' syndrome, the infiltrate is typically sparse
- Neutrophils and lymphocytes are often a component of the infiltrate
- Collections of neutrophils within vessel lumens is a helpful clue to the diagnosis

Differential Diagnosis

The differential diagnosis of urticaria includes other hypersensitivity reactions such as drug eruptions and arthropod bite reactions, as previously described above. It is generally not possible to distinguish urticaria unequivocally from other forms of hypersensitivity reactions (see below). Mastocytosis is in the histologic differential diagnosis. Recognition of increased mast cells allows distinction, which is discussed in detail below. It is important to remember that in urticaria the inflammatory infiltrate may be quite sparse on scanning magnification prompting misinterpretation as normal skin. Recognition of the mixed nature of the infiltrate and presence of intravascular neutrophils aid in establishing the diagnosis. Clinical correlation may be needed (see Table 5.10).

Table 5.10 Practical tips: urticaria

- An unequivocal diagnosis of urticaria is not possible in the absence of good clinical information
- The infiltrate is usually mild in nature, such that at first glance the biopsy may superficially resemble normal skin on low power examination
- If a dense mixed infiltrate is present, consider entities such as arthropod bite reaction
- "Dermal hypersensitivity reaction" is a useful nonspecific histologic term used to encompass a number of clinical disorders including urticaria, arthropod bite reaction, or drug eruption

Cutaneous Mastocytosis

Clinical Features

Cutaneous mastocytosis manifests in a variety of ways. The most common is urticaria pigmentosa, accounting for approximately 80% of cases. Urticaria pigmentosa usually presents within the first 4 years of life and resolves by puberty. The risk of systemic disease is low in this setting unless the initial presentation is in adulthood. Cases occurring in adults tend to persist and approximately 40% develop systemic disease. The typical clinical presentation is a generalized eruption of red-brown macules that urticate on stroking (Darier's sign).

Telangiectasia macularis eruptiva perstans (TMEP) primarily occurs in adults and presents as erythematous macules with telangiectasia on the trunk and proximal extremities. Systemic involvement is common in this form of mastocytosis.

Mastocytoma is the solitary tumor form of mastocytosis. It typically presents in children as an orange-yellow nodule. Most involute spontaneously.

Systemic mastocytosis, as mentioned above, develops in adult patients with urticaria pigmentosa or TMEP. Besides the skin, the bone marrow is most frequently involved. Bone marrow involvement may progress to mast cell leukemia.

Microscopic Features

The histologic features are similar across all subtypes of mastocytosis with minor variation. In urticaria pigmentosa, there is usually a moderately dense superficial perivascular infiltrate of mast cells (Fig. 5.9). In TMEP, the infiltrate is typically sparser (Fig. 5.10). In mastocytoma, the infiltrate is quite dense with sheets of mast cells (Fig. 5.11). Scattered eosinophils and lymphocytes are usually present (Table 5.11).

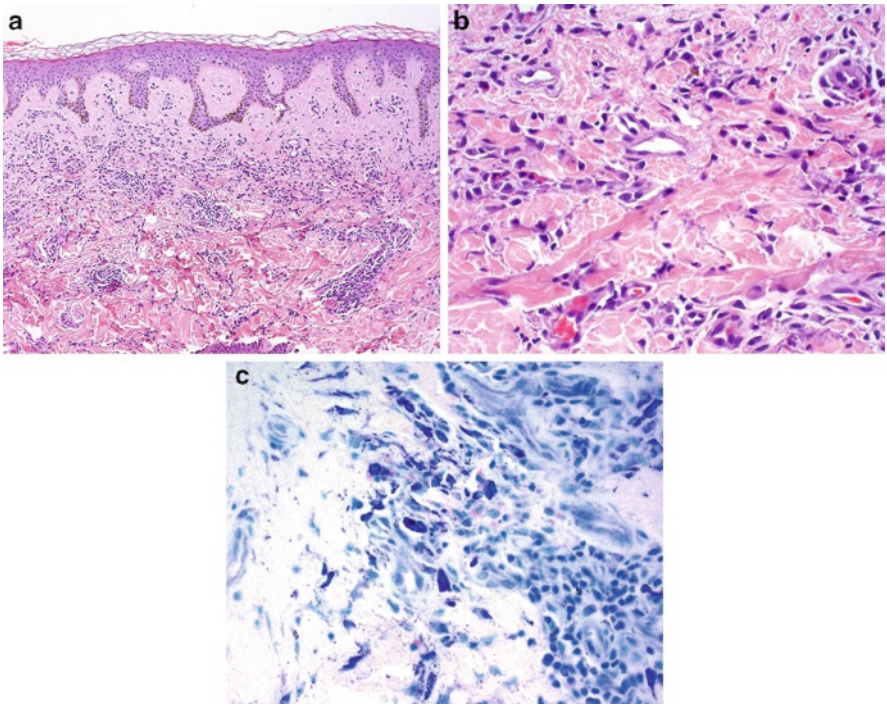

Fig. 5.9 *Urticaria pigmentosa*. (**a**) Within the dermis there is a moderate superficial to mid-dermal perivascular and interstitial inflammatory infiltrate composed of and mast cells admixed with lymphocytes and eosinophils. (**b**) The mast cells in the dermis have amphophilic to basophilic cytoplasm. Occasional eosinophils are typically present. (**c**) A Giemsa stain highlights the metachromatic granules in the mast cells

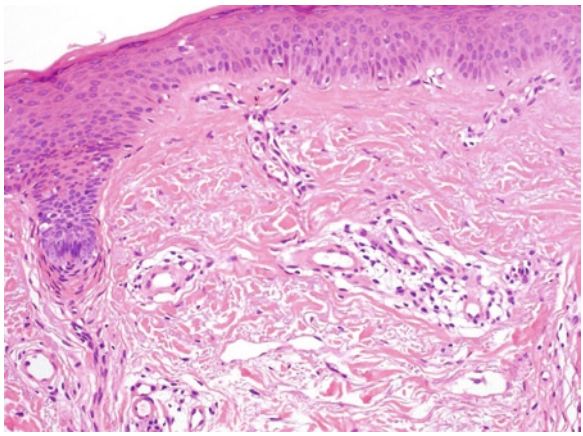

Fig. 5.10 *Telangiectasia macularis perstans eruptiva (TMEP)*. In TMEP the mast cell infiltrate is typically sparse and subtle

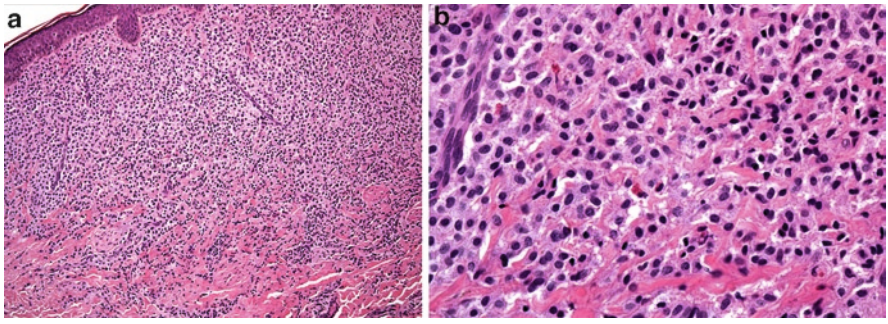

Fig. 5.11 *Cutaneous mastocytoma*. (**a**) Mastocytoma is characterized by sheets of mast cells in the dermis. No epidermal changes are evident. (**b**) In mastocytoma, the characteristic granular, amphophilic cytoplasm of the mast cells is more easily recognized on routine histologic examination. Occasional eosinophils are typically present

Table 5.11 Key microscopic features: cutaneous mastocytosis

- In urticaria pigmentosa, there is a moderately dense superficial perivascular infiltrate of mast cells. Eosinophils may be present and are a useful clue
- In telangiectasia macularis eruptiva perstans (TMEP), the mast cell infiltrate is typically sparse
- Cutaneous mastocytoma is characterized by a dense infiltrate with sheets of mast cells

Differential Diagnosis

Mastocytosis can sometimes be confused with drug eruptions if eosinophils are present as discussed above. Viral exanthems and nonspecific perivascular lymphoid infiltrates are also in the differential diagnosis of urticaria pigmentosa and TMEP. Mastocytoma can be confused with intradermal nevi and rarely cutaneous lymphoma. Essential to the diagnosis of mastocytosis is the recognition of the

mononuclear cells in the infiltrate as mast cells. Special stains such as Giemsa, toluidine blue or Leder stain highlight mast cells. Immunostains for tryptase and CD117 are also effective and more sensitive. In some cases of urticaria pigmentosa or TMEP, the question may arise as to just how many mast cells are too many mast cells? As a general rule of thumb, the possibility of mastocytosis should be considered if there are >15 mast cells in a single high power field (see Table 5.12).

Table 5.12 Practical tips: cutaneous mastocytosis

- How many mast cells are too many? A rule of thumb: >15 mast cells per HPF suggest mastocytosis
- In cases of TMEP, the infiltrate tends to be mild and it can be difficult to distinguish from normal skin. In some cases of TMEP, the quantitative mast cell count is around the upper limit of normal. A biopsy of normal skin for comparison purposes may be helpful. See sample reports
- If one is unsure of the clinical presentation a diagnosis of " cutaneous mastocytosis" is sufficient

Polymorphous Light Eruption

Clinical Features

Polymorphous light eruption (PMLE), or PMLE as it is often referred to, represents an idiopathic response to ultraviolet light. The eruption is characterized by pruritic papules, papulovesicles, and urticarial plaques involving sun-exposed skin. Characteristically, the history is appearance of these lesions 30–45 min to several days after exposure to either sun or ultraviolet light.

Microscopic Features

The histologic features are somewhat protean. Usually, there is a superficial and deep dermal perivascular dermal infiltrate composed predominantly of lymphocytes (Fig. 5.12). Prominent subepidermal edema is a helpful clue to the diagnosis, but is not entirely specific (Table 5.13). Eosinophils are only rarely observed.

Differential Diagnosis

The differential diagnosis of PMLE includes the gyrate erythemas, arthropod bite reaction, and connective tissue disease (lupus erythematosus). Gyrate erythemas, like erythema annulare centrifugum, usually do not have prominent edema. PMLE lacks the interface alteration and dermal mucin deposition

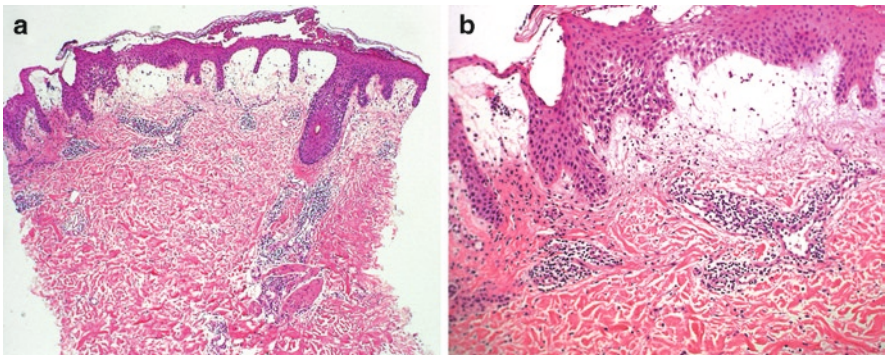

Fig. 5.12 *Polymorphous light eruption*. (**a**) Superficial and deep perivascular lymphocytic infiltrate. Papillary edema is observed even at lower magnification. (**b**) Striking papillary dermal edema is a useful clue to the diagnosis of polymorphous light eruption

Table 5.13 Key microscopic features: polymorphous light eruption

- On low power, the infiltrate shows a gradual tapering with a predominance of lymphocytes
- Prominent subepidermal edema
- Occasional extravasated erythrocytes may be seen
- Epidermal alterations may be present including spongiosis and focal necrotic keratinocytes

characteristic of connective tissue disease (see Table 5.14). Arthropod bite reactions typically have eosinophils as a prominent component of the infiltrate, whereas they are usually absent in PMLE. Ultimately, the recognition of PMLE is highly dependent on clinical presentation.

Table 5.14 Practical tips: polymorphous light eruption

- The clinical presentation of a pruritic eruption presenting in spring or early summer is a helpful clue to the diagnosis
- The main differential diagnosis in polymorphous light eruption is acute and chronic lupus erythematosus
- Acute lupus erythematosus demonstrates marked mucinosis and neutrophilic debris along the dermal/epidermal junction with attenuation of the epidermis
- Chronic lupus erythematosus typically shows basement membrane zone thickening with epidermal atrophy

Perniosis (Chilblains)

Clinical Features

Perniosis typically presents during cold damp weather, usually at the beginning of or at the end of winter. Patients present with painful erythematous nodules on the fingers and/or toes. The lesions can develop blisters and even ulcerate. This is considered a form of lymphocytic vasculitis, though frank vascular necrosis is not a typical feature.

Microscopic Features

On low power, the epidermis is usually unremarkable, but occasional cases show focal interface change. Frequently, there is papillary dermal edema. Within the dermis, there is a superficial and deep perivascular and peri-eccrine lymphocytic infiltrate (Fig. 5.13). The vessels often display what has been termed "fluffy edema" of the vessel walls (Fig. 5.14), but this feature is not invariable (Table 5.15).

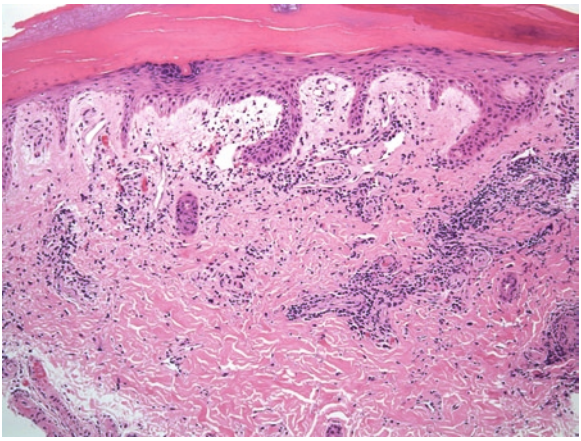

Fig. 5.13 *Perniosis* is characterized by a superficial and deep perivascular and peri-eccrine lymphocytic infiltrate involving the acral skin of fingers or toes. Papillary dermal edema is often present

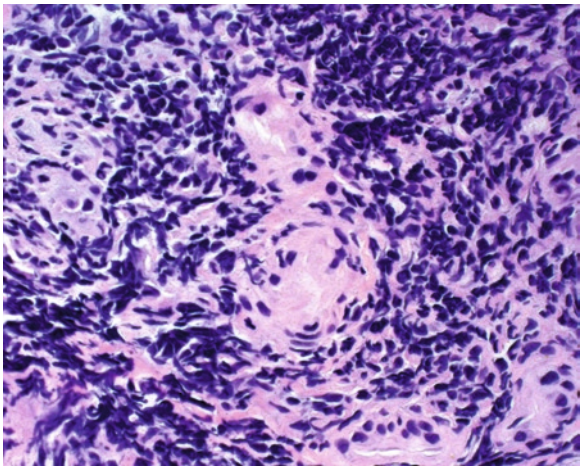

Fig. 5.14 *Lymphocytic vasculitis of perniosis*. In perniosis there may be histologic evidence of a true lymphocytic vasculitis with fluffy edema of the affected vessel

Table 5.15 Key microscopic features: perniosis

- Epidermis usually unremarkable (may have focal interface change)
- Papillary dermal edema common
- Superficial and deep perivascular lymphocytic infiltrate
- Lymphocytic vasculitis
- Fluffy edema of vessel walls
- Peri-eccrine infiltrate

Differential Diagnosis

The differential diagnosis includes other entities characterized by a superficial and deep perivascular lymphocytic infiltrate. Histologically, polymorphous light eruption could be considered, but the clinical presentation on the digits, especially toes, is not characteristic of polymorphous light eruption. Polymorphous light eruption also does not have the vascular changes that can be seen in perniosis. There is a form of lupus erythematosus, called chilblains lupus, that is essentially indistinguishable from the idiopathic form of perniosis. Interface change, when present, favors chilblains lupus. Distinction between these two entities ultimately rests with the clinician (Table 5.16).

Table 5.16 Practical tips: perniosis

- Idiopathic perniosis and the chilblains lupus may be histologically indistinguishable, requiring appropriate serologic studies
- Perniosis is considered to be the most common entity which exhibits a true "lymphocytic vasculitis" in which lymphocytes surround or infiltrate vessels, but frank necrosis is not seen
- Seasonal: seen in cold damp weather at the beginning and end of winter

Lymphomatoid Papulosis

The current WHO-EORTC classification includes lymphomatoid papulosis as a CD30+ lymphoproliferative disorder along with cutaneous anaplastic large cell lymphoma. The CD30+ lymphoproliferative disorders represent a biologic and histologic spectrum with lymphomatoid papulosis (a recurrent self-healing eruption) at one end and primary cutaneous anaplastic large cell lymphoma (an indolent CD30+ lymphoma) on the other. In between are borderline cases with overlapping features between the two entities.

Clinical Features

Lymphomatoid papulosis is characterized by a recurrent eruption of papulonecrotic lesions, which typically follow a benign course despite atypical histologic features. Lesions are generally asymptomatic, have a predilection for trunk and extremities, and tend to be less than 1 cm. All ages can be affected, including children, but the peak incidence is in the fifth decade. Approximately 10% of the patients may subsequently develop lymphoma (mycosis fungoides, anaplastic CD30+ lymphoma, and Hodgkin's disease).

Microscopic Features

Lymphomatoid papulosis is characterized by a superficial and deep perivascular and interstitial mononuclear cell infiltrate with atypical lymphocytes (Fig. 5.15). Three morphologic subtypes have been described. The vast majority of cases are type A with large atypical lymphocytes in a mixed background of neutrophils, eosinophils, histiocytes, and small lymphocytes (Fig. 5.16). Type B lesions, the rarest subtype, are composed of small to medium sized cerebriform cells that may demonstrate epidermotropism (mycosis fungoides-like). The so-called type C lesion shows nodules of large atypical lymphocytes cells and is histologically indistinguishable from CD30+ anaplastic large cell lymphoma (ALCL) (See below). The large atypical lymphocytes of lymphomatoid papulosis are positive for CD30 (Fig. 5.17), (Table 5.17). Immunoreactivity

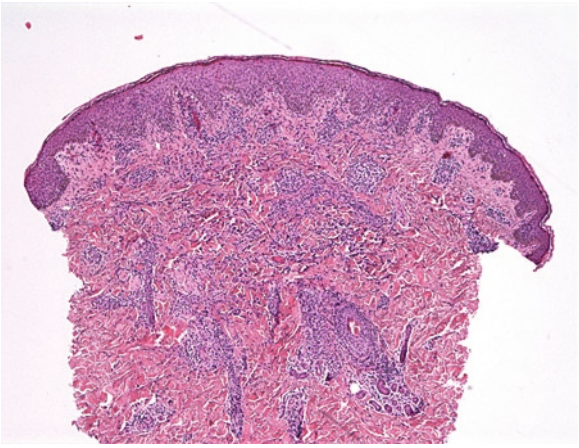

Fig. 5.15 *Lymphomatoid papulosis*. On low power examination there is usually a superficial and deep infiltrate in a wedge-shaped configuration

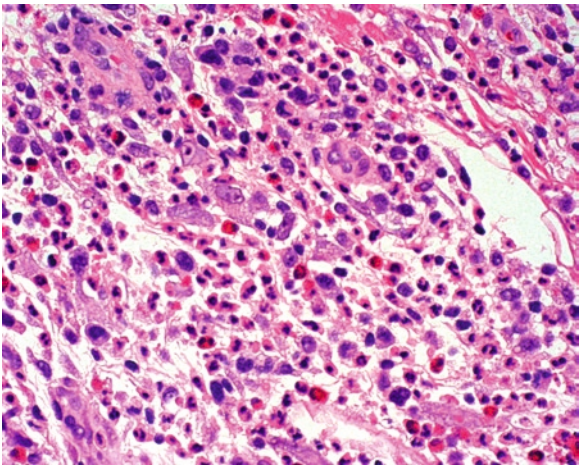

Fig. 5.16 *Lymphomatoid papulosis type A*. The atypical lymphocytes have enlarged pleomorphic nuclei and prominent nucleoli. There is a background of reactive lymphocytes, eosinophils and neutrophils

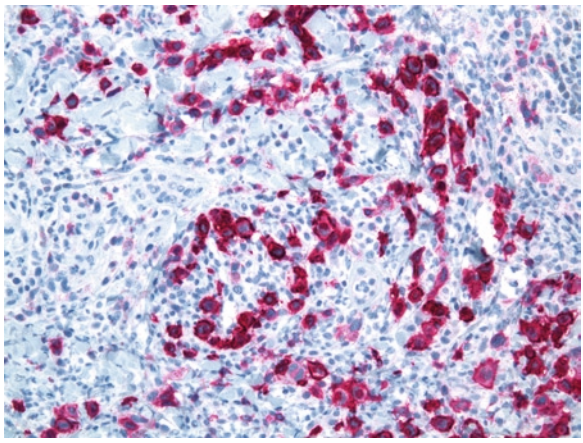

Fig. 5.17 The atypical cells of lymphomatoid papulosis are characteristically immunoreactive for CD30 and T-cell markers

Table 5.17 Key microscopic features: lymphomatoid papulosis

- Superficial and deep perivascular and interstitial mononuclear cell infiltrate with large, atypical lymphocytes
- Atypical lymphocytes are CD30+

for CD4 is more common than immunoreactivity for CD8. TIA-1 and/or granzyme-B are expressed in 74–100% of cases. It should be emphasized that the histologic subtypes are clinically and prognostically irrelevant and CD30+ large cells may be absent in very early lesions, resolving lesions, and type B lymphomatoid papulosis.

Differential Diagnosis

Reactive lymphoid proliferations (arthropod bite, scabies, and drug eruptions) may contain atypical cells, some of which may be CD30+. An eosinophil-rich infiltrate, without neutrophils, favors an arthropod bite reaction. Pityriasis lichenoides demonstrates single necrotic keratinocytes and lacks large CD30+ cells (see Chap. 4). Mycosis fungoides may be indistinguishable from type B lymphomatoid papulosis. Distinction between mycosis fungoides and type B lymphomatoid papulosis depends on knowledge of the lesions clinically presenting as waxing and waning papules rather than persistent plaques. Mycosis fungoides is discussed in more detail in Chap. 2. Type C lymphomatoid papulosis is histologically indistinguishable from anaplastic large cell lymphoma, though invasion of the subcutis favors the latter. Clinical correlation is paramount in establishing the diagnosis (see below) (Table 5.18).

Table 5.18 Practical tips: lymphomatoid papulosis

- A helpful clinical clue is to remember that the "papulonecrotic" differential diagnosis by dermatologists includes pityriasis lichenoides, arthropod bite reaction, and lymphomatoid papulosis
- Clinical correlation is paramount for the correct diagnosis
- Often best signed out as "CD30+ lymphoproliferative disorder, see comment" (see sample report)
- Be aware of mimics in the differential diagnosis! (arthropod bite reactions, ruptured cysts, various infections, and infestations/scabies)
- Three histologic subtypes have been described; however, they are clinically and prognostically irrelevant

Anaplastic Large Cell Lymphoma

Although a truly in-depth discussion is beyond the scope of this text, a brief description will be provided given its overlap with lymphomatoid papulosis.

Clinical Features

Anaplastic large cell lymphoma can present at any age with one or multiple, often ulcerated nodules. If multiple lesions are present, they usually have a regional distribution rather than the diffuse nature of lymphomatoid papulosis. Anaplastic large cell lymphoma may present in three ways. Primary cutaneous anaplastic large cell lymphoma, in which greater than 75% of tumor cells express CD30 antigen, is the more indolent form and patients have an excellent prognosis. Anaplastic large cell lymphoma may arise in association with pre-existing mycosis fungoides or lymphomatoid papulosis. Large cell transformation of mycosis fungoides carries a poor prognosis (5-year survival of 11–19%). Finally, there may be cutaneous involvement from a nodal-based CD30+ anaplastic large cell lymphoma. Immunoreactivity for ALK-1 and EMA indicate a high likelihood of a secondary cutaneous involvement by an underlying nodal lymphoma.

Microscopic Features

The histology is similar to that described above for lymphomatoid papulosis. Atypical lymphocytes with marked anaplasia are present in sheets or large clusters (Fig. 5.18). The infiltrate is dense and diffuse, and often extends into the subcutaneous tissue. There may be a brisk admixture of neutrophils and/or eosinophils. Epidermal ulceration is present in 30–50% of cases; epidermotropism is typically absent, except in cases of transformed mycosis fungoides.

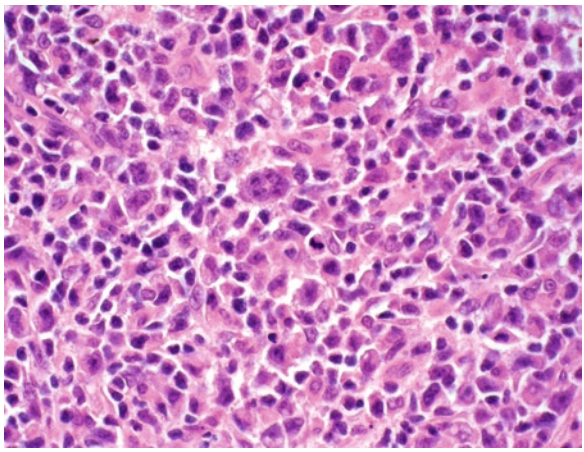

Fig. 5.18 *Cutaneous anaplastic large cell lymphoma*. The tumor cells resemble the atypical lymphocytes of nodal anaplastic large cell lymphoma and lymphomatoid papulosis. There is marked nuclear atypia and the tumor cells have vesicular nuclei with prominent nucleoli

Pseudoepitheliomatous epidermal hyperplasia may be so marked that it mimics carcinoma.

By immunohistochemistry, the large, atypical cells are similar to the cells of lymphomatoid papulosis. They are positive for CD30 and most are positive for CD4 rather than CD8. In a minority of cases, the tumor cells are positive for EMA (~30%) and rarely positive for CD15 (<10%). ALK-1 expression is associated with underlying systemic disease.

Differential Diagnosis

The major differential diagnosis includes lymphomatoid papulosis or cutaneous involvement by nodal anaplastic large cell lymphoma. As described above, knowledge of the clinical presentation is critical for distinction. Without such knowledge, a descriptive diagnosis of "atypical CD30+ lymphoproliferative disorder" can be used (see sample reports). Other entities to be excluded include non-lymphoid malignant tumors such as melanoma and carcinoma.

Arthropod Bite Reaction

Clinical Features

Arthropod bite reactions have a variable clinical appearance. Typically, patients present with pruritic, excoriated papules, and vesicles. Often, the clinical diagnosis is "papular urticaria." Lesions may be papulonecrotic in nature, prompting a clinical differential diagnosis of pityriasis lichenoides or lymphomatoid papulosis.

Microscopic Features

The infiltrate is eosinophil-rich, is often wedge-shaped, and frequently extends into the subcutis (Fig. 5.19). The punctum, or point at which the stinger enters the skin, is manifested pathologically by an intraepidermal spongiotic vesicle. However, the epidermal changes are quite variable. A spongiotic vesicle is typically present only in recent lesions, and recent lesions are rarely biopsied. In older lesions, the epidermis can show features similar to subacute or chronic spongiotic dermatitis or, as often the case, be relatively normal. The inflammatory infiltrate is often quite brisk and is composed of lymphocytes, histiocytes, and eosinophils. Eosinophils are often quite prominent (Fig. 5.20). Older lesions may be predominantly composed of lymphocytes with less conspicuous eosinophils (see Table 5.19 for summary of key microscopic features).

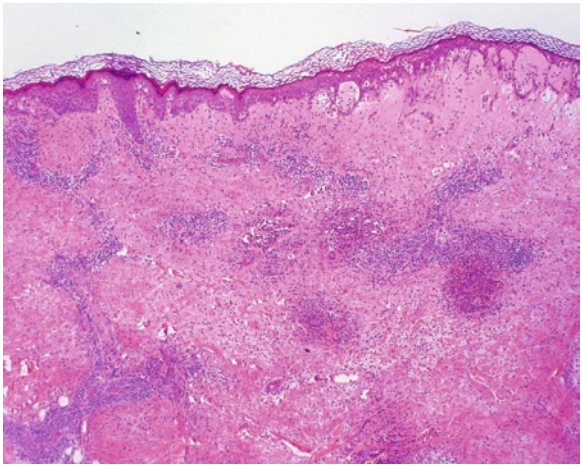

Fig. 5.19 *Arthropod bite reaction*. Arthropod bite reactions often have a brisk, superficial and deep perivascular wedge-shaped infiltrate with numerous eosinophils

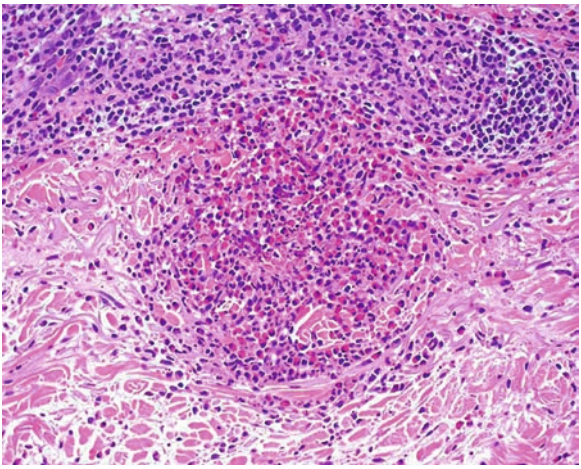

Fig. 5.20 *Arthropod bite reaction*. The prominent eosinophils are evident in this higher power image

Table 5.19 Key microscopic features: arthropod bite reaction

- Eosinophil-rich, often wedge-shaped infiltrate that may extend into the subcutis
- An intraepidermal spongiotic vesicle may be present at the point of the punctum (early lesions)
- Late lesions are more commonly biopsied than early lesions; epidermis often unremarkable
- Flame figures may be seen in arthropod bite reactions (or any eosinophil-rich dermatitis) and are not diagnostic of Wells' syndrome

Differential Diagnosis

Distinguishing histologic features of pityriasis lichenoides and lymphomatoid papulosis are discussed previously. Eosinophilic cellulitis (Wells' syndrome) is a condition characterized clinically by large erythematous plaques on the trunk or extremities, and histologically by a dense diffuse infiltrate of eosinophils with flame figures (degranulated eosinophils). Since the original description of this disorder, flame figures have been described in a number of eosinophil-rich processes including drug eruptions, bullous pemphigoid, and Churg–Strauss syndrome. Most authorities now believe Wells' is not an authentic disease as much as an exaggerated hypersensitivity response. In general, arthropod bites are not uncommonly biopsied and the presence of an eosinophil-rich dermal infiltrate should prompt consideration of the diagnosis (Table 5.20). Finally, as noted earlier, be aware that enlarged CD30 positive lymphocytes may be observed in bite reactions, prompting consideration of lymphomatoid papulosis. Clinical history may be of value in these cases.

Table 5.20 Practical tips: arthropod bite reaction

- Relatively commonly biopsied
- Infiltrate usually moderate to dense
- Numerous eosinophils: think arthropod bite reaction
  - Exception: flea bites may have a prominent neutrophilic component
- CD 30+ cells may be seen in arthropod bite reactions, prompting consideration of LYP (see above discussion)
- Patients with underlying chronic lymphocytic leukemia can have exaggerated reactions to arthropod bites
- Eosinophils may be less conspicuous in older lesions

Dermal Hypersensitivity Reaction

In many cases, arthropod bite reactions and other entities with a mixed infiltrate of lymphocytes and eosinophils fall into the general category of dermal hypersensitivity reaction. This is a nonspecific histologic term used to encompass a number of clinical disorders including arthropod bite reaction, urticaria, or drug eruption. They all share histologic features of a perivascular infiltrate of lymphocytes and eosinophils of varying intensity with minimal if any, epidermal alteration. In cases without a good

clinical history, or in which histologic distinction is not possible even with history, it is acceptable to use this generic diagnostic terminology. See sample reports.

Sample Reports: Morbilliform Drug Eruption

Example 1:

Clinical history: Erythematous papular eruption involving upper and lower extremities. Rule out drug eruption.

Diagnosis: Superficial perivascular dermatitis consistent with drug eruption, see comment.

Comment: The epidermis is relatively unremarkable. Within the dermis, there is a mild superficial perivascular predominately lymphocytic inflammatory infiltrate admixed with some eosinophils. The histologic features are consistent with a drug eruption in the appropriate clinical context. Other forms of dermal hypersensitivity reactions could also be considered. Clinical correlation is recommended.

Example 2:

Clinical history: Erythematous papular eruption involving upper and lower extremities.

Diagnosis: Superficial perivascular dermatitis, see comment.

Comment: The epidermis is relatively unremarkable. Within the dermis, there is a mild superficial, perivascular, and predominately lymphocytic inflammatory infiltrate admixed with some eosinophils. The histologic features are relatively nonspecific. The differential diagnosis includes dermal hypersensitivity reactions such as a drug eruption and urticaria. An arthropod bite reaction is less likely given the mild nature of the infiltrate. Clinical correlation is recommended.

Sample Report: Erythema Annulare Centrifugum

Clinical history: Annular, slightly scaly lesions on the trunk.

Diagnosis: Superficial perivascular dermatitis with lymphocyte cuffing, see comment.

Comment: There is very focal parakeratosis of the stratum corneum. In the subjacent dermis, there is a prominent sleeve-like cuff of lymphocytes around superficial to mid-dermal vessels. A PAS stain is negative for fungal organisms. This histologic pattern is compatible with a superficial gyrate erythema (erythema annulare centrifugum). Clinical correlation is recommended.

Sample Report: Pigmented Purpuric Dermatoses

Clinical history: Purpuric eruption on the lower extremities. Rule out vasculitis.
Diagnosis: Superficial perivascular dermatitis with extravasated erythrocytes, see comment.
Comment: There is a superficial perivascular lymphocytic infiltrate accompanied by foci of extravasated erythrocytes and hemosiderin-laden melanophages. The findings are most compatible with pigmented purpuric dermatosis (Schamberg's disease). Diagnostic features of a necrotizing vasculitis are not observed.

Sample Report: Urticaria

Clinical history: Erythematous papules and plaques.
Diagnosis: Superficial perivascular dermatitis with eosinophils consistent with dermal hypersensitivity reaction, see comment.
Comment: The papillary dermis is edematous. There is a mild perivascular infiltrate of lymphocytes and relatively numerous eosinophils. There are collections of neutrophils with vessel lumens, but no vasculitis is seen. The histologic features are consistent with a dermal hypersensitivity reaction such as urticaria. Other forms of dermal hypersensitivity reactions such as a drug eruption could be considered. Clinical correlation is recommended.
Note to reader: If the clinician specifically suggests urticaria, the top line diagnosis can reflect that the findings are consistent with the clinical diagnosis.

Sample Report: Mastocytosis

Example 1: Urticaria pigmentosa.
Clinical history: Child with generalized eruption of red–brown macules which urticate on stroking (positive Darier's sign).
Skin, punch biopsy: Cutaneous mastocytosis, see comment.
Comment: There is a moderately dense superficial perivascular infiltrate of monomorphous cells with cuboidal nuclei and abundant cytoplasm. By immunohistochemistry, the cells are strongly positive for CD117. Given the clinical presentation, the findings are most compatible with urticaria pigmentosa. Clinical correlation is recommended.

Example 2: TMEP.
Clinical history: Erythematous macules with telangiectasia.
Diagnosis: Superficial perivascular mononuclear cell infiltrate, see comment.
Comment: Within the dermis, there is a mild superficial perivascular mononuclear cell infiltrate. An immunostain for tryptase demonstrates that the majority of the infiltrate is composed of mast cells that number from 10 to 15 per HPF. Quantitatively, the mast cells are at the upper limit of normal, but could be compatible with mild mastocytosis/TMEP in the appropriate clinical context. A biopsy of adjacent normal skin for comparative purposes may be helpful.

Sample Report: Polymorphous Light Eruption

Clinical history: Erythematous papules and plaques on the chest of an adult female.
Diagnosis: Superficial and deep perivascular dermatitis with marked papillary dermal edema, see comment.
Comment: There is a brisk, superficial, and deep perivascular lymphocytic inflammatory infiltrate accompanied by prominent subepidermal edema. Slight spongiosis is noted, but no interface alteration is observed. The findings are most compatible with polymorphous light eruption. Lack of interface alteration and mucin deposition speaks against the diagnosis of lupus erythematosus, and the lack of significant numbers of eosinophils makes an arthropod bite reaction less likely. Clinical correlation is recommended.

Sample Report: Perniosis (Chilblains)

Clinical history: A 24-year-old woman with painful violaceous nodules on toes.
Diagnosis: Superficial and deep perivascular dermatitis, see comment.
Comment: There is prominent hyperorthokeratosis consistent with acral surface. In the underlying dermis, there is a brisk superficial and deep perivascular and focal peri-eccrine lymphocytic infiltrate. Mild papillary dermal edema is noted as are foci of extravasated erythrocytes. The clinical presentation together with the histologic features is consistent with perniosis. Chilblains lupus may be histologically indistinguishable from idiopathic perniosis. Clinical correlation, including appropriate serologic studies, is recommended.

Sample Report: Lymphomatoid Papulosis

Clinical history: A 24-year-old woman presents with a recurrent, papular eruption.
Diagnosis: Atypical CD30+ lymphoproliferative process, see comment.
Comment: There is a superficial and deep, perivascular and interstitial mononuclear cell infiltrate composed of scattered CD30+ large, atypical lymphocytes in a mixed background of neutrophils, eosinophils, and a small population of CD3+ lymphocytes. Occasional miotic figures are noted. The overlying epidermis is acanthotic with a small central focus of ulceration. No epidermotropism is observed. Given the clinical presentation of a recurrent papular eruption, the findings favor lymphomatoid papulosis. However, the differential diagnosis includes anaplastic large cell lymphoma, which may be histologically indistinguishable from some forms of lymphomatoid papulosis. Definitive diagnosis requires clinical correlation.

Sample Report: Arthropod Bite Reaction

Clinical history: Erythematous papules.
Diagnosis: Superficial and deep mixed infiltrate with numerous eosinophils, see comment.
Comment: The epidermis is unremarkable. There is a moderately brisk superficial perivascular mixed inflammatory infiltrate composed of lymphocytes and eosinophils. These findings are compatible with a dermal hypersensitivity reaction. The intensity of the infiltrate and numerous eosinophils suggest the possibility of an arthropod bite reaction. The histologic differential diagnosis includes other hypersensitivity reactions including a drug eruption. Clinical correlation is recommended.

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Chapter 6
Vasculitis and Thrombotic Disorders

Keywords Leukocytoclastic vasculitis • Henoch–Schönlein purpura • Urticarial vasculitis • Wegener's granulomatosis • Churg–Strauss syndrome • Polyarteritis nodosa • Cryoglobulinemia • Coumadin necrosis • Atrophie blanche • Antiphospholipid antibody syndrome • Cholesterol emboli

This chapter will focus on different forms of leukocytoclastic vasculitis and cutaneous diseases that are the result of vascular occlusion. There are a group of entities that some consider lymphocytic vasculitides (e.g., pigmented purpuric dermatosis and perniosis), but histologic evidence of vascular damage is often subtle in entities considered lymphocytic vasculitides and some dermatopathologists do not consider them a true vasculitis. Therefore, that group of entities will not be discussed in this chapter, but some entities considered to represent lymphocytic vasculitis are discussed in the chapter on perivascular dermatitis. This first part of the chapter will focus on entities that are the result of different forms of leukocytoclastic vasculitis. Leukocytoclastic vasculitis in many respects is a reaction pattern with a perivascular infiltrate of neutrophils and evidence of vascular damage (Fig. 6.1). The second part of the chapter will discuss disease processes that occlude vessels resulting in ischemic damage, but are not associated with significant inflammation (Fig. 6.2).

Leukocytoclastic Vasculitis (Cutaneous Leukocytoclastic Angiitis)

Clinical Features

Leukocytoclastic vasculitis most commonly affects middle-aged adults, but a broad age range may be seen. The lesions present as palpable purpura usually on the lower extremities. This entity is also referred to as hypersensitivity or allergic vasculitis. The most common triggering agents are drugs or infections.

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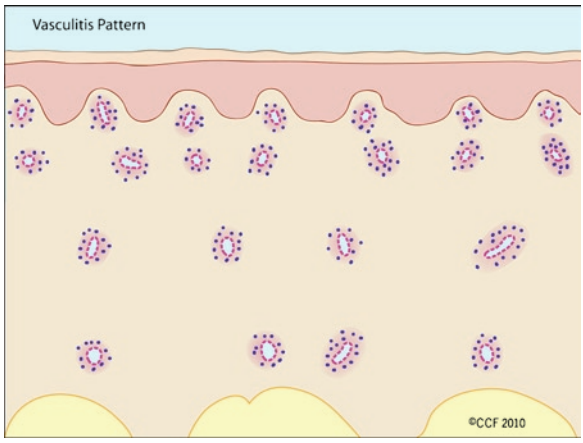

Fig. 6.1 *Schematic representation of leukocytoclastic vasculitis*. Leukocytoclastic vasculitis is characterized by a perivascular infiltrate of neutrophils with evidence of vascular damage

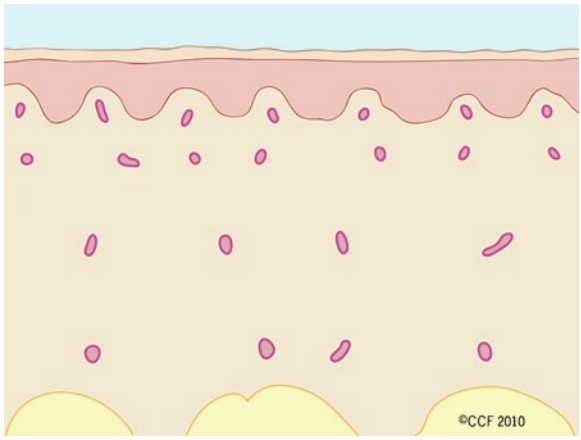

Fig. 6.2 *Schematic representation of vaso-occlusive disease*. There is thrombosis of blood vessels with little to no inflammation

Microscopic Features

The superficial vascular plexus has a perivascular infiltrate of neutrophils with fragmentation of the neutrophils resulting in nuclear dust (leukocytoclasis), extravasation of erythrocytes, and fibrin deposition in the vessel wall with or without overt fibrinoid necrosis of the blood vessels (Fig. 6.3). In reality, all of these features are not necessarily present. The histologic features are dependent on the timing of the biopsy. Early in the course, there may be a perivascular neutrophilic infiltrate with extravasation of erythrocytes, but no evident fibrin deposition or fibrinoid necrosis. Ideally, the biopsy will be from a lesion that is 24 h old. Lesions at this stage will typically demonstrate diagnostic features. After 48 h, the infiltrate is largely composed of lymphocytes. In such cases, the vessels need to be scruti-

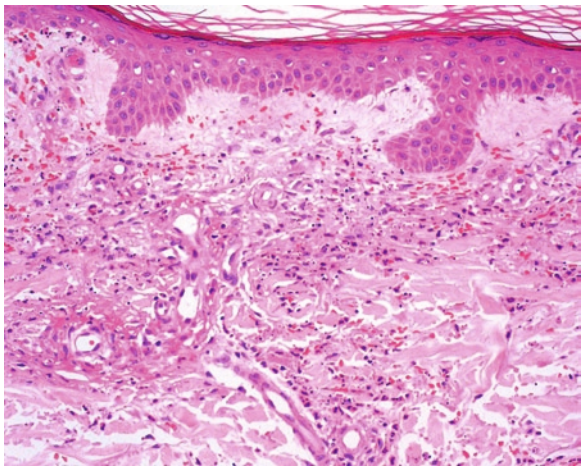

Fig. 6.3 *Leukocytoclastic vasculitis*. There is a perivascular infiltrate of neutrophils with associated leukocytoclasis, hemorrhage and fibrin deposition in the vascular walls

Table 6.1 Key microscopic features: leukocytoclastic vasculitis

- Perivascular infiltrate of neutrophils
- Fragmented nuclear debris (leukocytoclasis)
- Extravasation of erythrocytes
- Fibrin deposition in vessel walls
- Variable fibrinoid necrosis of blood vessels

nized closely for evidence of injury. Direct immunofluorescence (DIF) is often performed in the evaluation of leukocytoclastic vasculitis, mostly in the setting of possible Henoch–Schönlein purpura (HSP) (see below). In hypersensitivity type leukocytoclastic vasculitis, DIF usually demonstrates perivascular deposits of complement C3 and fibrinogen without IgA deposition. Microscopic features of leukocytoclastic vasculitis are summarized in Table 6.1.

Differential Diagnosis

The primary differential diagnosis is other, more specific forms of leukocytoclastic vasculitis that will be discussed in greater detail below. For example, HSP is histologically indistinguishable from leukocytoclastic vasculitis/cutaneous leukocytoclastic angiitis. Distinction requires DIF (see below). Systemic forms of leukocytoclastic vasculitis (e.g., Wegener's granulomatosis) tend to affect vessels in the deeper dermis as well as the superficial dermis, but may show significant overlap and be practically indistinguishable if other differentiating features are not present, such as palisading granulomatous inflammation or true granulomatous vasculitis. Changes of leukocytoclastic vasculitis may be seen as a reactive secondary process adjacent to ulcers. It is important to remember that primary leukocytoclastic

vasculitis rarely results in the formation of an ulcer despite the vascular damage. If there is a clinical history of an ulcer, the vasculitis process is likely to be secondary in nature. Practical tips for the diagnosis are summarized in Table 6.2.

Table 6.2 Practical tips: leukocytoclastic vasculitis

- Fully developed features not always present
- Early cases may show perivascular neutrophils, leukocytoclasis, and hemorrhage without significant fibrin deposition or vessels necrosis
- If epidermis is ulcerated, consider secondary vasculitis

Henoch–Schönlein Purpura

Clinical Features

HSP accounts for approximately 10% of all cases of cutaneous vasculitis and almost all pediatric cases of vasculitis (≥90%). Although primarily considered a pediatric disease, it may also be seen in adults. The clinical presentation is that of palpable purpura in addition to various combinations of arthritis, gastrointestinal involvement, and nephritis. Some patients develop chronic renal failure as a result of the renal involvement.

Microscopic Features

The histologic findings are those of a leukocytoclastic vasculitis as outlined above in the preceding section. DIF findings are the key to diagnosis. DIF will reveal perivascular deposits of IgA around both involved and uninvolved vessels in the dermis (Fig. 6.4). As a caveat, the DIF findings may not be evident in biopsies of lesions >48 h old (Table 6.3).

Differential Diagnosis

HSP needs to be differentiated from other forms of vasculitis. Typically, the differential diagnosis is a hypersensitivity type vasculitis as outlined in the preceding chapter. The histologic distinction rests on findings of perivascular IgA deposits and the appropriate clinical context (Table 6.4). Without such information, one needs to use a descriptive diagnosis of leukocytoclastic vasculitis (see sample reports).

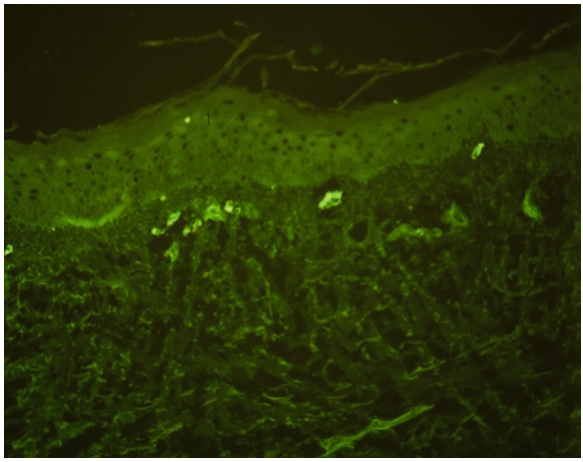

Fig. 6.4 *Henoch–Schönlein purpura (HSP) direct immunofluorescence (DIF)*. DIF demonstrate perivascular deposits of IgA characteristic of HSP

Table 6.3 Key microscopic features: Henoch–Schönlein purpura (HSP)

- Leukocytoclastic vasculitis
- Perivascular IgA deposits on direct immunofluorescence (DIF)

Table 6.4 Practical tips: Henoch–Schönlein purpura (HSP)

- Correlation with clinical history is critical
- More common in children but adult cases are also seen
- DIF requisite for definitive diagnosis

Urticarial Vasculitis

Clinical Features

Urticarial vasculitis occurs in about 20% of patients with chronic urticaria. Unlike leukocytoclastic vasculitis discussed previously, patients have urticarial plaques rather than just palpable purpura. Systemic symptoms such as fever, arthralgias, angioedema, and abdominal pain are common. Urticarial vasculitis can be subdivided into hypocomplementemic or normocomplementemic forms. Hypocomplementemic forms are associated with connective tissue disease (e.g., systemic lupus erythematosus and Sjögren's disease) and more severe disease.

Microscopic Features

Urticarial vasculitis can be quite subtle. The infiltrate tends to be sparse and the vascular damage is focal (Fig. 6.5). Perivascular eosinophils are often present, more commonly in normocomplementemic forms (Table 6.5).

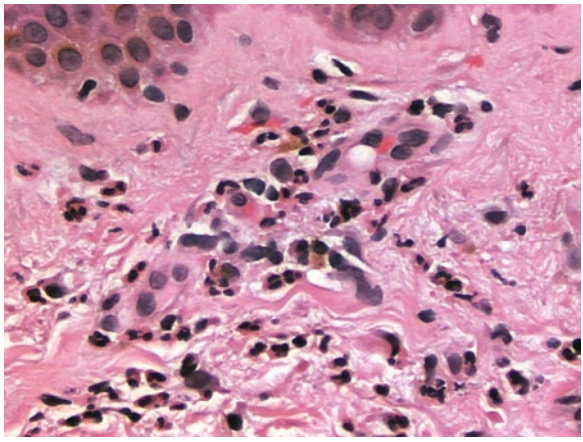

Fig. 6.5 *Urticarial vasculitis*. In urticarial vasculitis the evidence of vascular damage is often very subtle. The presence of a mild perivascular neutrophilic infiltrate and nuclear debris may be the only evidence of a vasculitis. (Courtesy of Dr. J. Andrew Carlson)

Table 6.5 Key microscopic features: urticarial vasculitis

- Subtle leukocytoclastic vasculitis
- Usually mild perivascular neutrophils with leukocytoclasis
- Evidence of vascular damage, typically focal
- Eosinophils are frequently present

Differential Diagnosis

The primary differential consideration is urticaria. Urticaria has a similar sparse infiltrate (see Chap. 5), but no evidence of vascular damage. Because of the subtler findings in most cases of urticarial vasculitis, multiple levels may be necessary to distinguish it from urticaria. In cases with a more prominent inflammatory infiltrate, other forms of leukocytoclastic vasculitis need to be considered. Knowledge of the clinical presentation of the lesions as plaques supports the diagnosis of urticarial vasculitis (Table 6.6).

Table 6.6 Practical tips: urticarial vasculitis

- Deeper levels are often required to make diagnosis
- Lesions are present as urticarial plaques
- Criteria less stringent
  - Neutrophilic infiltrate with any leukocytoclasis sufficient to suggest diagnosis

Wegener's Granulomatosis

Clinical Features

Wegener's granulomatosis (WG) is a systemic vasculitis associated with granulomatous inflammation. Necrotizing granulomas of the respiratory tract and

glomerulonephritis are commonly present, but the disorder can affect any organ system. A subset of patients with WG develops cutaneous manifestations. Most commonly, the cutaneous manifestations present as palpable purpura, but patients may also develop nodules, ulcers and digital gangrene, or polymorphic lesions with rheumatoid papules and pyoderma gangrenosum-like ulcers. Serology for c-ANCA is positive in approximately 80% of cases. Untreated, WG has a high mortality.

Microscopic Features

The microscopic features of cutaneous WG are variable. Biopsies may reveal only small vessel vasculitis. The leukocytoclastic vasculitis of WG overlaps with other forms of leukocytoclastic vasculitis. There does tend to be an involvement of vessels in the deeper dermis as well as the more superficially located vessels (Fig. 6.6). Patients may have ulcers with geographic necrosis resembling pyoderma gangrenosum. Extravascular granulomatous inflammation may also be seen. The granulomas palisade around central karyorrhectic, basophilic debris (Fig. 6.7). True granulomatous vasculitis is rare (Table 6.7).

Differential Diagnosis

The differential diagnosis depends on the clinical manifestations. The most common differential diagnosis in our experience includes other forms of leukocytoclastic vasculitis. The vasculitis of WG has an identical appearance, but the vasculitis in WG tends to be more diffuse with involvement throughout the dermis rather than concentrated in the upper half of the dermis. In this respect, WG is similar to mixed cryoglobulinemia, Churg–Strauss syndrome, and microscopic polyangiitis. In the vabsence of characteristic granulomatous inflammation, WG is rarely a purely

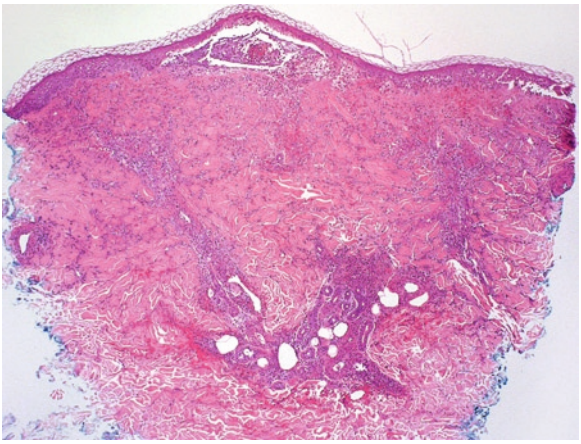

Fig. 6.6 *Wegener's granulomatosis*. In the vasculitis of Wegener's granulomatosis, there is diffuse involvement of dermal vessels

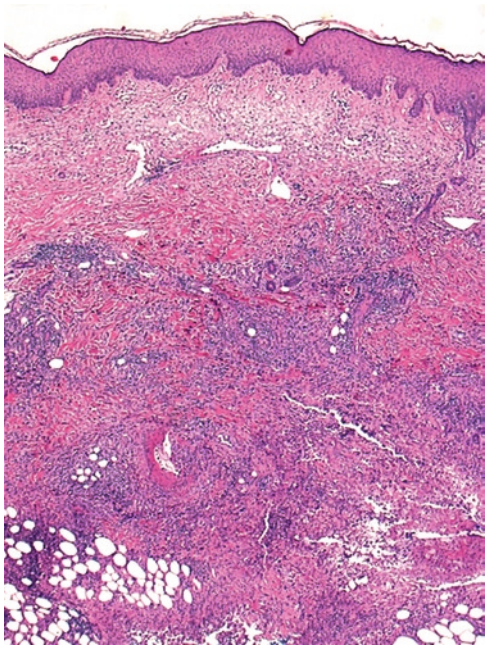

Fig. 6.7 *Wegener's granulomatosis*. Low power image demonstrating the palisading granulomas that can be seen in Wegener's granulomatosis. (Courtesy of Dr. J. Andrew Carlson)

Table 6.7 Key microscopic features: Wegener's granulomatosis

- Leukocytoclastic vasculitis involving superficial and deep dermis
- Pyoderma gangrenosum like ulcers may be present
- Palisading granulomatous inflammation
- True granulomatous vasculitis is rare

histologic diagnosis; correlation with other clinical information is essential (see sample reports) (Table 6.8).

Table 6.8 Practical tips: Wegener's granulomatosis

- Histologic findings are variable
- May present with only one of the histologic features (usually leukocytoclastic vasculitis)
- Correlation with clinical presentation and serology (c-ANCA) critical

Churg–Strauss Syndrome

Clinical Features

This syndrome, also called allergic granulomatosis, is characterized by the combination of asthma, other allergic symptoms (e.g., allergic rhinitis), peripheral and tissue eosinophilia, and systemic vasculitis. Cardiac and peripheral nerve

involvement is relatively common. Asthma and allergic symptoms develop early in the course; vasculitis is a late manifestation. The cutaneous disease presents as palpable purpura, petechiae, ecchymoses, or hemorrhagic bullae. Patients may also develop subcutaneous nodules on the scalp or extremities.

Microscopic Features

The most common finding is an eosinophil-rich, neutrophilic, leukocytoclastic vasculitis in the superficial to mid dermis (Fig. 6.8). Interstitial eosinophils are present, and flame figures characterized by a palisading arrangement of eosinophils and eosinophilic debris encrusting collagen fibers are sometimes seen (Fig. 6.9; Table 6.9).

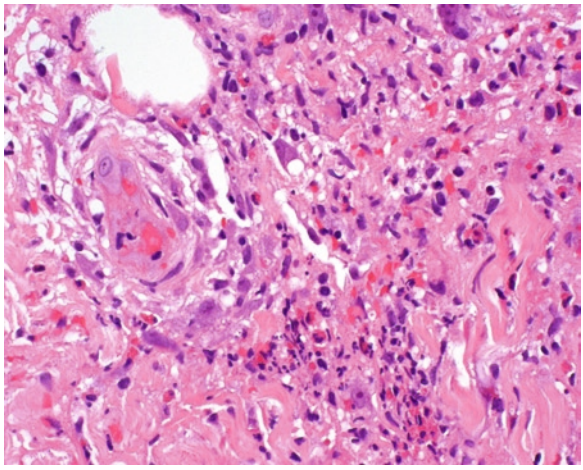

Fig. 6.8 *Churg–Strauss syndrome*. There is leukocytoclastic vasculitis in association with numerous eosinophils

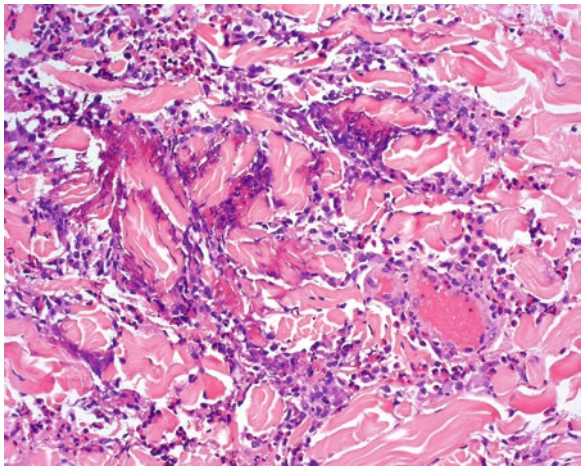

Fig. 6.9 *Churg–Strauss syndrome*. Palisading granulomas with eosinophils and flame figures are a characteristic, though not invariable, feature of Churg–Strauss syndrome

Table 6.9 Key microscopic features: Churg–Strauss syndrome

- Eosinophil-rich neutrophilic leukocytoclastic vasculitis
- Interstitial eosinophils
- Variable flame figures

Differential Diagnosis

The differential diagnosis includes other forms of vasculitis already discussed. Urticarial vasculitis is especially in the differential diagnosis because of the presence of eosinophils in the infiltrate. The perivascular infiltrate of Churg–Strauss syndrome is much denser than that in urticarial vasculitis (Table 6.10). Entities such as Wells' syndrome could be considered, but Wells' syndrome and other dermal hypersensitivity reactions lack vasculitis.

Table 6.10 Practical tips: Churg–Strauss syndrome

- If a leukocytoclastic vasculitis has significant numbers of eosinophils, consider Churg–Strauss syndrome
- Correlation with history is critical

Microscopic Polyangiitis

Clinical Features

Microscopic polyangiitis is a systemic vasculitis that is not associated with granulomatous inflammation or asthma. Associated renal disease in the form of focal segmental necrotizing glomerulonephritis is common. Cutaneous manifestations most commonly include palpable purpura and petechiae. About one-fourth of patients have splinter hemorrhages, palmar erythema, subcutaneous nodules, and/or livedo. Approximately 80% of patients have p-ANCA antibodies.

Microscopic Features

Sections demonstrate leukocytoclastic vasculitis. Vessels throughout the dermis and even subcutis are affected similar to Wegener's granulomatosis (Table 6.11).

Table 6.11 Key microscopic features: microscopic polyangiitis

- Diffuse leukocytoclastic vasculitis involving superficial and deep dermis
- No granulomas

Differential Diagnosis

The differential diagnosis includes any other form of leukocytoclastic vasculitis, especially Wegener' granulomatous or conventional leukocytoclastic vasculitis. There are no truly distinct histologic features of microscopic polyangiitis. Differentiation requires correlation with clinical information (e.g., positive p-ANCA serology) (Table 6.12).

Table 6.12 Practical tips: microscopic polyangiitis

- Histologic features are not distinctive
- Correlation with clinical presentation and serology (p-ANCA) is critical

Cryoglobulinemia

Clinical Features

Cryoglobulinemia is a form of systemic vasculitis associated with the presence of cryoglobulins. Cryoglobulins are immunoglobulins that precipitate at colder temperatures and resolubilize when rewarmed. Cryoglobulinemia can be divided into monoclonal cryoglobulinemia and mixed cryoglobulinemia. In monoclonal, or type I, cryoglobulinemia, there is a monoclonal IgG of IgM cryoglobulin. There is usually an associated underlying disease such as multiple myeloma, Waldenström's macroglobulinemia, or chronic lymphocytic leukemia. Mixed cryoglobulinemia occurs in two forms. In type II, the patients have both a monoclonal IgM rheumatoid factor and polyclonal IgG cryoglobulins. In type III, the patients have polyclonal IgM and polyclonal IgG cryoglobulins. Mixed cryoglobulinemia is seen in association with autoimmune disease, hematologic malignancies, and hepatitis, especially hepatitis C.

As the effects are the result of cryoglobulins, the cutaneous manifestations tend to occur in the distal extremities. Mixed cryoglobulinemia is a vasculitic process, and patients present with intermittent palpable purpura, Raynaud's phenomenon, and polyarthralgia. Patients may develop ulcers and digital necrosis in more severe cases. Glomerulonephritis is sometimes present. In the monoclonal cryoglobulinemia, the disease is primarily thrombotic in nature, and patients present with acral cyanosis and ulcers. By far, the majority of cases are of the mixed type.

Microscopic Features

Mixed cryoglobulinemia is a vasculitic process and biopsies reveal a leukocytoclastic vasculitis throughout the dermis and into the subcutis. Monoclonal cryoglobulinemia

is pauci-inflammatory. The vessels are occluded by intravascular eosinophilic deposits of the monoclonal cryoglobulins. There may be a mild perivascular lymphocytic infiltrate but a true vasculitis is not present (see Table 6.13).

Table 6.13 Key microscopic features: cryoglobulinemia

Mixed cryoglobulinemia
• Leukocytoclastic vasculitis
• Affects superficial and deep dermis to subcutis
Monoclonal cryoglobulinemia
• Dermal vessels occluded with eosinophilic material (immunoglobulin)
• No vasculitis

Differential Diagnosis

Mixed cryoglobulinemia can be indistinguishable from other forms of systemic vasculitis on biopsy. Recognizing this entity requires knowledge of the clinical presentation; ultimately the diagnosis depends on demonstration of cryoglobulins by serologic testing. Lacking that crucial information, a descriptive diagnosis is most appropriate (see sample reports). For monoclonal cryoglobulinemia, the differential diagnosis includes thrombotic processes described in the latter half of this chapter (e.g., antiphospholipid antibody syndrome). Histologically, this form of cryoglobulinemia is indistinguishable from other thrombotic processes. Clinical history and serology are required before this diagnosis can be rendered (Table 6.14).

Table 6.14 Practical tips: cryoglobulinemia

Mixed cryoglobulinemia
• Presents on distal extremities, upper and lower
• Seen in cold weather
• Associated with underlying disease (e.g., hepatitis C)
Monoclonal cryoglobulinemia
• Clinical history of underlying disease
• Presents on distal extremities, upper and lower
• Seen during cold weather

Cutaneous Polyarteritis Nodosa

Clinical Features

Cutaneous polyarteritis nodosa presents in middle-aged to older adults as painful nodules on the extremities, leg more frequently than arm. Patients may have livedo and rarely patients develop acral gangrene or digital necrosis. Associated neuropathy is commonly present.

Microscopic Features

Unlike other forms of vasculitis previously discussed, cutaneous polyarteritis nodosa is a neutrophilic vasculitis involving muscular arteries in the subcutis or dermis–subcutis interface (Fig. 6.10). Later stages may show neovascularization of the adventitia and fibrosis of the vessel wall (see Table 6.15).

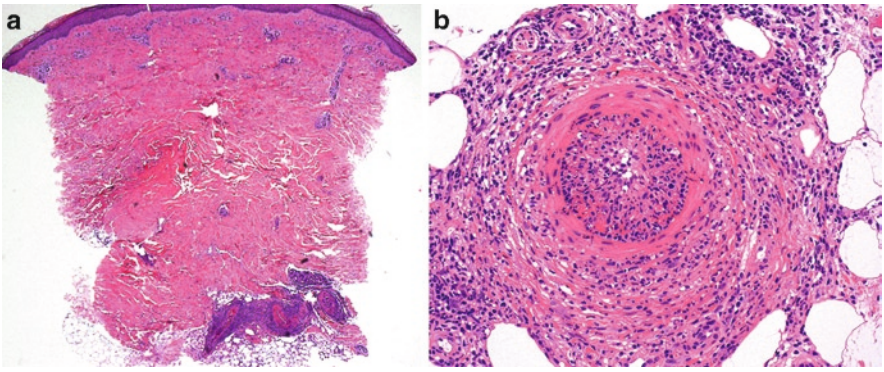

Fig. 6.10 *Cutaneous polyarteritis nodosa*. (**a**) In polyarteritis nodosa the medium sized vessels at the dermoepidermal junction or subcutis are involved. (**b**) In this case there is a leukocytoclastic vasculitis affecting a muscular artery in the subcutis. There is some adjacent fat necrosis

Table 6.15 Key microscopic features: polyarteritis nodosa

- Affected vessels are in deep dermis/subcutis
- Medium-sized muscular arteries are involved by leukocytoclastic vasculitis

Differential Diagnosis

Erythema induratum (nodular vasculitis) has some overlap, but this entity has an associated lobular panniculitis (see Chap. 11). In polyarteritis nodosa, the damage to adjacent adipose tissue is restricted to the area surrounding the vessel (Table 6.16).

Table 6.16 Practical tips: polyarteritis nodosa

- Diagnostic features can be focal
- Deeper levels may be necessary
- No associated diffuse lobular panniculitis

Vaso-Occlusive Disease

This group of disorders is generally characterized by occlusion of vessels, often with associated ischemic necrosis.

Coumadin Necrosis

Clinical Features

Lesions begin several days after initiation of therapy with coumadin. The lesions are ecchymotic and progress to necrotic lesions. It most commonly presents in the thighs, buttocks, and breasts, typically in obese women. It is associated with low levels of protein C.

Microscopic Features

Within the dermis and often subcutis, there are numerous fibrin thrombi within venules and arterioles (Fig. 6.11). There may be associated hemorrhage and ischemic necrosis (Table 6.17).

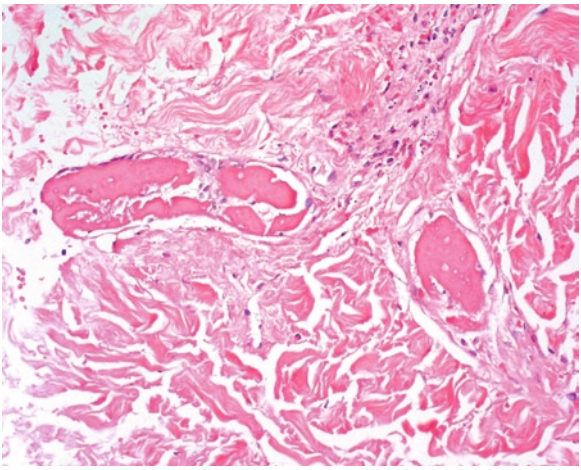

Fig. 6.11 *Coumadin necrosis*. In coumadin necrosis there is thrombosis of dermal venules and arterioles without significant inflammation

Table 6.17 Key microscopic features: Coumadin necrosis

- Thrombi in venules and arterioles
- Non-inflammatory

Differential Diagnosis

The primary differential diagnosis includes other hypercoagulable states such as antiphospholipid antibody syndrome or monoclonal cryoglobulinemia (see above). Distinction rests on clinical information, but it is usually suspected based on history of recent initiation of coumadin therapy (Table 6.18).

Table 6.18 Practical tips: Coumadin necrosis

- Clinical history is critical
- Occurs within days of initiation of anticoagulant therapy
- Histologic features are not distinctive from other hypercoagulable states

Atrophie Blanche (Livedoid Vasculopathy)

Clinical Features

This condition usually presents in elderly women. This disease initially presents as purpuric areas that ulcerate and over time develop into irregular smooth atrophic plaques with a hyperpigmented border and surrounding telangiectasias. The lower extremities are by far the most common site of involvement. The pathogenesis is poorly understood, but at least some cases, patients have an underlying hypercoagulable state such as Factor V Leiden mutation or antiphospholipid antibody syndrome. Therefore, this condition may represent in part a reaction pattern.

Microscopic Features

Biopsies demonstrate fibrin deposition in the walls of superficial dermal vessels and fibrin thrombi in association with hemorrhage (Fig. 6.12). A true vasculitis is not present, but a perivascular infiltrate may develop in later lesions. The overlying epidermis and surrounding tissue may be necrotic. See Table 6.19.

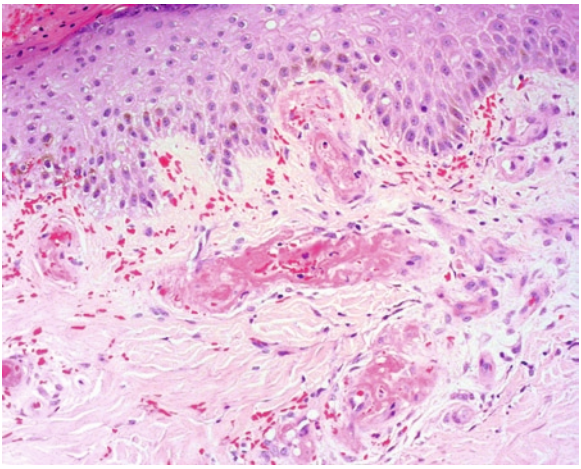

Fig. 6.12 *Atrophie blanche* is characterized by fibrin deposition and thrombosis of superficial dermal blood vessels in association with prominent hemorrhage

Table 6.19 Key microscopic features: atrophie blanche

- Primarily superficial vessels
- Fibrin deposition and thrombosis
- Hemorrhage

Differential Diagnosis

The diagnosis primarily depends on clinical presentation. Histologically, it can be indistinguishable from other hypercoagulable states, and indeed other hypercoagulable states may be the cause of the clinical presentation as alluded to above. See Table 6.20.

Table 6.20 Practical tips: atrophie blanche

- Most common on distal lower extremities
- Clinical correlation critical

Antiphospholipid Antibody Syndrome

Clinical Features

Young adult women are most commonly affected. The syndrome is the result of autoantibodies directed against phospholipid. Patients have recurrent episodes of thrombosis and associated thrombocytopenia and spontaneous abortions. The causative autoantibodies are found in patients with systemic lupus erythematosus in up to 50% of patients with this disease. Other factors play a role in developing sequelae of hypercoagulability as roughly half of the patients with the antibody develop thromboses. Cutaneous lesions manifest as livedo reticularis, Raynaud's phenomenon, ulcerations, necrosis, painful nodules, splinter hemorrhages, and atrophie blanche. The ulcerations and necrosis can be quite severe.

Microscopic Features

Biopsies demonstrate fibrin thrombi in venules and arterioles much like that seen in coumadin necrosis. There is often extensive surrounding necrosis. No true vasculitis is present (Table 6.21).

Table 6.21 Key microscopic features: antiphospholipid antibody syndrome

- Vascular thrombosis without significant inflammation
- Venules and arterioles involved

Differential Diagnosis

The histologic features are not distinctive from other occlusive vasculopathies. Diagnosis requires clinical evaluation and appropriate serologic testing (Table 6.22).

Table 6.22 Practical tips: antiphospholipid antibody syndrome

- Young adult women
- If there is a history of spontaneous abortion or connective tissue disease, suspect antiphospholipid antibody syndrome
- Correlation with serology is critical

Cholesterol Emboli

Clinical Features

This presents in patients who have significant atheromatous plaques in large vessels, especially the abdominal aorta. They can develop spontaneously or as a result of dislodgement from a vascular procedure. Cutaneous lesions manifest on the distal lower extremities as purpura, cyanosis, painful nodules, or necrosis.

Microscopic Features

The affected vessels demonstrate thrombosis with cholesterol clefts (Fig. 6.13). The affected vessels are in the deep dermis or subcutis (Table 6.23).

Differential Diagnosis

The histologic features are sufficiently distinct that essentially no other entity is in the differential diagnosis. However, the finding is often focal and multiple levels may need to be obtained (Table 6.24).

Calciphylaxis

Clinical Features

Calciphylaxis usually presents in patients with end-stage renal disease. It presents as painful, often ulcerated, nodules, and plaques, most commonly on the lower extremities. Breasts, buttocks, penis, and upper extremities may also be involved. Mortality rates approach 60%.

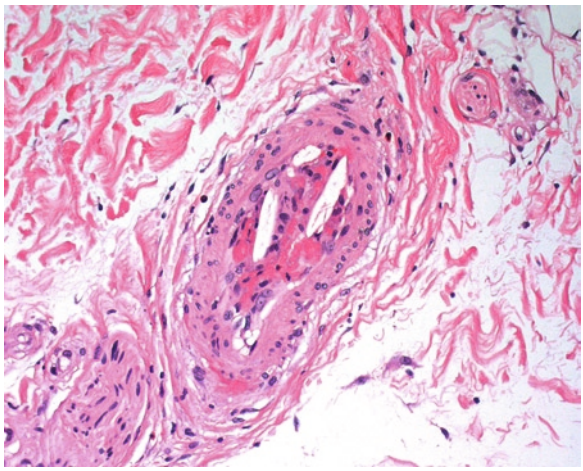

Fig. 6.13 *Cholesterol emboli* are characterized by thrombosis with cholesterol clefts

Table 6.23 Key microscopic features: cholesterol emboli

- Vascular thrombus in deep dermis or subcutis
- Cholesterol clefts are required for the diagnosis

Table 6.24 Practical tips: cholesterol emboli

- Multiple levels are often needed
- Occurs on distal extremities
- History of prior vascular procedure is common

Microscopic Features

Calciphylaxis is characterized by calcification of small to medium-sized arteries and arterioles that may be associated with intimal fibroblastic proliferation and intravascular fibrin thrombi (Fig. 6.14). Associated fat necrosis is common and often extensive (Table 6.25).

Differential Diagnosis

Fat necrosis could be considered in the differential diagnosis. Mönckeberg's calcification could be considered, but that is a sequela of aging, tends to involve larger vessels, and is not associated with necrosis. Calciphylaxis is usually suspected clinically, so this entity is rarely a diagnostic problem. It is important that a sufficiently large and deep biopsy is obtained as the involved vessels are usually in the subcutis (Table 6.26). Superficial biopsies may not be diagnostic (see sample report).

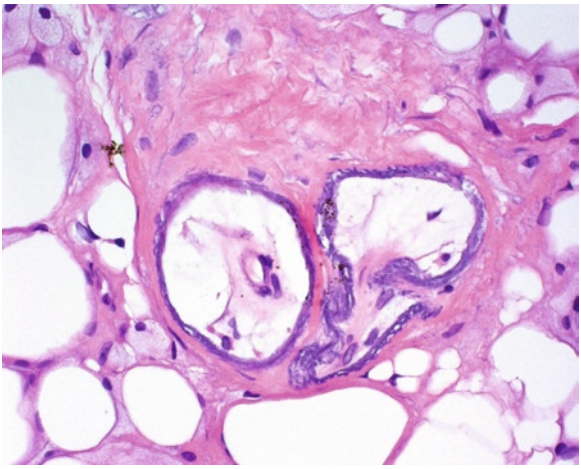

Fig. 6.14 *Calciphylaxis*. There is calcification of the vascular wall. Note the adjacent evidence of fat necrosis

Table 6.25 Key microscopic features: calciphylaxis

- Calcification of small to medium-sized arteries
- Associated necrosis

Table 6.26 Practical tips: calciphylaxis

- Usually requires deep biopsy; affected vessels usually in subcutis
- Clinical history of renal failure

Sample Reports: Leukocytoclastic Vasculitis

Example 1: This report represents a biopsy from an early leukocytoclastic vasculitis in which the findings are not well developed.

Clinical history: Rule out LCV.

Diagnosis: Superficial perivascular neutrophilic infiltrate consistent with leukocytoclastic vasculitis, see comment.

Comment: The epidermis is relatively normal. Within the upper dermis, there is a perivascular infiltrate of neutrophils with some nuclear debris and extravasated erythrocytes. No significant fibrin deposition in vessels of fibrinoid necrosis is seen. The histologic features are consistent with the clinical impression of leukocytoclastic vasculitis. Clinicopathologic correlation is recommended.

Example 2: A classic case.

Clinical history: Palpable purpura.

Diagnosis: Leukocytoclastic vasculitis, see comment.

Comment: The epidermis is relatively normal. Within the upper dermis, there is a perivascular infiltrate of neutrophils with prominent

nuclear debris, extravasated erythrocytes, and fibrin deposition in blood vessel walls.

Example 3:
Clinical history: Ulcer.
Diagnosis: Reactive epidermal changes and mixed dermal infiltrate, see comment.
Comment: The epidermis shows reactive epidermal hyperplasia. Within the dermis, there is a mixed infiltrate with lymphocytes and neutrophils. There is proliferation of blood vessels. Neutrophils are present in some of the blood vessel walls as is fibrin deposition. Given the clinical history of an ulcer, the vasculitis may represent a secondary vasculitis related to the ulcer rather than a primary leukocytoclastic vasculitis.

Sample Report: Henoch–Schönlein Purpura

Example: In this case, a specimen for DIF is not available.
Clinical history: Rule out HSP.
Diagnosis: Leukocytoclastic vasculitis, see comment.
Comment: Within the dermis, there is a leukocytoclastic vasculitis characterized by a perivascular infiltrate of neutrophils with leukocytoclasis, hemorrhage, and fibrin deposition in blood vessel walls. The histologic features are compatible with Henoch–Schönlein purpura in the appropriate clinical context. However, confirmation requires DIF testing. A repeat biopsy submitted in Michel's solution for DIF is recommended.
Note to reader: If a specimen for DIF is submitted and the predominant finding is perivascular deposits of IgA, the diagnosis could be changed to leukocytoclastic vasculitis consistent with Henoch–Schönlein purpura.

Sample Report: Wegener's Granulomatosis

Example: In this case, only vasculitis is present.
Clinical history: Rule out Wegener's.
Diagnosis: Leukocytoclastic vasculitis, see comment.
Comment: Within the dermis, there is a leukocytoclastic vasculitis characterized by a perivascular infiltrate of neutrophils with leukocytoclasis, hemorrhage, and fibrin deposition in blood vessel walls. Superficial and deep vessels are involved. The histologic features are compat-

ible but not entirely specific for the diagnosis of Wegener's granulomatosis. Clinicopathologic correlation is recommended.

Sample Report: Churg–Strauss Syndrome

Example: In this case, Churg–Strauss syndrome is not specifically mentioned in the clinical history.

Clinical history: Rule out vasculitis.

Diagnosis: Leukocytoclastic vasculitis with numerous eosinophils, see comment.

Comment: Within the superficial and deep dermis, there is a leukocytoclastic vasculitis characterized by a perivascular infiltrate of neutrophils with leukocytoclasis, hemorrhage, and fibrin deposition in blood vessel walls. Numerous eosinophils are present. The extent of the dermal infiltrate and the numerous eosinophils suggest the possibility of Churg–Strauss syndrome. Clinicopathologic correlation is recommended.

Note to reader: In this scenario, it might be a good idea to pick up the phone and call the clinician to see if the patient has a history of asthma or allergic rhinitis.

Sample Reports: Hypercoagulable States (e.g., antiphospholipid antibody syndrome)

Example: In this case, a specific diagnosis is not suggested in the clinical history.

Clinical history: Rule out vasculitis.

Diagnosis: Numerous intravascular thrombi, see comment.

Comment: Within the dermis, there are numerous intravascular thrombi in association with hemorrhage and ischemic necrosis. No significant inflammation is present. The histologic features are compatible with an underlying hypercoagulable state. Clinicopathologic correlation is recommended.

Note to reader: If the clinician suggests a specific diagnosis (e.g., coumadin necrosis), the diagnosis can read "Intravascular fibrin thrombi consistent with _____," with the pathologist filling in the blank with what the clinician is suspecting.

Sample Report: Calciphylaxis

Example: In general, the diagnosis of calciphylaxis is relatively easy. However, diagnostic findings may not be present on superficial biopsies. This report reflects that situation.

Clinical history: Ulcerated plaque, rule out calciphylaxis.

Diagnosis: Ulcer with dermal necrosis, see comment.

Comment: The epidermis is ulcerated and there is underlying necrosis. The biopsy is relatively superficial and only a limited amount of subcutaneous fat is present. Diagnostic features of calciphylaxis are not seen, but that possibility cannot be excluded based on this biopsy. A repeat, excisional biopsy including a generous sampling of subcutaneous fat is recommended if calciphylaxis remains a strong clinical possibility. Clinicopathologic correlation is recommended.

Selected References

1. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. American Journal of Dermatopathology. 27:504–528, 2005.
2. Carlson JA, Chen KR. Cutaneous pseudovasculitis. American Journal of Dermatopathology. 29:44–55, 2007.

Chapter 7
Nodular and Diffuse Dermatitis

Keywords Lymphoid hyperplasia • Sweet's syndrome • Granuloma faciale • Sarcoidosis

There is a significant overlap with the nodular and diffuse pattern and the superficial and deep perivascular pattern; indeed, some entities discussed in Chap. 5 could arguably be included in this chapter as well (e.g., arthropod bite reaction). Other entities discussed in this chapter could also conceivably be discussed in the chapter on perivascular dermatitis (e.g., Sweet's syndrome). The primary difference in the nodular and diffuse patterns from the perivascular pattern is that the inflammation is not just centered on vessels. On scanning magnification, nodular dermatitis is characterized by discrete areas of inflammation, separated by uninvolved areas (Fig. 7.1). In contrast, the diffuse pattern demonstrates dense dermal inflammation without intervening areas of sparing (Fig.7.2). Distinction in individual cases is admittedly arbitrary and subject to individual interpretation. As with automobiles, your mileage may vary.

Reactive Lymphoid Hyperplasia

Clinical Features

Reactive lymphoid hyperplasia (also known as lymphocytoma cutis, pseudolymphoma, and lymphadenosis benigna cutis) refers to a group of conditions in which both the clinical and histologic appearance of lymphocytic infiltrates in the skin closely mimic cutaneous lymphomas. Lymphoid hyperplasia may be provoked by chronic antigenic stimulation (arthropod bite, infections, and contactants) or certain medications (especially anticonvulsant and antidepressant drugs). The clinical presentation is variable, but typically the lesions present as persistent erythematous papules or nodules.

S.D. Billings and J. Cotton, *Inflammatory Dermatopathology: A Pathologist's Survival Guide*, 119
DOI 10.1007/978-1-60327-838-6_7,

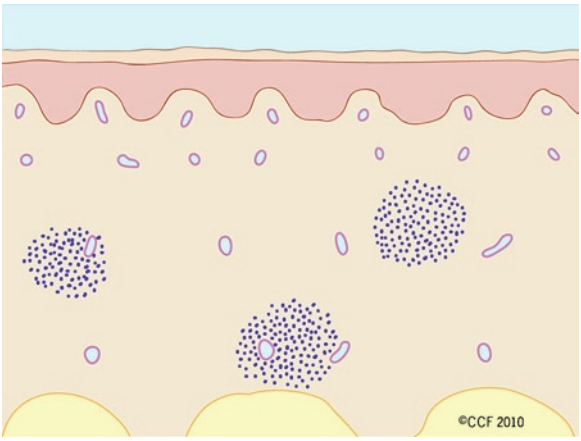

Fig. 7.1 *Schematic representation of nodular pattern.* Inflammatory diseases with a nodular pattern demonstrate nodular collections of inflammatory cells that are not vasculocentric. There are areas of uninvolved dermis

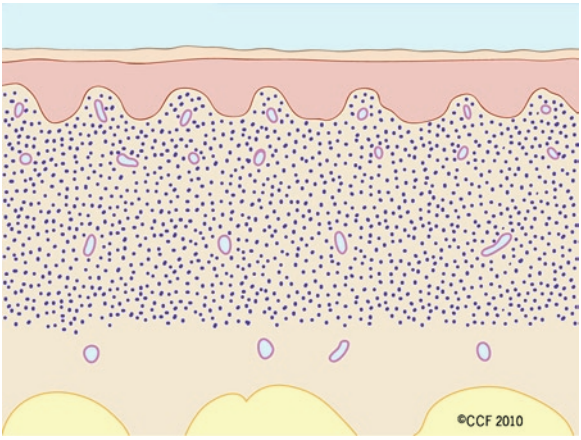

Fig. 7.2 *Schematic representation of diffuse pattern.* In the diffuse pattern, the entire dermis is involved by the inflammatory process

Microscopic Features

Classically, in reactive lymphoid hyperplasia, there are well-demarcated germinal centers with a peripheral cuff of small lymphocytes (zonation) (Figs. 7.3 and 7.4), tingible body microphages, and high mitotic activity (Fig. 7.5). The germinal centers may have a polarized appearance, appearing paler on one side versus the other due to the distribution of centroblasts and centrocytes. The surrounding lymphocytes outside of the germinal center are predominantly T-cells with a minor B-cell component. Some plasma cells are often present, but they lack light chain restriction. In some cases, germinal center formation is absent and the infiltrate is predominantly composed of T-cells with only scattered B-cells (see Table 7.1 for summary of key microscopic features).

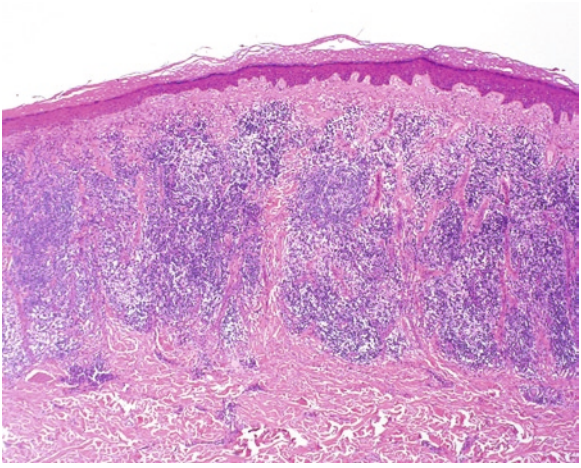

Fig. 7.3 *Reactive lymphoid hyperplasia*. At scanning magnification there is a nodular and diffuse lymphocytic infiltrate with formation of prominent germinal centers

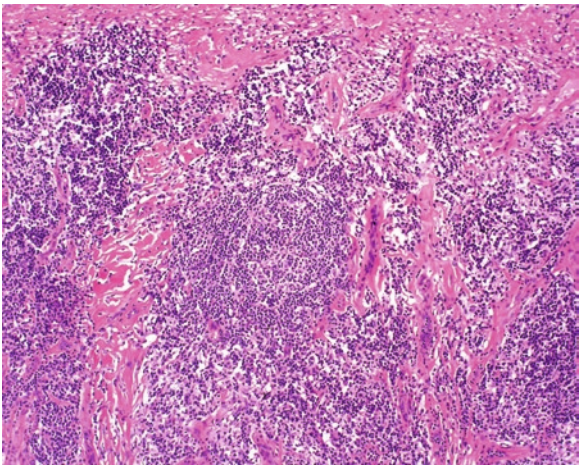

Fig. 7.4 *Reactive lymphoid hyperplasia*. Well-demarcated pale germinal centers accompanied by peripheral cuff of small lymphocytes

Differential Diagnosis

As alluded to above, the main differential diagnosis includes cutaneous B-cell lymphoma; primarily, follicular center and marginal zone subtypes. A detailed discussion of these entities is beyond the scope of this book; however, a few comments will be provided. In general, the architecture of the germinal center is very helpful in distinguishing lymphoid hyperplasia from follicle center cell lymphoma. In follicle center cell lymphoma, the germinal centers are not polarized, but more uniform in appearance. They tend to lack tingible body macrophages. Low-grade follicle center lymphomas also have a low mitotic rate and low Ki-67 proliferative index. They may also have more numerous B-cells outside the follicles. Marginal zone B-cell lymphomas may have a component of reactive germinal centers that can cause confusion

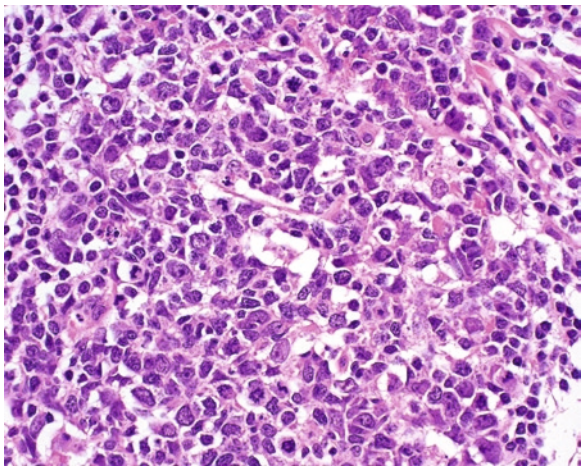

Fig. 7.5 *Reactive lymphoid hyperplasia*. Reactive germinal center demonstrating a mixture of small and large lymphocytes, tingible body macrophages and high mitotic activity

Table 7.1 Key microscopic features: cutaneous lymphoid hyperplasia

- Polarized reactive germinal centers with tingible body macrophages
- Predominantly T-cells surrounding the germinal centers
- B-cells are largely restricted to germinal centers
- Plasma cells and eosinophils may be present
- No light chain restriction

with reactive lymphoid infiltrates. The germinal centers are often disrupted by migration of the neoplastic cells into the germinal center. This can be demonstrated with an immunostain for CD21 to highlight the disrupted follicular dendritic cell network. In marginal zone lymphoma, there may be numerous plasma cells. The plasma cells may show atypical features and are light-chain restricted. Molecular studies for detection of clonal re-arrangements of the immunoglobulin heavy chain may be helpful. While no means entirely sensitive or specific, the presence of a monoclonal population of B-cells is uncommon in reactive lymphoid infiltrates. In general, one must be very cautious in dealing with cases of suspected reactive lymphoid hyperplasia. Table 7.2 highlights histologic features that favor reactive lymphoid infiltrates over low-grade lymphoma. Please refer to select references for a more complete discussion of these lymphomas.

In the cases where the population is predominantly composed of T-cells with very few B-cells, the true nature of the process is somewhat elusive. This may represent the end stages of a resolving inflammatory process. It is important to consider the possibilities of T-cell lymphomas such as folliculocentric mycosis fungoides. Reactive T-cell proliferations have a mixture of CD4 and CD8 positive lymphocytes. In general, the ratio of CD4 to CD8 positive cells can range from 1:1 up to 6:1, and still be consistent with a reactive process. As a practical matter, it is important to remember that histiocytes are immunoreactive for CD4 also. Therefore, when interpreting ratios, one must take this into account and correlate CD4 stains with a CD3 stain.

The diagnosis of reactive lymphoid hyperplasia is tricky. Even in relatively straight forward cases, we often employ a descriptive diagnosis (see sample reports at the end of the chapter). This also reflects the fact that some patients with reactive lymphoid hyperplasia can progress to development of cutaneous lymphoma.

Table 7.2 Practical tips: cutaneous lymphoid hyperplasia

- Differentiation of reactive lymphoid infiltrates from low-grade B-cell lymphoma (follicular center, marginal zone) may be quite difficult
- Features that favor lymphoid hyperplasia include the following:
  - Polarized germinal centers with tingible body macrophages
  - Clinical correlation is paramount to the diagnosis
  - "Top-heavy" (superficial and mid-dermal) infiltrate with preservation of adnexal structures,
  - Mixed cell infiltrate, B-cells generally limited to germinal centers
  - Lack of light chain restriction
  - However, be aware that these are not hard and fast rules
- Immunophenotypic studies are almost always required
- Molecular studies may be helpful in border-line cases

Sweet Syndrome (Acute Febrile Neutrophilic Dermatosis)

Clinical Features

Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by the acute onset of fever and leukocytosis associated with arthralgias and erythematous plaques. Lesions are most often found on the extremities and face. This entity most often occurs in middle-aged women after a nonspecific respiratory or gastrointestinal infection. An association with an underlying malignancy such as leukemia is seen in about 10% of cases. It is often seen in patients with inflammatory bowel disease, connective tissue disease, and underlying infection. The pathogenesis is not known. The clinical course is usually short-lived, and lesions respond to systemic corticosteroids.

Microscopic Features

Sweet syndrome is a classic manifestation of neutrophilic dermatosis, a histologic pattern characterized by the presence of a heavy dermal infiltrate of neutrophils and variable leukocytoclasis (Fig. 7.6). Despite the latter finding, vascular damage is not a characteristic feature of this syndrome (Fig. 7.7 and Table 7.3). Although a recent report described the presence of some vascular damage in Sweet syndrome, this tends to be seen in older lesions and is presumed to represent secondary vascular damage due to the release of neutrophilic enzymes. Interestingly, recent studies have demonstrated that some cutaneous lesions of Sweet syndrome are histopathologically characterized by an inflammatory infiltrate composed of histiocyte-like immature myeloid cells, not polymorphonuclear leukocytes as is the norm. Deemed "histiocytoid Sweet syndrome" by the authors, this variant may be confused with histiocytic interstitial processes such as granuloma annulare.

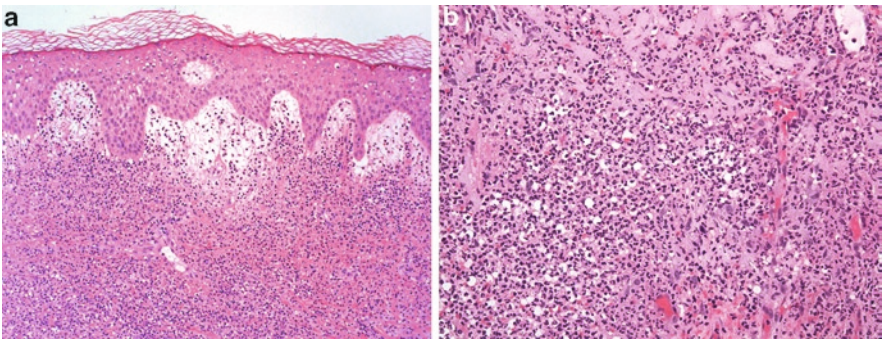

Fig. 7.6 *Sweet syndrome*. (**a**) There is a dense, diffuse infiltrate involving the upper and mid dermis. Papillary dermal edema is also observed. (**b**) The higher power image demonstrates a diffuse infiltrate of neutrophils with associated leukocytoclasis

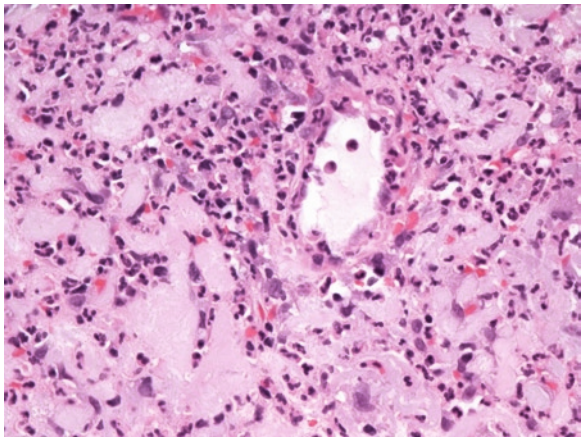

Fig. 7.7 *Sweet syndrome*. There is leukocytoclasis of the neutrophils. Blood vessels may show endothelial swelling with some extravasation of erythrocytes but a true vasculitis is typically absent

Table 7.3 Key microscopic features: Sweet syndrome

- Diffuse infiltrate of neutrophils
- Leukocytoclasis but no vasculitis

Differential Diagnosis

Other neutrophilic dermatoses to be considered in the differential diagnosis include bowel bypass syndrome, which presents as pustular lesions and arthritis in patients who have undergone bowel bypass surgery for obesity. Rheumatoid neutrophilic dermatosis represents a rare manifestation of rheumatoid arthritis characterized clinically by symmetric nodules on extensor surfaces of joints and histologically by neutrophilic infiltrates indistinguishable from Sweet syndrome. Pyoderma gangrenosum, characterized by ulcers with a raised undermined border and diffuse dermal neutrophilic infiltrate, is a diagnosis of exclusion. Leukocytoclastic vasculitis refers to a histologic combination of intramural neutrophils, leukocytoclasis, and

Table 7.4 Practical tips: Sweet syndrome

- No true vasculitis
- Ulceration uncommon in Sweet syndrome
- If an infectious process is a clinical consideration, tissue culture should be pursued
- If Sweet syndrome is considered clinically, but infiltrate looks histiocytic, consider immunostains for myeloperoxidase to exclude histiocytoid Sweet syndrome

fibrinoid necrosis of vessel walls with extravasated erythrocytes (Chap. 6). Granuloma faciale, considered a chronic form of leukocytoclastic vasculitis, is discussed below. Finally, it is of upmost importance to exclude an infectious etiology by liberal use of special stains and tissue culture before rendering an unequivocal diagnosis of Sweet Syndrome (Table 7.4).

Granuloma Faciale

Clinical Features

Granuloma faciale is an uncommon condition characterized by single or multiple asymptomatic nodules that typically involve the face. Lesions are reddish-brown to violaceous in color and may darken with sun exposure. The clinical differential diagnosis includes sarcoidosis, discoid lupus erythematosus, or fixed drug eruption.

Microscopic Features

Granuloma faciale has a fairly distinctive microscopic appearance. On low power examination, there is usually a dense, diffuse infiltrate in the dermis (Fig. 7.8). In well-developed lesions, the infiltrate is polymorphous, composed of neutrophils, eosinophils, plasma cells, and lymphocytes (Fig. 7.9). Often, there is characteristic sparing of the papillary and periadnexal (adventitial) dermis forming a Grenz zone (Fig. 7.10). Granuloma faciale is considered a form of chronic vasculitis, and biopsies of early lesions may show foci of leukocytoclasis accompanied by fibrin in the vessel walls. However, vasculitic changes are often not apparent by the time the lesion is biopsied. In general, the polymorphous nature of the infiltrate combined with the lack of overt vasculitis are features diagnostic of granuloma faciale (Table 7.5).

Table 7.5 Key microscopic features: granuloma faciale

- Polymorphous infiltrate with neutrophils, eosinophils, and plasma cells, and sparing of adventitial dermis is diagnostic
- Evidence of leukocytoclastic vasculitis may be seen in early cases
- Extravasated erythrocytes and hemosiderin may be observed and contribute to the reddish-brown color of the lesions clinically

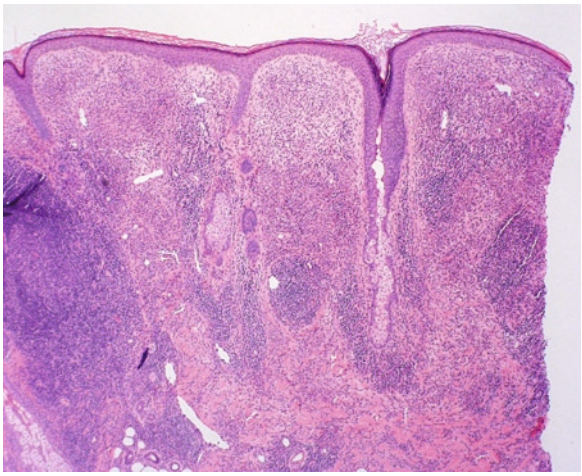

Fig. 7.8 *Granuloma faciale* is characterized by dense, diffuse infiltrate of the dermis. The epidermis is typically unremarkable

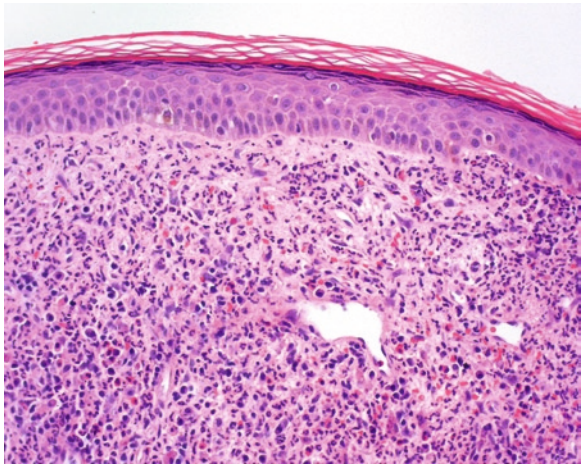

Fig. 7.9 *Granuloma faciale*. In granuloma faciale, the infiltrate is polymorphous, composed of lymphocytes, neutrophils and eosinophils

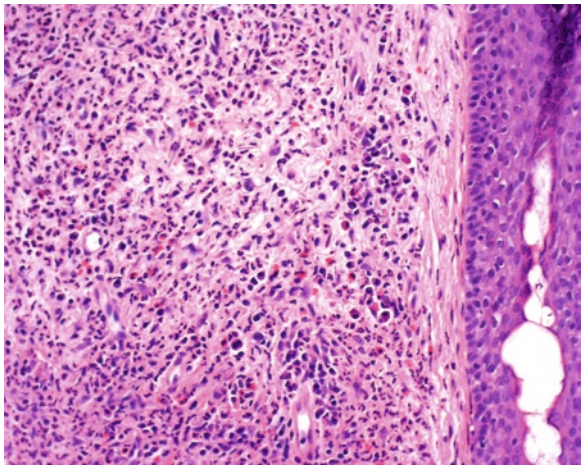

Fig. 7.10 *Granuloma faciale*. The infiltrate typically spares the adventitial and papillary dermis forming a Grenz zone. Note the polymorphous nature of the infiltrate

Differential Diagnosis

The microscopic features together with the clinical information are generally diagnostic. The histologic differential diagnosis includes Sweet's syndrome, arthropod bite reaction, or other hypersensitivity reaction; however, the mixed nature of the infiltrate in GF is fairly distinctive (Table 7.6).

Table 7.6 Practical tips: granuloma faciale

- Polymorphous infiltrate is key to the diagnosis
- Polymorphous infiltrate helps distinguish granuloma faciale from Sweet's syndrome
- May see vasculitis in early lesions; remember, it is rare to see other forms of vasculitis on face

Sarcoidosis

Clinical Features

Sarcoidosis is a common systemic disease of unknown etiology, defined by the presence of non-caseating granulomata usually affecting multiple organ systems. It is more common in women, and in USA, it is relatively common in African–American patients. Although it may present at any age, it most commonly presents in young to middle-aged adults. Between 10 and 35% of patients with systemic sarcoidosis have cutaneous lesions. A diversity of clinical forms of cutaneous sarcoidosis has been described. Violaceous plaques and nodules on the nose, ears, and cheeks are a classic clinical presentation of cutaneous sarcoidosis. The clinical term "lupus pernio" has been used to describe this presentation. It is important to remember that the term lupus pernio has absolutely nothing to do with lupus erythematosus. Cutaneous sarcoidosis is characterized by clinical heterogeneity; indeed, lesions can present on any anatomic location. Moreover, sarcoidosis or sarcoid-like lesions can also present at sites of trauma as a reaction to exogenous substances (e.g., tattoo ink). A subset of this patient group will have underlying systemic sarcoidosis, and patients with sarcoidosis have an increased likelihood of having sarcoidal reactions at sites of trauma. Cutaneous and pulmonary sarcoidosis can also be triggered by interferon treatment that typically resolves with cessation of therapy.

Microscopic Features

Sarcoidosis typically has a superficial and deep nodular pattern (Fig. 7.11), but may have only superficial dermal involvement. The nodules usually have an interstitial pattern without associated dermal appendages. A perivascular pattern can sometimes be seen. The *sine qua non* of sarcoidosis is the non-caseating "naked" granuloma (Fig. 7.12). These granulomas are characterized by relatively tight clusters of

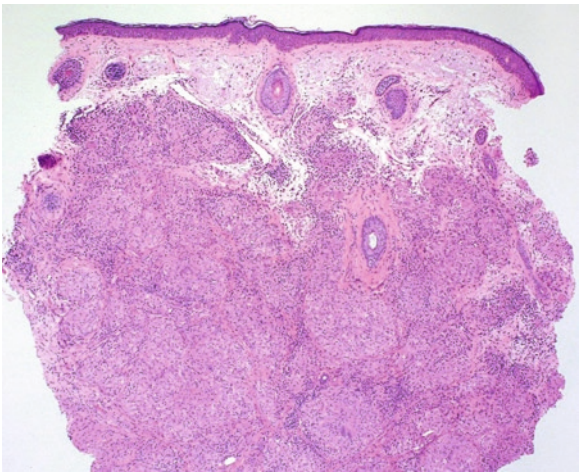

Fig. 7.11 *Sarcoidosis*. The pattern of the infiltrate of sarcoidosis is variable. This case demonstrates diffuse involvement of the dermis

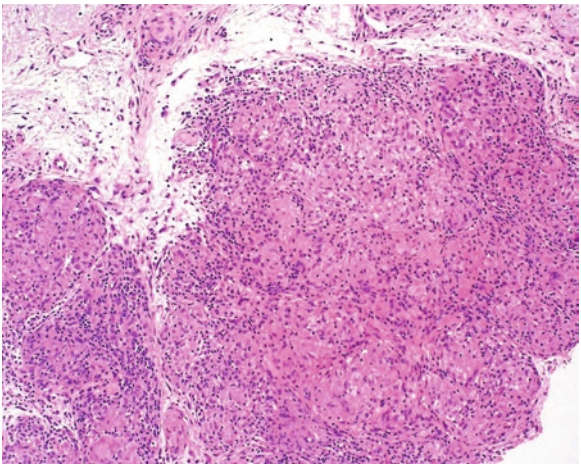

Fig. 7.12 *Sarcoidosis*. Epithelioid granulomas with poorly developed lymphocytic cuffs, so-called naked epithelioid granulomas are characteristic of sarcoidosis

Table 7.7 Key microscopic features: sarcoidosis

- Epithelioid granulomas
- Poorly developed lymphocytic cuff

epithelioid histiocytes with a poorly developed or absent lymphocytic cuff (Table 7.7). Small amounts of centrally located fibrinous or granular material are occasionally seen in some granulomas. Occasional inclusion bodies (Schaumann body and asteroid body) may be evident (Fig 7.13). In some cases, there may be evident or polarizable foreign material (Fig. 7.14). This has been termed scar sarcoidosis. Lesions of sarcoidosis often arise at sites of trauma. In a patient without a history of underlying sarcoidosis, this finding should prompt the pathologist to suggest further evaluation for possible systemic disease.

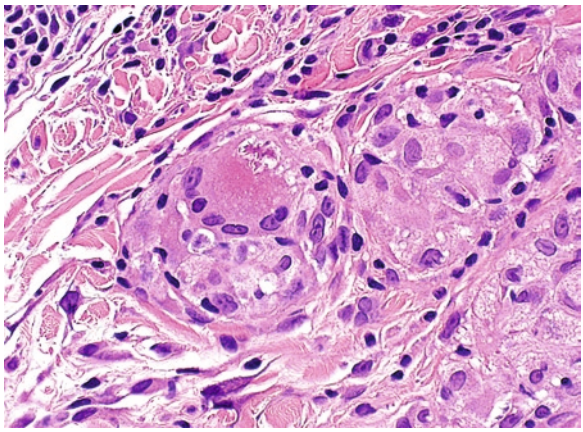

Fig. 7.13 *Sarcoidosis*. Within the multinucleated histiocyte there is a Schaumann, or asteroid body. These are stellate eosinophilic inclusions

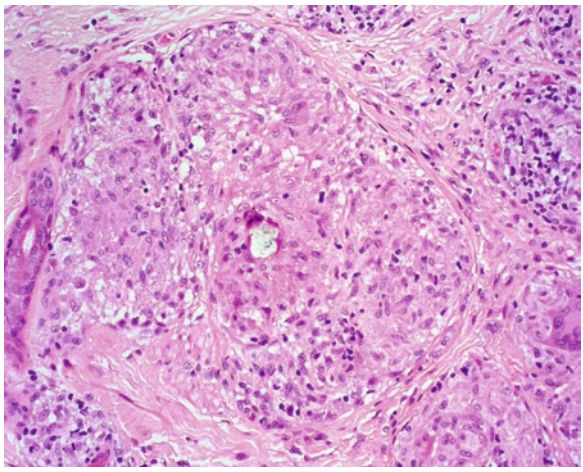

Fig. 7.14 *Scar sarcoidosis*. Within the sarcoidal granuloma, foreign material is evident. Lesions of sarcoidosis often develop at sites of trauma

Differential Diagnosis

Sarcoidosis is a diagnosis of exclusion. In the absence of a well-established underlying diagnosis of systemic disease, it is imperative to exclude infection with appropriate special stains (e.g., GMS and Fite stains) to exclude fungal or mycobacterial infections. Non-infectious entities in the differential diagnosis include cutaneous Crohn's disease. Cutaneous Crohn's disease also has epithelioid granulomas, but usually presents in a perianal location. The cutaneous manifestations of Crohn's disease may precede gastrointestinal involvement. Therefore, the possibility of cutaneous Crohn's disease should always be considered before making the diagnosis of sarcoidosis in a perianal location. Necrobiosis lipoidica may have sarcoidal granulomas, but the altered collagen, lymphoid aggregates, and lymphoplasmacytic infiltrate usually allow discrimination (see Chap. 9). Reactions to

foreign material can also have the appearance of sarcoidosis. When this is seen, the possibility of potential underlying systemic disease should be mentioned. Table 7.8 highlights key points regarding the diagnosis of sarcoidosis.

Table 7.8 Practical tips: sarcoidosis

- Sarcoidosis is a diagnosis of exclusion
- Special stains and tissue culture should be liberally used, especially if there is no history of sarcoidosis
- Polarizable foreign material has been described in patients with sarcoidosis

Sample Report: Reactive Lymphoid Hyperplasia

Clinical history: Erythematous nodule on the left temple of a 25-year-old male.
Diagnosis: Nodular and diffuse lymphoid infiltrate with prominent germinal center formation, see comment.
Comment: There is a nodular and diffuse lymphoid infiltrate that focally extends into the subcutaneous fat. Lymphoid follicles with germinal centers, clear-cut mantle zones, and tingible body macrophages are observed. The interfollicular population includes lymphocytes, plasma cells, histiocytes, and occasional eosinophils. The germinal centers are highlighted with immunostains for CD20, and the germinal center has a high Ki-67 proliferative index. The dominant, surrounding population of cells is CD3+. The histologic and immunophenotypic features together with the clinical findings are most compatible with a reactive lymphoid process, such as to persistent arthropod bite. Recommend clinical follow-up; if lesions persist or progress, re-biopsy is suggested.

Sample Report: Sweet Syndrome

Clinical history: A 32-year-old woman presents with erythematosus nodules and plaques on the face.
Diagnosis: Neutrophilic dermatosis, see comment.
Comment: There is a dense, diffuse dermal infiltrate of neutrophils accompanied by foci of leukocytoclasis. No vasculitis is identified. The epidermis demonstrates slight spongiosis. The histologic findings are consistent with Sweet syndrome. If there is a clinical suspicion of an infectious etiology, tissue culture is recommended.

Sample Report: Granuloma Faciale

Clinical history: A 30-year-old man with erythematous plaque on the nose.
Diagnosis: Diffuse mixed infiltrate with neutrophils, eosinophils, and plasma cells consistent with granuloma faciale, see comment.
Comment: There is a diffuse dermal infiltrate and telangiectatic vessels with sparing of the adventitial dermis. The infiltrate is composed of neutrophils, eosinophils, and plasma cells. Foci of leukocytoclasis are identified. Ectatic vessels with prominent endothelial cells are also observed. These findings are consistent with granuloma faciale. Clinical correlation is recommended.

Sample Report: Sarcoidosis

Remember that sarcoidosis is a diagnosis of exclusion. A descriptive diagnosis of "granulomatous dermatitis" is usually the best approach.

Example 1: (In the setting of an established diagnosis of sarcoidosis)
Diagnosis: Granulomatous dermatitis consistent with sarcoidosis, see comment.
Comment: The biopsy demonstrates numerous epithelioid granulomas. Given the history of underlying sarcoidosis, these findings are consistent with cutaneous sarcoidosis. If there is a suspicion for a potential infectious process, special stains for microorganisms can be performed upon request.

Example 2: (In the setting without an established diagnosis of sarcoidosis)
Diagnosis: Granulomatous dermatitis, see comment.
Comment: The biopsy demonstrates numerous epithelioid granulomas without lymphocytic cuffs. GMS and Fite stains are negative for fungi and mycobacteria. Polariscopy reveals no polarizable foreign material. The histologic features are consistent with sarcoidosis in the appropriate clinical context, but an infectious process cannot entirely be excluded. Clinicopathologic correlation is recommended.

Example 3: (In the setting of sarcoid-like granulomas and foreign material)
Diagnosis: Granulomatous dermatitis and foreign material, see comment.
Comment: There are numerous sarcoidal granulomas in association with polarizable foreign material. Special stains for fungi (GMS) and mycobacteria (Fite stain) are negative. This could represent an idiopathic sarcoidal reaction to a foreign material. The possibility of underlying sarcoidosis should also be considered. Clinicopathologic correlation is recommended.

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Chapter 8
Palisading Granulomatous Dermatitis

Keywords Palisading granuloma • Granuloma annulare • Necrobiosis lipoidica • Rheumatoid nodule

This pattern is characterized by an interstitial infiltrate of histiocytes admixed with other inflammatory cells, principally lymphocytes, and zones of altered collagen (Fig. 8.1). Classically, the inflammatory infiltrate surrounds the zones of altered collagen in a wall-like or fence-like fashion, hence the term "palisading." The classic entities in this differential diagnosis include granuloma annulare, necrobiosis lipoidica, and rheumatoid nodule.

Granuloma Annulare

Clinical Features

Granuloma annulare is a common, usually asymptomatic dermatosis of unknown etiology. Clinical subtypes include localized, generalized, perforating, subcutaneous, and papular granuloma annulare. The localized variant is the most common type and usually occurs in young adults with a female preponderance. Skin colored papules in an annular or arcuate arrangement are most commonly located at acral sites, particularly the knuckles and fingers, but lesions may be seen in a variety of anatomic locations. Lesions tend to chronicity and recurrences are common.

Generalized granuloma annulare presents as multiple lesions (dozens to hundreds), on the trunk and either upper or lower extremities. The generalized form occurs most frequently in middle aged to older patients.

The subcutaneous variant also referred to as deep granuloma annulare, most often presents as deep nodules with or without overlying papules on the lower extremities. Young children are most commonly affected.

The most unusual variant is perforating granuloma annulare. It usually presents in adults and is remarkable for a crusted, umbilicated area in the central portion of

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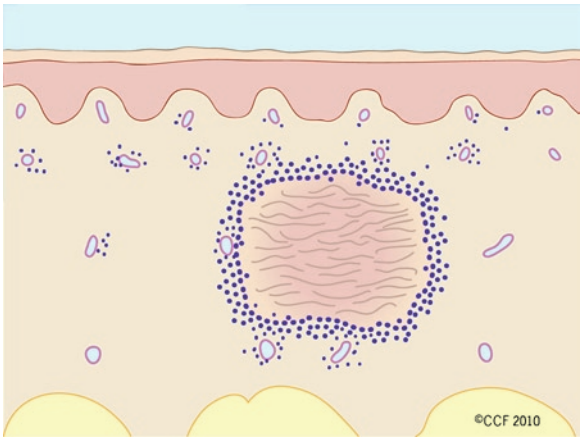

Fig. 8.1 *Schematic representation of palisading granuloma.* In palisading granulomatous dermatitides, there is an infiltrate of histiocytes admixed with other inflammatory cells that surrounds zones of altered collagen

the papule or plaque. It usually presents on acral surfaces, and for some reason appears to have a higher incidence in Hawaii (even paradise has its consequences).

Microscopic Features

With the exception of perforating granuloma annulare and subcutaneous granuloma annulare, all of the clinical variants have the same histologic features. Granuloma annulare most commonly involves the upper and mid reticular dermis. Frequently in biopsies, the infiltrate has a zonal appearance, with only portions of the dermis involved. The *sine qua non* of granuloma annulare is the palisading granuloma: a palisade of histiocytes admixed with lymphocytes surrounding a central zone of altered collagen fibers associated with increased dermal mucin (Fig. 8.2). The altered collagen fibers frequently appear more eosinophilic/red than the unaffected collagen. (This altered collagen has also been referred to as "necrobiotic" collagen.) The associated dermal mucin in the central portion of the palisading granuloma can be highlighted by colloidal iron stains, but this is generally unnecessary for the diagnosis (Fig. 8.3). There may be multinucleated giant cells and eosinophils that are found in approximately 50% of cases. Plasma cells are usually absent. In some cases, the palisading granuloma is not well-formed and the infiltrate has a more subtle, interstitial pattern (Fig. 8.4). Subtle alterations of the dermal collagen can usually be appreciated with careful observation on low to medium power. Rare cases have epithelioid granulomas reminiscent of sarcoidosis. The perforating variant has the palisading granulomas in the dermis with an ulcerated epidermis that shows transepidermal extrusion of collagen fibers (Fig. 8.5). Subcutaneous granuloma annulare resembles conventional granuloma annulare, but occurring in the subcutis and deep dermis (Fig. 8.6). See Table 8.1 for a summary of microscopic features.

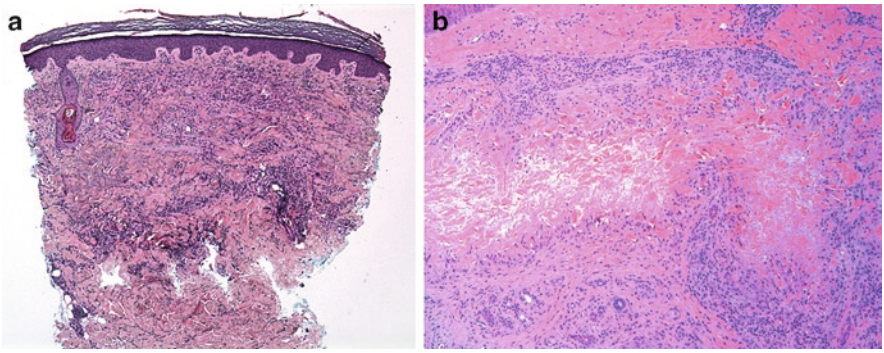

Fig. 8.2 *Granuloma annulare*. (**a**) In this scanning magnification image, the palisade of inflammatory cells surrounding the zone of altered collagen can be appreciated. (**b**) The palisading granuloma in this case is well-developed with histiocytes surrounding the altered collagen that has a more eosinophilic appearance

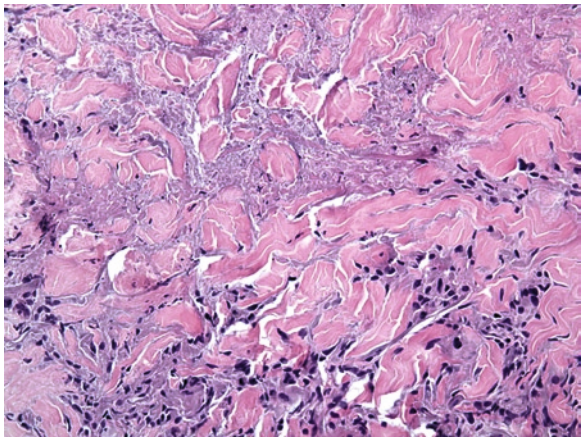

Fig. 8.3 *Granuloma annulare*. In the central portion of the palisading granuloma there is altered collagen and dermal mucin deposition

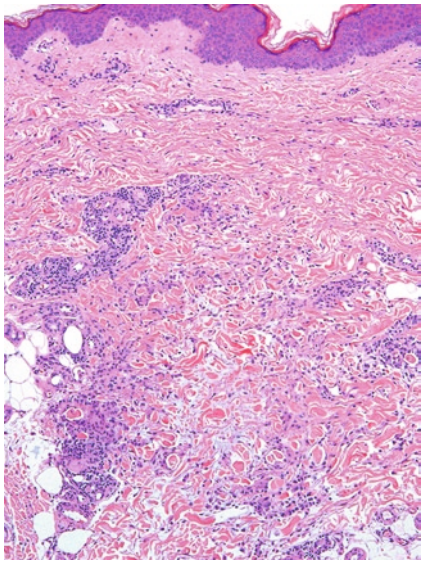

Fig. 8.4 *Granuloma annulare*. In this case, the palisading nature of the infiltrate is more subtle

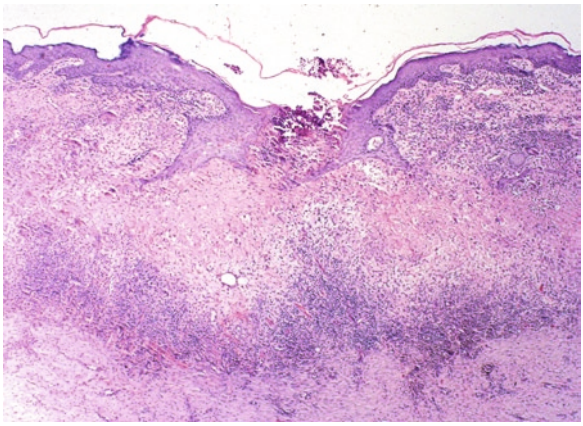

Fig. 8.5 *Perforating granuloma annulare*. In addition to palisading granulomas in the dermis there is transepidermal extrusion of the altered collagen fibers

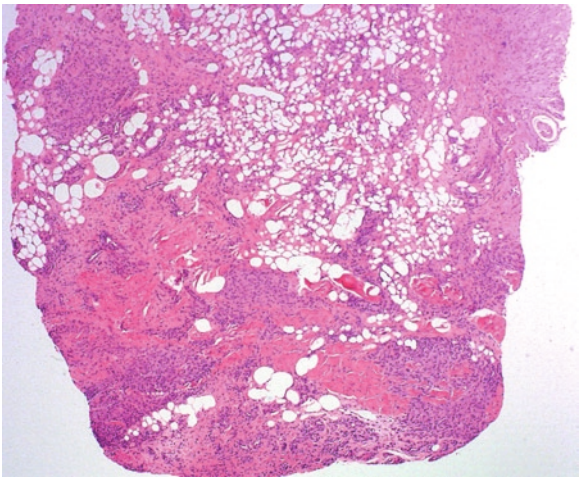

Fig. 8.6 *Subcutaneous granuloma annulare*. The subcutaneous form is predominantly or exclusively in the subcutaneous fat. It otherwise resembles granuloma annulare presenting in the dermis

Table 8.1 Key microscopic features: granuloma annulare

- Regional involvement of dermis
- Palisading granuloma with interstitial infiltrate of histiocytes surrounding altered collagen fibers
- Altered collagen in granuloma has dermal mucin
- Interstitial pattern has infiltrate of histiocytes intercalating around altered collagen bundles

Differential Diagnosis

The differential diagnosis predominantly includes other palisading granulomatous dermatoses, especially necrobiosis lipoidica, so-called actinic granuloma, and rheumatoid nodule. Other entities in the differential diagnosis can include a granulomatous drug eruption and dermatofibroma.

Necrobiosis lipoidica will be discussed in detail below. Briefly, in necrobiosis lipoidica, the dermis is more diffusely affected and the inflammatory infiltrate is arranged in a tiered fashion resulting in a striped pattern of inflammatory cells alternating with zones of altered collagen. Lymphoid aggregates with plasma cells are a feature of necrobiosis not typically seen in granuloma annulare.

Actinic granuloma, also called actinic granuloma of O'Brien, occurs in sun damaged skin of the head and neck, upper chest and upper extremities. There is controversy over the true nature of this entity. Some consider it merely a variant of granuloma annulare occurring in sun-damaged skin while others consider it a distinctly separate granulomatous dermatosis. Actinic granuloma does bear a striking resemblance to granuloma annulare (Fig. 8.7). There are palisading granulomas within the dermis associated with frequent multinucleated giant cells. The diagnostic feature in addition to the low power pattern is the phagocytosis of actinically damaged collagen (i.e., solar elastosis) by the multinucleated giant cells (Fig. 8.7). There is supposed to be less altered normal collagen and no dermal mucin in the infiltrate.

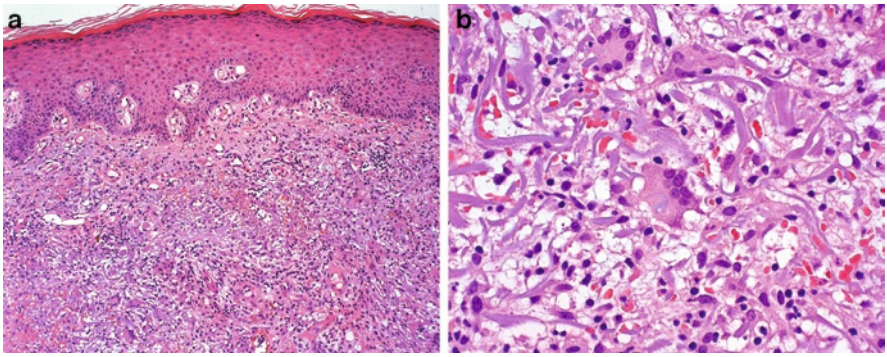

Fig. 8.7 *Actinic granuloma*. (**a**) At low to medium power, a subtle palisading granuloma is evident. (**b**) The granulomas lack significant dermal mucin deposition and contain multinucleated cells with phagocytosed actinically damaged collagen fibers (solar elastosis phagocytosis)

Rheumatoid nodule will also be discussed in more detail below. Briefly, rheumatoid nodule typically occurs in association with a joint and is located in the deep dermis/subcutis. The central portion of the palisading granuloma is eosinophilic and lacks dermal mucin.

Interstitial granulomatous drug eruptions are poorly understood entities. They can bear a striking resemblance to interstitial granuloma annulare. They usually have interface change in association with the granulomatous infiltrate, an important clue to the diagnosis. They usually have conspicuous eosinophils and rarely flame figures (collagen fibers encrusted with eosinophilic granules from eosinophils). Well-formed palisading granulomas are not a typical feature.

Finally, on a quick glance, granuloma annulare can be confused with dermatofibroma. Dermatofibroma will have epidermal hyperplasia and peripheral collagen trapping, and lacks the altered/necrobiotic collagen of granuloma annulare (see Table 8.2).

Table 8.2 Practical tips: granuloma annulare

- Low power examination is critical to seeing the palisading pattern
- Palisade not always well developed
- Infiltrate usually does not involve the entire dermis
- Interstitial pattern common; may be subtle
- Plasma cells not a typical feature of granuloma annulare
- Certain drug eruptions may have a GA-like pattern; interface change argues for a drug eruption
- In granuloma annulare-like eruption on actinically damaged skin, think about actinic granuloma and look for solar elastotic collagen fiber phagocytosis by multinucleated cells

Necrobiosis Lipoidica

Clinical Features

Necrobiosis lipoidica, also referred to as necrobiosis lipoidica diabeticorum, or NLD, most commonly presents as yellowish brawny indurated plaques on the lower extremities, particularly the pretibial areas. There is an association with diabetes (either type 1 or type 2) in a subset of cases, but coexisting diabetes mellitus is not a consistent feature.

Microscopic Features

Necrobiosis lipoidica is characterized by relatively diffuse dermal involvement, though there is often some sparing of the superficial dermis. The process may extend onto the superficial subcutis. The pattern of the palisading necrobiotic granulomas have a characteristic tiered arrangement of the inflammatory cells alternating with broad zones of necrobiotic collagen that run parallel to the overlying epidermis (Fig. 8.8). This pattern has been likened to the appearance of a layered cake or tiger stripes and is best appreciated on low power examination. The degenerated collagen is eosinophilic and lacks associated dermal mucin (Fig. 8.9). The inflammatory infiltrate is composed of an admixture of lymphocytes, histiocytes, multinucleated histiocytes, and plasma cells (Fig. 8.10). Lymphoid aggregates, sometimes with germinal centers, may be present. Some cases have sarcoid-like epithelioid granulomas (Fig. 8.11). The altered necrobiotic collagen has a more eosinophilic appearance, but increased dermal mucin is not a typical feature (see Table 8.3).

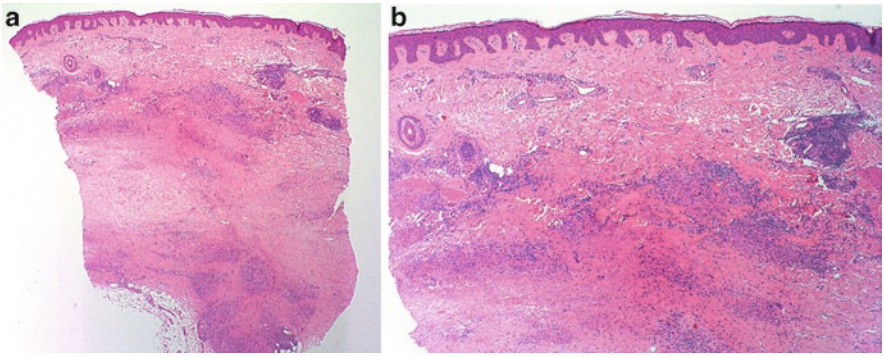

Fig. 8.8 *Necrobiosis lipoidica*. (**a**) Scanning magnification reveals that almost the entire dermis is affected. (**b**) At slightly higher power the tiered arrangement of inflammatory cells alternating with zones of altered collagen is apparent

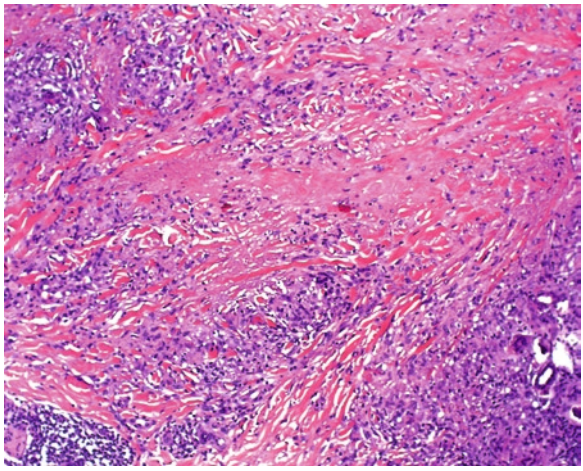

Fig. 8.9 *Necrobiosis lipoidica*. The degenerated necrobiotic collagen is eosinophilic and does not have associated dermal mucin

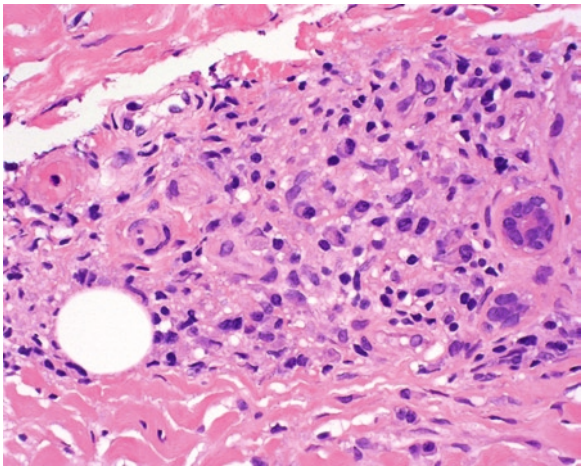

Fig. 8.10 *Necrobiosis lipoidica*. The inflammatory infiltrate is composed of varying numbers of histiocytes, lymphocytes and plasma cells. The presence of plasma cells can help differentiate necrobiosis lipoidica from granuloma annulare

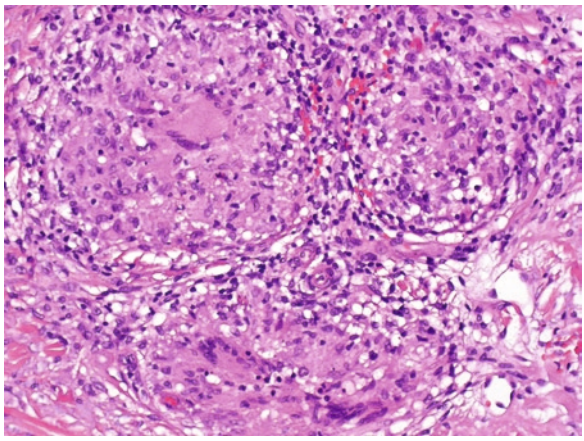

Fig. 8.11 *Necrobiosis lipoidica*. In some cases the granulomas can resemble the granulomas of sarcoidosis

Table 8.3 Key microscopic features: necrobiosis lipoidica

- Diffuse dermal involvement
- Tiered pattern of inflammatory infiltrate alternating between necrobiotic collagen
- Lymphoid aggregates
- Plasma cells

Differential Diagnosis

The primary entities in the differential diagnosis are granuloma annulare and sarcoidosis. In contrast to granuloma annulare, the dermal involvement in necrobiosis is more diffuse. Granuloma annulare does not have the tiered pattern, and plasma cells are not a feature of granuloma annulare. Necrobiosis lipoidica may have sarcoidal granulomas but sarcoidosis lacks the associated altered collagen and tiered pattern. Necrobiotic xanthogranuloma is a palisading granulomatous dermatitis associated

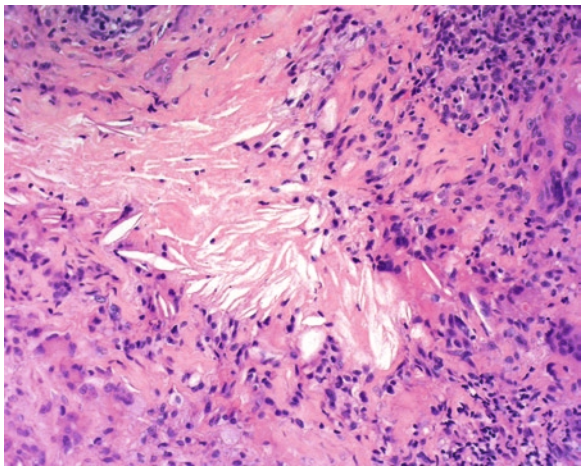

Fig. 8.12 *Necrobiotic xanthogranuloma*. This palisading granuloma contains numerous cholesterol clefts characteristic of necrobiotic xanthogranuloma

with monoclonal gammopathy. It usually presents with periorbital yellowish plaques. The infiltrate is more diffuse with less of a tiered pattern, has conspicuous multinucleated cells, foamy histiocytes and cholesterol clefts (Fig. 8.12) (Table 8.4).

Table 8.4 Practical tips: necrobiosis lipoidica

- Low power examination is the key to recognizing the tiered pattern
- The dermal is diffusely involved
- Plasma cells favor necrobiosis lipoidica over granuloma annulare
- In some cases the differential between granuloma annulare and necrobiosis lipoidica is not clear. In these cases a descriptive diagnosis of "granulomatous dermatitis, see comment" is helpful. See sample reports at the end of the chapter

Rheumatoid Nodule

Clinical Features

Rheumatoid nodules are subcutaneous/deep dermal lesions that tend to occur over bony prominences such as the extensor aspect of the forearms, elbows, hands, feet, and knees. However, they can occur at virtually any site. There is a correlation between severity of underlying arthritis and development of rheumatoid nodules.

Microscopic Features

Lesions are located in the deep dermis, subcutaneous fat or soft tissue. Centrally, areas of acellular fibrin are surrounded by histiocytes and giant cells in a palisaded pattern (Fig. 8.13). Variable numbers of lymphocytes, plasma cells, and eosinophils may be present, but the granulomas usually have a somewhat "naked" appearance (Table 8.5).

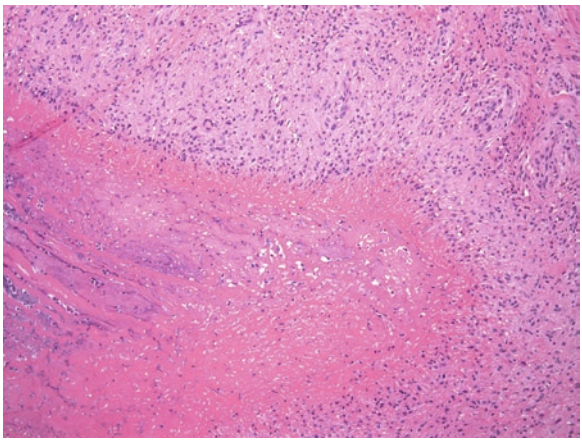

Fig. 8.13 *Rheumatoid nodule* is characterized by a granuloma with histiocytes surrounding a central zone of fibrin

Table 8.5 Key microscopic features: rheumatoid nodule

- Palisading granuloma of histiocytes surrounding acellular fibrin
- No abundant mucin in granuloma
- Granulomas often lack significant surrounding lymphocytic cuff

Differential Diagnosis

Deep granuloma annulare may be histologically indistinguishable from a rheumatoid nodule. Abundant mucin favors deep granuloma annulare, but definitive diagnosis requires careful clinicopathologic correlation. The differential diagnosis can also include entities such as epithelioid sarcoma. Epithelioid sarcoma can resemble granulomatous processes, but the pseudogranulomas that contain necrotic cellular debris rather than acellular fibrin, usually show subtle atypia, and are immunoreactive for epithelial markers. Rheumatoid nodules are typically well-defined palisading granulomas; they lack the tiered arrangement of necrobiosis lipoidica (Table 8.6).

Table 8.6 Practical tips: rheumatoid nodule

- Usually over bony prominences
- Is not present in superficial dermis
- Central portion of granulomas contain brightly eosinophilic fibrin
- Usually associated with rheumatoid arthritis
- If no known history of rheumatoid arthritis, consider descriptive diagnosis. See sample reports at end of chapter

Sample Reports: Granuloma Annulare

Example 1: (classic case):
Clinical history: Annular lesion.
Diagnosis: Granuloma annulare, see comment.
Comment: The epidermis is relatively normal. Within the dermis, there is a palisading granuloma characterized by histiocytes and lymphocytes surrounding a zone of altered collagen. The histologic features are characteristic of granuloma annulare.

Example 2:
Clinical history: Annular lesion.
Diagnosis: Interstitial granulomatous dermatitis, see comment.
Comment: The epidermis is relatively normal. Within the dermis, there is an interstitial infiltrate of histiocytes and lymphocytes. The collagen fibers surrounded by the infiltrate show subtle features of necrobiosis. The histologic features are compatible with interstitial granuloma annulare. Clinicopathologic correlation is recommended.

Sample Report: Necrobiosis Lipoidica

Example 1: (classic case):
Clinical history: Yellow plaque on leg.
Diagnosis: Necrobiosis lipoidica, see comment.
Comment: Throughout the dermis, there is a tiered arrangement of histiocytes admixed with lymphocytes alternating with broad zones of necrobiotic collagen. Focal lymphoid aggregates with plasma cells are present. The histologic features are characteristic of necrobiosis lipoidica.

Example 2: (equivocal case):
Clinical history: R/o necrobiosis lipoidica vs. granuloma annulare.
Diagnosis: Palisading granulomatous dermatitis, see comment.
Comment: Within the dermis, there is an infiltrate of histiocytes with admixed lymphocytes surrounding zones of altered collagen. The pattern varies from interstitial to having a somewhat tiered arrangement. There are focal lymphoid aggregates with plasma cells. The differential diagnosis includes granuloma annulare vs. necrobiosis lipoidica. The presence of lymphoid aggregates with plasma cells favors necrobiosis lipoidica. Clinicopathologic correlation is recommended.

Sample Report: Rheumatoid Nodule

Clinical history: Nodule on wrist.
Diagnosis: Palisading granuloma, see comment.
Comment: The biopsy demonstrates a palisading granuloma with histiocytes surrounding acellular fibrinous debris. The differential diagnosis includes deep granuloma annulare vs. a rheumatoid nodule. The latter is favored. Clinicopathologic correlation is recommended.
Note to reader: If the clinician is suspecting rheumatoid nodule or other clinical history is suggestive, it would be acceptable to be more definitive in the diagnosis.

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Chapter 9
Sclerosing Dermatitis

Keywords Morphea • Scleroderma • Lichen sclerosus

The sclerosing dermatitis pattern is generally characterized by dermal sclerosis, usually with little inflammation (Fig. 9.1).

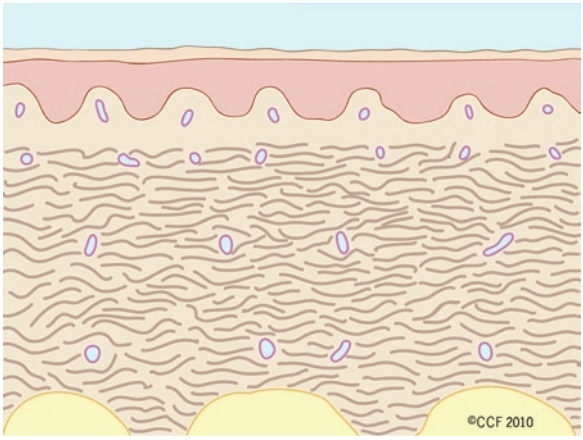

Fig. 9.1 *Schematic representation of fibrosing dermatitis*. This pattern is characterized by fibrosis/sclerosis of the dermal collagen. It manifests as thickened swollen collagen fibers with decreased space between collagen bundles and loss of adnexal structures. The inflammatory infiltrate is usually sparse

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Morphea/Scleroderma

Clinical Features

Morphea, also known as localized scleroderma, is characterized by localized, indurated plaques, usually on the trunk. The plaques frequently have a hypopigmented center surrounded by a violaceous border. Scleroderma is a multisystem connective tissue disease, which is divided into two major clinical groups:

Group 1: Limited disease involving hands, forearms and face, often have calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias (CREST) syndrome.

Group 2: Diffuse cutaneous sclerosis and frequent visceral involvement. Patients have indurated skin, sclerodactyly, hyperpigmentation with perifollicular pigment retention and telangiectasias.

Microscopic Features

Morphea and scleroderma are both characterized by fibrosing inflammation in the dermis and are histologically indistinguishable from each other. Early lesions of morphea are characterized by superficial and deep, perivascular and interstitial infiltrate of lymphocytes and plasma cells (Fig. 9.2). Occasionally, eosinophils or neutrophils are seen, and some lymphocytes may be seen in the basal layer. In the early phase, thickening of collagen bundles is subtle and may be unrecognizable. It is uncommon for the early forms of the lesions to be biopsied, but it is important to be aware of these features when presented with a clinical diagnosis of morphea

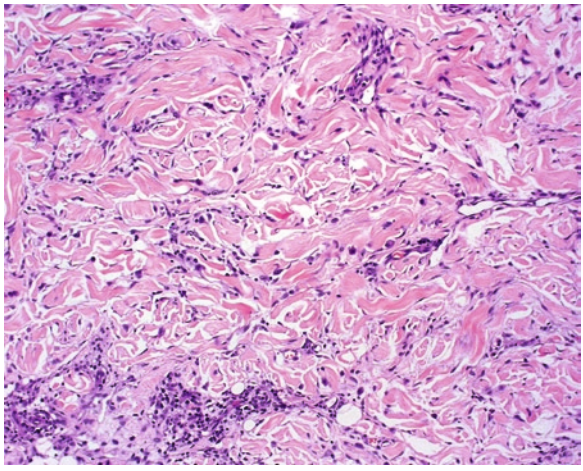

Fig. 9.2 *Early morphea*. In the early, inflammatory phase, a biopsy may demonstrate a superficial and deep perivascular lymphoplasmacytic infiltrate without appreciable dermal sclerosis

Table 9.1 Key microscopic features: morphea/scleroderma

- Dermal fibrosis with swollen collagen bundles
- Early lesions have perivascular lymphoplasmacytic infiltrate
- Decreased periadnexal fat
- Loss of adnexal structures in late lesions

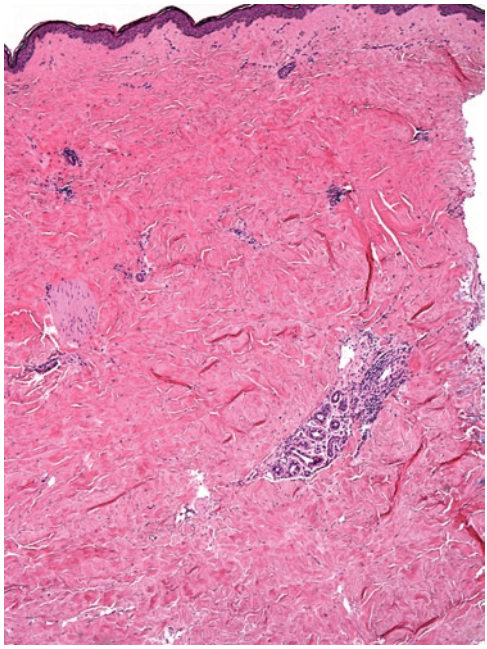

Fig. 9.3 *Well-developed morphea*. In more developed lesions there is dermal sclerosis with swollen collagen fibers and decreased space between collagen bundles of the reticular dermis. This case still has a perivascular inflammatory infiltrate, which is not always present in advanced lesions

without histologic evidence of significant dermal fibrosis (see sample reports at the end of the chapter).

In fully developed lesions, the inflammatory infiltrate is less dense and may be absent, and the dermal collagen changes are pronounced. The collagen bundles of the reticular dermis are thickened and swollen resulting in a compacted appearance with decreased space between collagen bundles of the reticular dermis (Fig. 9.3). The fibrosis of the dermis results in the so-called square biopsy sign. In most punch biopsies, the scanning appearance is somewhat wedge-shaped with the biopsy tapering with increasing depth. In contrast, punch biopsies from morphea or scleroderma are not wedge-shaped. Due to the sclerotic changes in the dermis, the peripheral edges of punch biopsies of morphea or scleroderma are parallel to each other resulting in a square or rectangular appearance to the biopsy on scanning magnification (Fig. 9.4). There is a sparse to mild perivascular lymphoplasmacytic infiltrate (Fig. 9.5). Some cases also show homogenization of the papillary dermis. See Table 9.1.

As the process develops, there is a loss of periadnexal fat and adnexal structures may degenerate or be completely absent. Over time, the fibrosing process can

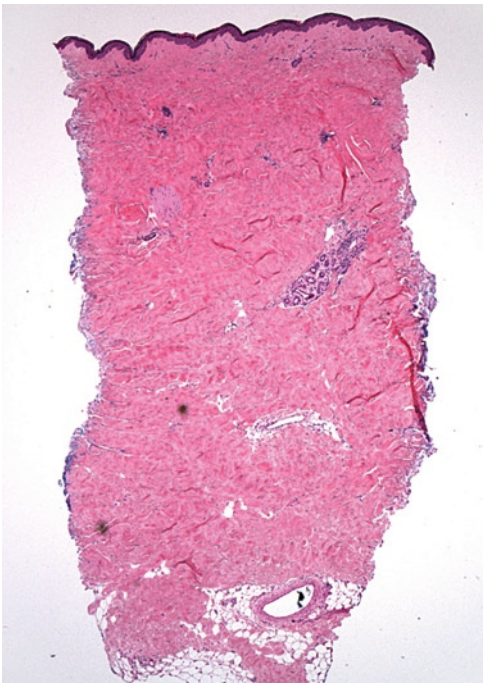

Fig. 9.4 *Square-biopsy sign*. On scanning magnification, punch biopsies from morphea/scleroderma have parallel, rather than tapered, sides

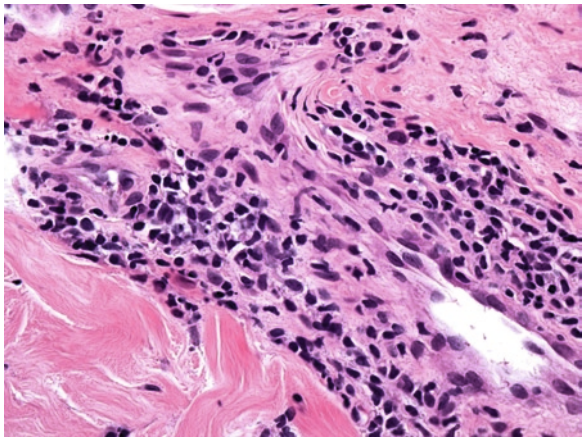

Fig. 9.5 *Perivascular infiltrate of morphea/scleroderma*. Frequently, even in advanced lesions, there is a remnant of the perivascular lymphoplasmacytic infiltrate

impinge on the superficial subcutaneous fat. Some cases can show extension of the fibrosing process along the subcutaneous septae (Fig. 9.6). Occasional cases of morphea show preferential involvement of the subcutaneous septae with limited involvement of the dermis. Cases with this pattern have been termed morphea profundus, or deep morphea.

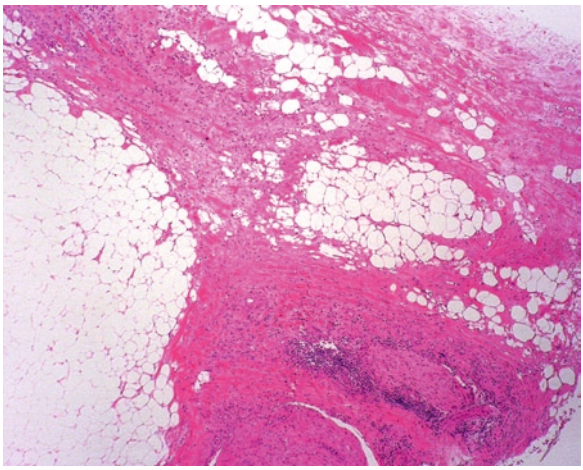

Fig. 9.6 *Deep morphea.* In some cases the process may extend along subcutaneous septae or be centered in the subcutis

Differential Diagnosis

The differential diagnosis of morphea and scleroderma includes each other. They are indistinguishable except by clinical findings. There can be significant overlap with lichen sclerosus, especially in earlier lesions of morphea. The collagen changes of lichen sclerosus are predominantly found in the papillary dermis and superficial reticular dermis. There is usually some evidence of interface change. Interface change is not a typical feature of morphea. There are some cases with sufficiently overlapping features suggesting that at least some cases of lichen sclerosus (usually cases presenting outside the anogenital area) and morphea exist along a spectrum. See the section on lichen sclerosus below for a more detailed description.

It is also important to distinguish morphea from normal back skin. Skin from the back normally has a thicker reticular dermis. As a result, the biopsy may show the "square biopsy" sign on scanning magnification, but does not have the decreased spaces between collagen bundles.

Late stage lesions of necrobiosis lipoidica can simulate morphea. In the former, granulomatous changes can be subtle and fibrosis marked. Both conditions can have plasma cells. A clue to the diagnosis of necrobiosis lipoidica is that an elastic tissue stain will show near absence of elastic fibers, while elastic fibers are mostly preserved in morphea.

Nephrogenic systemic fibrosis, formerly named nephrogenic fibrosing dermatopathy, occurs in patients with renal disease, and most (~90%), but not all, are undergoing renal dialysis. It has been associated with the use of the radiologic contrast agent Gadolinium. Patients develop large symmetric areas of hardened skin on the extremities, often with brawny hyperpigmentation. Histologically, biopsies show an increase in CD34-positive fibroblasts in the dermis and subcutis, associated with

thickened collagen bundles (Fig. 9.7). The fibrosing process of morphea has fewer fibroblasts. Unlike morphea, increased mucin may be seen. Plasma cells are not a feature of nephrogenic systemic fibrosis.

Chronic radiation dermatitis is a complication of radiation exposure. Changes in the reticular dermis can resemble those of morphea with decreased space between collagen bundles and loss of adnexal structures. The dermal blood vessels are ectatic and may show prominent hyalinization. Characteristic pleomorphic fibroblasts, so-called "radiation fibroblasts," help distinguish this entity from morphea/scleroderma (Fig. 9.8).

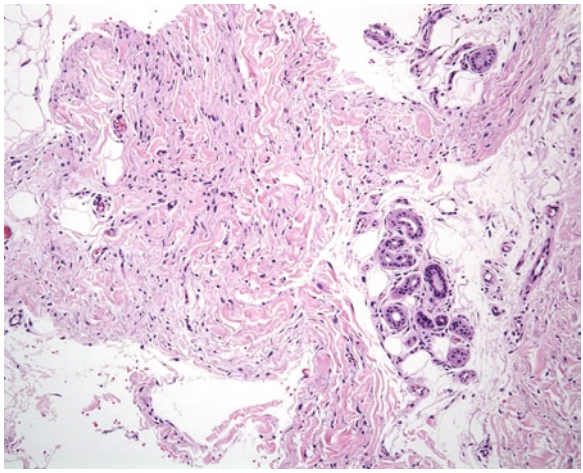

Fig. 9.7 *Nephrogenic systemic fibrosis*. This fibrosing dermatitis is characterized by a proliferation of fibroblasts and dermal fibrosis

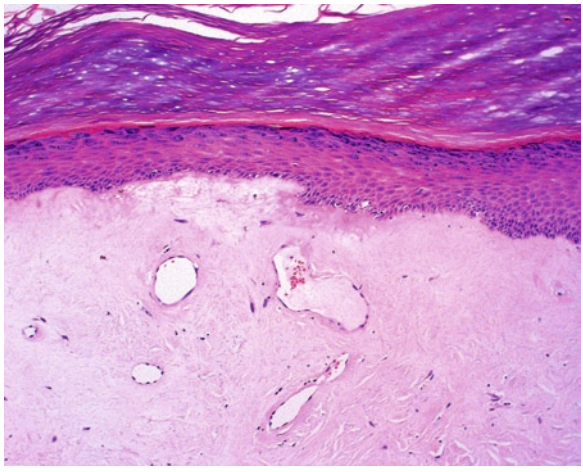

Fig. 9.8 *Chronic radiation dermatitis*. In radiation associated dermal sclerosis, there is dermal fibrosis with ectatic blood vessels and pleomorphic radiation fibroblasts

Eosinophilic fasciitis can be confused with morphea profundus. It is a fibrosing process that extends along fibrous septae with no or only limited involvement of the reticular dermis. Although called eosinophilic fasciitis, eosinophils are only infrequently seen in the biopsy specimen. It is associated with peripheral eosinophilia. Distinction from morphea profunda usually requires correlation with clinical parameters. Eosinophilic fasciitis is widespread, associated with joint symptoms and approximately half of the cases are associated with recent strenuous activity.

Finally, scar can be confused with morphea, especially in later stages of the scar, when the fibroblastic proliferation has receded. For practical purposes, this is less of an issue as a history of trauma, or prior procedure is usually known in the setting of scars. Practical tips are summarized in Table 9.2.

Table 9.2 Practical tips: morphea/scleroderma

- On low power "square biopsy" – but must differentiate from normal back!
- Fibrosis recognized by decreased spaces between collagen fibers of reticular dermis
- Early lesions may not show significant fibrosis but still clinically resemble morphea: look for lymphoplasmacytic infiltrate

Lichen Sclerosus

Clinical Features

Lichen sclerosus, also referred to as lichen sclerosus et atrophicus, presents as white plaques with overlying epidermal atrophy. The atrophy results in a wrinkled appearance to the overlying epidermis. Lesions are frequently pruritic. There is a predilection for the anogenital region, but approximately 20% may present in other locations. There is a small risk (<5%) for development of squamous cell carcinoma, typically in cases involving genital skin.

Microscopic Features

The earliest lesions resemble interface dermatitis with basal vacuolization and a lichenoid infiltrate resembling lichen planus (Fig. 9.9). Basement membrane thickening is a feature as well as telangiectatic blood vessels with or without papillary dermal hemorrhage. Follicular plugging and psoriasiform hyperplasia may be present in focal areas. The epidermis in lichen sclerosus frequently shows reactive changes related to excoriation consisting of compact hyperkeratosis and a thickened granular layer. As the lesions progress, the epidermis becomes atrophic and the characteristic dermal changes develop with edema and homogenization of the papillary dermis (Fig. 9.10). In later lesions, the superficial dermis is sclerotic, resembling

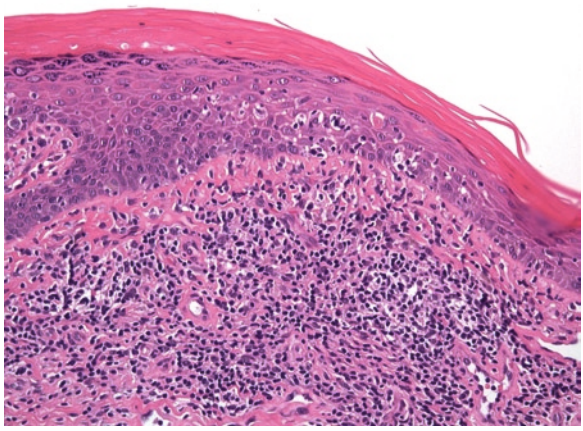

Fig. 9.9 *Early lichen sclerosus* has the appearance of an interface dermatitis resembling lichen planus with a band-like lymphocytic infiltrate, hyperkeratosis and a thickened granular layer

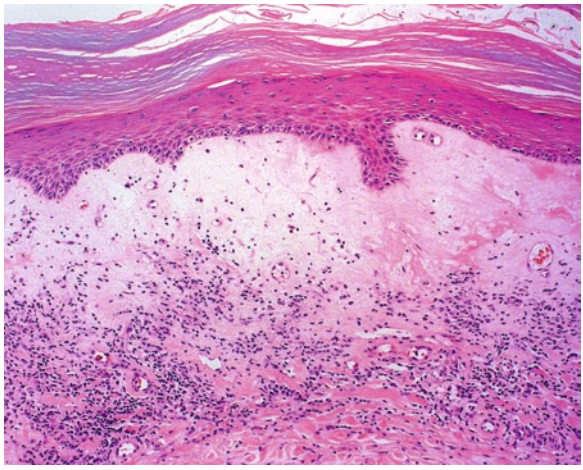

Fig. 9.10 *Lichen sclerosus*. The epidermis has compact hyperkeratosis with some thickening of the granular layer. The papillary dermis has the characteristic edema and homogenization of the papillary dermis. Note how the lichenoid infiltrate is beneath the zone of altered collagen

the changes of morphea (Fig. 9.11). There is a loss of dermal elastic fibers that can be demonstrated by elastic tissue stains, though this is not necessary for the diagnosis. See Table 9.3 for a summary of microscopic features.

Differential Diagnosis

The primary differential diagnosis of early lichen sclerosus is lichen planus. Distinguishing between these entities may not always be possible. Basement membrane thickening and psoriasiform hyperplasia are not features of lichen planus,

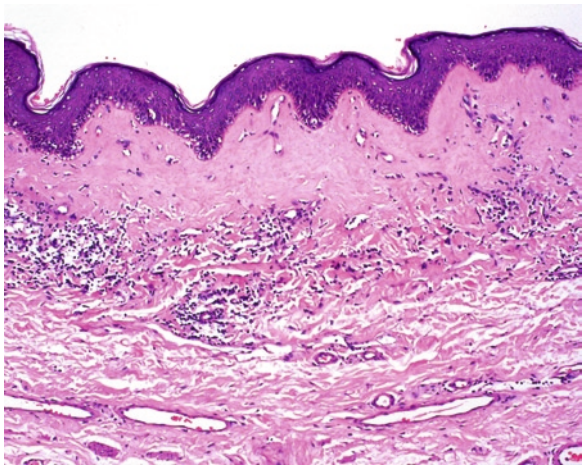

Fig. 9.11 *Lichen sclerosus, late stage*. As the process evolves the papillary dermis can become fibrotic

Table 9.3 Key microscopic features: lichen sclerosus

- Early lesions
  - Lichenoid infiltrate of lymphocytes and plasma cells
  - Psoriasiform epidermal hyperplasia may be present early
  - Basement membrane thickening may be present
- Established lesions
  - Homogenized or sclerotic papillary dermis
  - Scattered lymphocytes and plasma cells beneath altered collagen
  - Atrophic epidermis with compact hyperkeratosis and thickened granular layer

and when present, allows for distinction. Loss of papillary dermal elastic fibers is also not seen in lichen planus. Plasmacytosis mucosae, so-called Zoon's balanitis or Zoon's vulvitis, may also be confused with early lichen sclerosus. In men, plasmacytosis mucosae occurs exclusively on the glans/foreskin in uncircumcised older patients. In women, the labia minora or vestibule are affected, though it is much less common in women. Microscopically, there is a band like infiltrate of lymphocytes and plasma cells, but the epidermis has a different appearance than lichen sclerosus. There is spongiosis, parakeratosis, a diminished or absent granular layer and lozenge, or diamond-shaped keratinocytes (Fig. 9.12). Neutrophils are also commonly seen in the stratum corneum. Established lesions of lichen sclerosus with fibrosis of the papillary dermis can be confused with morphea if the alteration of the collagen extends into the upper reticular dermis. In such cases, it may be necessary to provide a descriptive diagnosis (see sample reports). See Table 9.4.

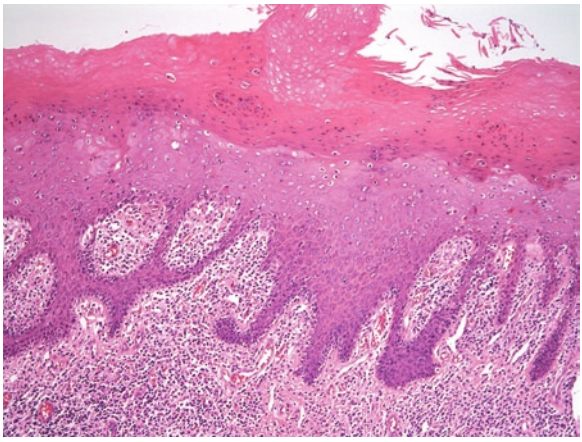

Fig. 9.12 *Plasmacytosis mucosae (Zoon's balanitis/ vulvitis).* Plasmacytosis mucosae also has a band-like infiltrate that can be confused with early lichen sclerosus or lichen planus. The epidermal features are different with spongiosis and a diminished granular layer

Table 9.4 Practical tips: lichen sclerosus

- Consider the possibility of early lichen sclerosus in any interface dermatitis of genital skin
- Distinguishing early lichen sclerosus from lichen planus can be very difficult (i.e., basement membrane thickening and other distinguishing features may not be evident). A descriptive of lichenoid interface dermatitis is acceptable in this situation (see sample reports)
- Remember that lichen sclerosus may occur outside the anogenital area
- In cases with histologic overlap with morphea, a descriptive diagnosis of "sclerosing dermatitis" is appropriate (see sample reports)

Sample Reports: Morphea/Scleroderma

Example 1: This sample report reflects the setting where morphea is suspected, but there is no significant dermal fibrosis.

Clinical history: R/O morphea.

Diagnosis: Superficial and deep perivascular lymphoplasmacytic infiltrate, see comment.

Comment: Within the dermis, there is a mild superficial perivascular lymphoplasmacytic infiltrate. No significant dermal fibrosis is seen. In the appropriate clinical context, this could represent the early, inflammatory phase of a lesion of morphea. Clinicopathologic correlation is recommended.

Example 2: In this example, the clinical diagnosis is not provided, but the features are classic for morphea/scleroderma.

Clincial history: Depressed plaque on trunk.

Diagnosis: Morphea/scleroderma, see comment.

Comment: The dermis shows marked sclerosis characterized by swollen, compacted collagen fibers with loss of adnexal structures. There is a sparse perivascular lymphoplasmacytic infiltrate. Depending

on the clinical presentation, the biopsy findings are consistent with morphea or scleroderma. Clinicopathologic correlation is recommended.

Sample Reports: Lichen Sclerosus

Example 1: This is a sample report for a case where it is difficult to distinguish lichen sclerosus from lichen planus.
Clinical history: R/O lichen sclerosus.
Diagnosis: Lichenoid interface dermatitis, see comment.
Comment: There is some compact hyperkeratosis and a mildly thickened granular layer. Within the dermis, there is a lichenoid infiltrate of lymphocytes with admixed plasma cells associated with interface change. The histologic features are compatible with early lichen sclerosus, but the possibility of lichen planus cannot be entirely excluded.

Example 2: This sample report reflects a biopsy outside the anogenital area where there are overlapping features of morphea and lichen sclerosus.
Clinical history: R/O lichen sclerosus.
Diagnosis: Sclerosing dermatitis, see comment.
Comment: The epidermis is atrophic with effacement of the normal rete peg architecture. There is homogenization of the papillary dermis, and sclerosis of the upper reticular dermis. This biopsy has overlapping features of lichen sclerosus and morphea. Some consider these entities to represent a morphologic spectrum of the same process. Clinicopathologic correlation is recommended.

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Chapter 10
Bullous Dermatitis

Keywords Pemphigus • Transient acantholytic dermatosis • Grover's disease • Bullous pemphigoid • Cicatricial pemphigoid • Pemphigoid gestationis • Dermatitis herpetiformis • Bullous lupus erythematosus • Linear IgA disease • Epidermolysis bullosa acquisita • Porphyria cutanea tarda • Pseudoporphyria

The bullous dermatitis pattern is characterized by intraepidermal or subepidermal blister formation (Figs. 10.1 and 10.2). This discussion will be limited to diseases in which blister formation is the primary manifestation rather than blisters as a secondary phenomenon (i.e., blisters secondary to contact dermatitis, as discussed in Chap. 2). An understanding of the concept of acantholysis is paramount to any discussion of the intraepidermal vesicular disorders. Acantholysis is the result of loss of appropriate keratinocyte–keratinocyte adherence. This adherence is mediated by tight junctions, adherens junctions, gap junctions, and desmosomes. Desmosomes are critical to keratinocyte adhesion, and they are the last structures to split when acantholysis occurs. Acantholytic disorders that have been well characterized develop as sequelae of desmosomal dysfunction or disruption of the desmosomal connections with the intracellular keratin structural matrix. Keratinocyte–keratinocyte adhesion is a dynamic process because the relationship of one keratinocyte to another must change during epidermal maturation. Thus, acantholysis may be viewed as a loss of equilibrium between the formation and dissolution of junctions. This dysequilibrium may occur primarily when the adhesion junctions are impaired directly or secondarily when keratinocytic viability is affected. Histologically, acantholytic keratinocytes are rounded with condensed eosinophilic cytoplasm, large nuclei, peripheral marginated chromatin and prominent nucleoli. In intraepidermal blistering disease, the blister forms as the result of acantholysis within the epidermis.

In contrast, with subepidermal blistering disease, the split occurs at the dermal-epidermal junction. The integrity of dermo-epidermal adhesion is maintained thorugh focal attachment sites with the cutaneous basement membrane zone known

S.D. Billings and J. Cotton, *Inflammatory Dermatopathology: A Pathologist's Survival Guide*, 157
DOI 10.1007/978-1-60327-838-6_10,

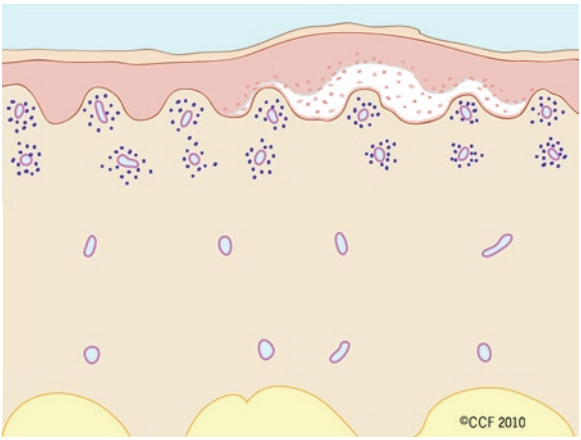

Fig. 10.1 *Schematic representation of intraepidermal blister*. Intraepidermal bullous dermatoses are characterized by formation of an intraepidermal blister via acantholysis. The basal layer remains attached to the basement membrane

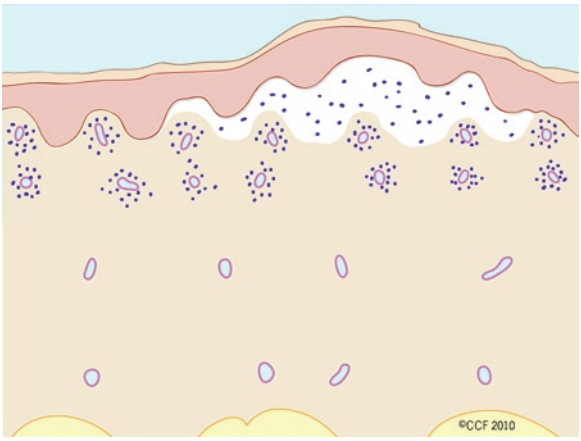

Fig. 10.2 *Schematic representation of subepidermal blister*. In subepidermal bullous dermatoses the entire epidermis is separated from the underlying dermis

as anchoring complexes. Patients with acquired autoimmune subepidermal blistering disorders have autoantibodies directed against components of the anchoring complex, resulting in disruption of the basement membrane zone and blister formation. Location of the level of blister formation, the composition of the inflammatory infiltrate, and correlation with direct immunfluorescence is required for definitive diagnosis. This chapter will focus on intraepidermal and subepidermal blistering disorders that are of importance to the general surgical pathologist. Where relevant, the underlying pathogenesis of the blistering disorder is discussed, as this aids in understanding the histologic findings.

In the evaluation of autoimmune blistering disease, examination of biopsies with direct immunofluorescence is often required for confirmation of the diagnosis. These biopsies should be perilesional (between 0.5 and 1 cm away from an adjacent bliser). Importantly, the specimen should be placed in Michel's solution rather than formalin. Formalin fixation results in autofluorescence, thereby resulting in nonspecific positivity.

Intraepidermal Vesicular Dermatitis

Pemphigus Vulgaris

Clinical Features

Pemphigus vulgaris presents as large, flaccid bullae on a normal, or erythematous base. Lesions typically involve oral mucosa, face, scalp, central chest, and intertriginous zones in older individuals. Oral lesions are the first manifestation in 10–15% of patients and almost invariably develop during the course of the disease. Blisters break easily leaving large eroded and crusted ulcers. Pemphigus vulgaris is a severe disease, that, if left untreated, can often lead to death.

Microscopic Features

The antibodies in pemphigus vulgaris are directed against desmoglein 3, a desmosomal cadherin that mediates cell binding. Desmoglein 3 is expressed in greater concentration in the lower epidermis, the location of the suprabasal acantholytic blister of pemphigus vulgaris. More than half of sera from patients with pemphigus vulgaris also have circulating antibodies against desmolglein 1.

Established lesions of pemphigus vulgaris demonstrate suprabasilar acantholysis with frequent involvement of follicular external root sheaths (Fig. 10.3). The basal keratinocytes separate from one another but remain attached to the dermis, reminiscent of a "row of tombstones" (Fig. 10.4). Acantholytic cells may be arranged as solitary units or groups of cells separated from the adjacent keratinocytes (Fig. 10.5). Nuclei are pyknotic, hyperchromatic, and often surrounded by a perinuclear halo. In the superficial dermis, there is typically a superficial perivascular lymphoid infiltrate with occasional eosinophils. Rarely, lesions in pemphigus vulgaris may demonstrate eosinophilic spongiosis (i.e., eosinophils within the overlying epidermis).

All patients with active pemphigus have IgG autoantibodies directed against the cell surface of keratinocytes detectable by direct and often indirect immunofluorescence. Direct immnofluorescence demonstrates intercellular squamous staining of IgG and, in most cases, complement C3 (Fig. 10.6). Pemphigus should not be diagnosed if only C3 is present. About 30% of patients exhibit deposition of IgM and/or IgA. (Table 10.1 highlights key microscopic and immunofluorescence features).

Table 10.1 Key microscopic features: pemphigus vulgaris

- Suprabasilar blister with acantholysis which extends into the follicular epithelium
- Basal layer spared ("tombstone")
- Rarely, eosinophilic spongiosis observed
- DIF: IgG and possibly C3 deposited in the intercellular regions of the epidermis

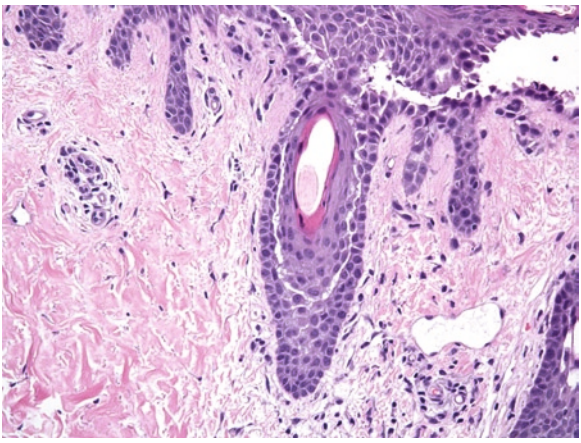

Fig. 10.3 *Pemphigus vulgaris* is characterized by acantholysis. Extension down follicles is common

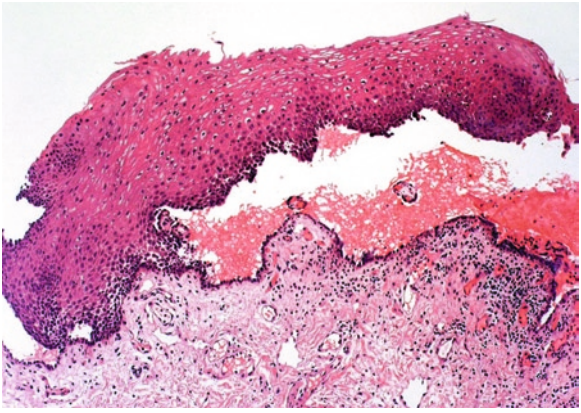

Fig. 10.4 *Pemphigus vulgaris*. This is a biopsy from the oral mucosa involved by pemphigus vulgaris. Note the suprabasilar blister formation with sparing of the basal layer of keratinocytes. The basal keratinocytes cling to the basement membrane in a tombstone pattern. This case has relatively little suprabasilar acantholysis

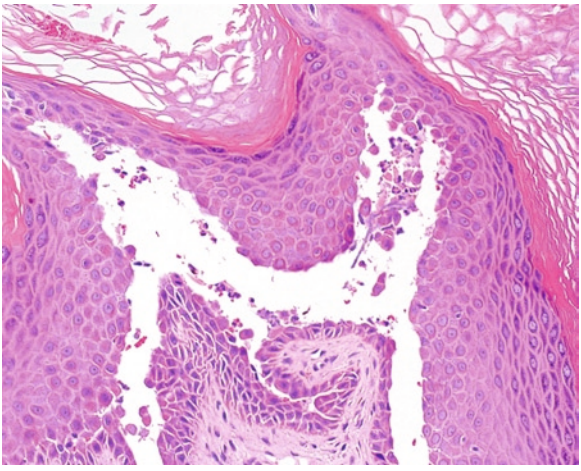

Fig. 10.5 *Pemphigus vulgaris*. This higher power image from a case of pemphigus vulgaris demonstrates the acantholysis and the tombstone pattern of basal layer

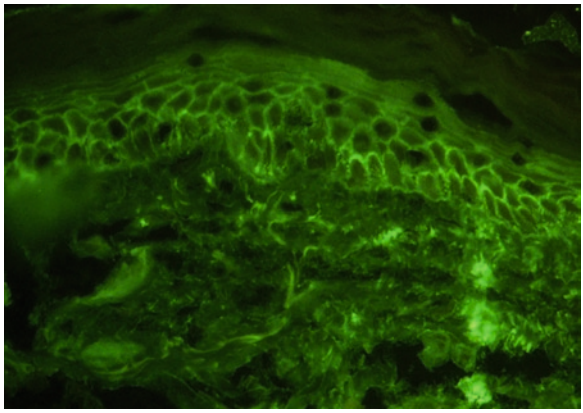

Fig. 10.6 *Pemphigus vulgaris direct immunofluorescence*. Direct immunofluorescence of perilesional skin demonstrates intercellular staining of IgG resulting in a net-like or chicken wire staining pattern of the epidermis

Differential Diagnosis

Although the clinical and histopathologic features of pemphigus vulgaris are often distinctive, other acantholytic disorders including pemphigus foliaceus, drug-induced pemphigus, IgA pemphigus, paraneoplastic pemphigus, familial benign pemphigus, focal acantholytic dyskeratosis, herpesvirus infection, and acantholytic variants of actinic keratosis may enter into the differential diagnosis.

In pemphigus foliaceus, the majority of the authoantibodies are directed against desmoglein 1, which is expressed in higher concentrations in the upper epidermis. Histologically, this manifests as superficial intraepidermal blister formation, often with loss of the stratum corneum and granular layer (Fig. 10.7) in contrast to the suprabasilar cleaveage of pemphigus vulgaris. A clear association with a drug may be necessary to separate drug-induced pemphigus from pemphigus vulgaris. IgA pemphigus differs from pemphigus vulgaris by demonstrating subcorneal or intraepidermal neutrophilic pustules with mininimal or no acantholysis and positive immunoreactivity for intraepidermal intercellular IgA. Paraneoplastic pemphigus is distinctive because of a close relationship with an underlying maligiancy, the clinical heterogeneity of the eruption, and striking mucocutaneous involvement. Histologically, the presence of interface alteration and dyskeratosis (erythema multiforme-like pattern), coupled with acantholysis, and both intercellular and basement membrane zone patterns of immunofluorescence distinguish paraneoplastic pemphigus from pemphigus vulgaris. Familial benign pemphigus (Hailey–Hailey disease) is differentiated from pemphigus by the presence of acanthosis, acantholysis involving at least half of the epidermis in a diffuse pattern, occasional dyskeratosis, lack of appendageal involvement, and negative immunofluorescence results. Other acantholytic disorders that fall in the differential diagnosis include Darier's disease and Grover's disease. In contrast to Darier's and Grover's disease, pemphigus vulgaris exhibits greater breadth of involvement of the epidermis with periappendageal extension. In contrast, Grover's disease involves smaller, more discrete foci of epithelium; Darier's disease demonstrates dyskeratotic cells (see Table 10.2). Occasionally, pemphigus vulgaris may mimic herpesvirus infection by

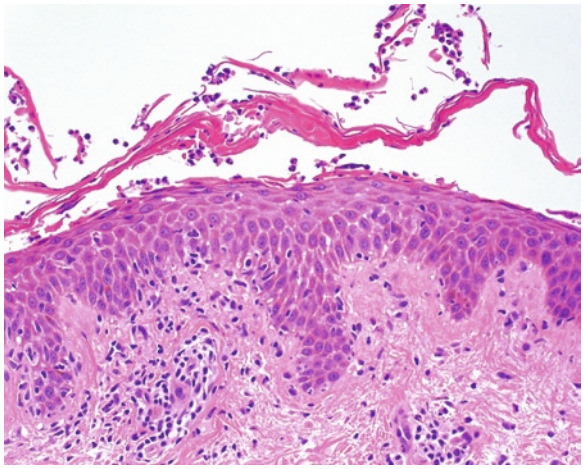

Fig. 10.7 *Pemphigus foliaceus*. In pemphigus foliaceus the blister formation is superficial, occurring at the stratum corneum or granular layer

Table 10.2 Practical tips: pemphigus vulgaris

- The clinical and histologic/direct immunofluorescence findings are usually distinctive
- If presenting in intertriginous areas consider Hailey–Hailey disease
- Other acantholytic disorders to be considered include Darier's disease and Grover's disease
  - In contrast to Darier's and Grover's disease, pemphigus vulgaris involves broad areas of the epidermis with periadnexal extension. In contrast, Grover's disease involves smaller more discrete foci of epithelium; Darier's disease demonstrates dyskeratotic cells
- Not all histologic features are necessarily seen in a given biopsy

showing acantholysis and alterations suggesting viral cytopathic changes of herpes ("ground glass" nucleus). Acantholytic variants of actinic keratosis are distinguished from pemphigus vulgaris by the presence of parakeratosis, crowding and atypia of the basilar keratinocytes, as well as clinical presentation.

Transient Acantholytic Dermatosis (Grover's Disease)

Clinical Features

Also known as Grover's disease, transient acantholytic dermatosis is characterized by pruritic discrete papulovesicles on the chest, back, and thighs, usually in middle-aged or elderly males.

Microscopic Features

Four histologic patterns have been described. These include Darier-like, Hailey–Hailey, pemphigus-like and spongiosis with acantholysis. Regardless of the pattern,

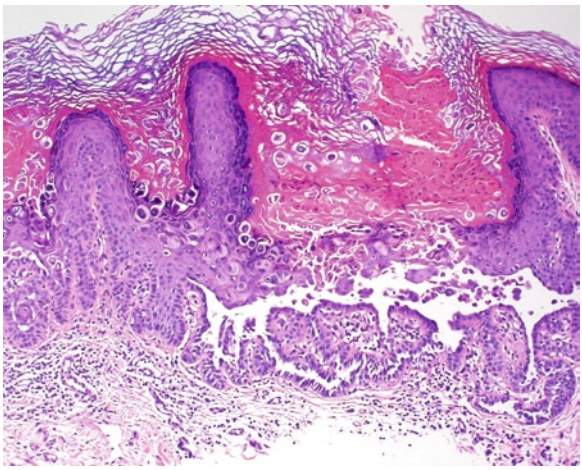

Fig. 10.8 *Transient acantholytic dermatosis (Grover's disease)*. Sharply circumscribed foci of suprabasilar acantholysis (pemphigus pattern) with hyperkeratosis, parakeratosis, and dyskeratotic round cells with abundant keratohyaline granules (corps ronds/Darier pattern)

Table 10.3 Key microscopic features: transient acantholytic dermatosis (Grover's disease)

- Discrete foci of acantholytic dyskeratosis (focal acantholytic dyskeratosis)
- Four histologic patterns have been described: Darier's-like, Hailey–Hailey-like pemphigus vulgaris-like (most common) and spongiotic dermatitis
- Superficial perivascular lymphocytic infiltrate in the dermis

all lesions are characterized by the circumscribed, focal nature of histologic changes, often, only several rete wide. Moreover, any or all of these histologic patterns may be present in an individual biopsy from an individual patient. The most common pattern is pemphigus vulgaris-like, followed by Darier-like. The pemphigus-type is characterized by discrete foci of suprabasilar acantholysis. Darier-like lesions demonstrate a suprabasilar split with corps ronds and corps grains and elongation of rete ridges. The patterns frequently coexist (Fig. 10.8). Given the focal nature of the process in a given biopsy specimen, multiple levels may be needed to reveal the characterisitic findings. Key microscopic features of Grover's disease are highlighted in Table 10.3.

Differential Diagnosis

Given the different patterns described with transient acantholytic dyskeratosis, the differential diagnosis includes Darier's disease, Hailey–Hailey disease, pemphigus, and a spongiotic dermatitis. Transient acantholytic dermatosis is distinguished from the latter entities based on the presence of two or more histologic patterns and limitation to small foci, often only several rete wide. Clinical information is also of value as the clincial presentation is distinctly different from the other acantholytic diseases in the histologic differential diagnosis. Important clues to the diagnosis of Grover's disease are summarized in Table 10.4.

Table 10.4 Practical tips: transient acantholytic dermatosis (Grover's Disease)

- The focal nature of the acantholytic process is a clue to the diagnosis
- Multiplicity of histologic patterns is a clue to the diagnosis
- Multiple levels may be necessary to establish the diagnosis
- The pattern of focal acantholytic dyskeratosis may be seen as an incidental finding in otherwise benign keratoses
- Direct immunofluorescence negative

Subepidermal Vesicular Dermatitis

The subepidermal blistering disorders are defined by the presence of a blister beneath the epidermis. They can also be subdivided as to the nature of the associated inflammatory cells, or lack thereof.

Subepidermal Vesicular Dermatitis with Predominant Eosinophils

Bullous Pemphigoid

Clinical Features

Bullous pemphigoid (BP) is the most common autoimmune blistering disorder. It affects elderly patients and is characterized by tense bullae arising on normal skin or an erythematous base. The sites of predilection are the groin and lower abdomen. Oral mucosal involvement develops in one third of patients. Pruritus is a common feature at presentation. In the early stages of the eruption, there are urticarial papules and plaques.

Microscopic Features

Patients with BP have circulating IgG autoantibodies against two BMZ antigens: BPAg1, a 230-kD protein, and BPAg2, a 180-kD protein. Fully developed lesions of bullous pemphigoid are characterized by a subepidermal vesicle with eosinophils and other inflammatory cells in and around the vesicle (Fig. 10.9). Rarely, the inflammatory process can be neutrophil- predominant or cell-poor. Early urticarial forms of bullous pemphigoid demonstrate eosinophilic spongiosis and/or a perivascular lymphoid infiltrate with eosinophils (Fig. 10.10). Eosinophils tagging the basal layer can be a clue to the diagnosis in the urticarial phase. Direct immunofluorescence of perilesional skin shows linear deposition of C3 (100%) and IgG (65–95%) along the dermoepidermal junction (Fig. 10.11). Indirect immunofluorescence examination with patient's sera applied to normal human skin as substrate

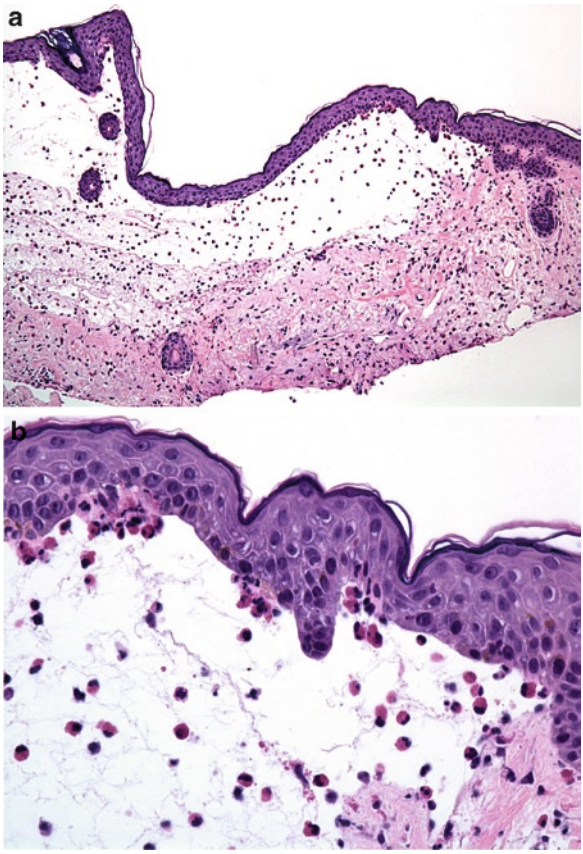

Fig. 10.9 (**a**) *Bullous pemphigoid* is characterized by a subepidermal blister. (**b**) The higher power image demonstrates eosinophils in the blister cavity

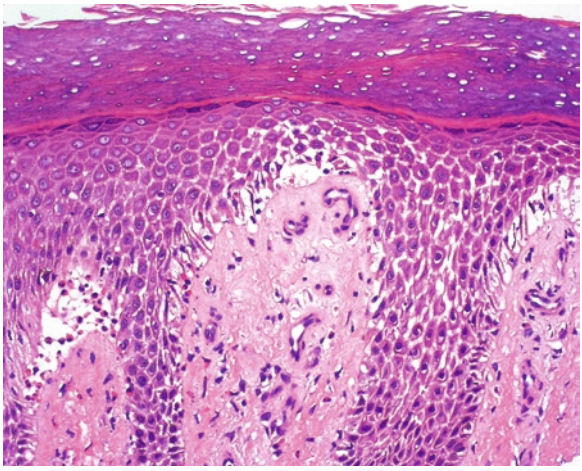

Fig. 10.10 *Urticarial bullous pemphigoid*. Biopsies from urticarial (pre-bullous) lesions of bullous pemphigoid demonstrate eosinophilic spongiosis and eosinophils tagging the epidermis along the dermoepidermal junction and in papillary dermis

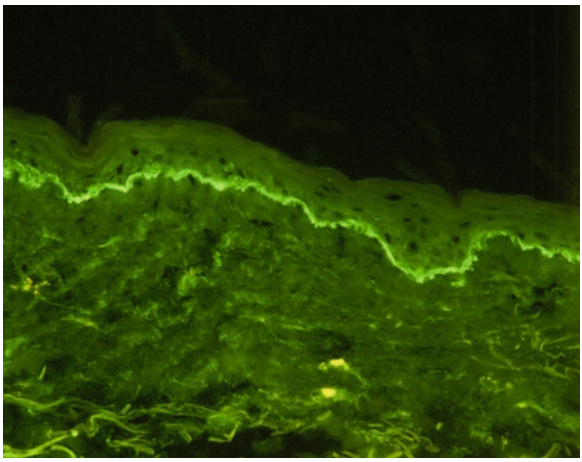

Fig. 10.11 *Direct immunofluorescence of bullous pemphigoid*. Direct immunofluorescence of perilesional skin demonstrating strong linear deposition of complement C3

Table 10.5 Key microscopic features: bullous pemphigoid

- Subepidermal blister with eosinophils and other inflammatory cells in and around the blister
- Rarely the inflammatory process can be neutrophil-predominant or cell-poor
- Dermal infiltrate is generally confide to the papillary dermis and is composed of lymphocytes, eosinophils and rarely neutrophils
- Urticarial forms of bullous pemphigoid may show eosinophilic spongiosis and eosinophils tagging the basal layer
- Direct immunofluorescence of perilesional skin demonstrates linear C3 (100%) and IgG (65–95%) at the dermoepidermal junction
- Direct immunofluorescence of perilesional salt-split skin usually demonstrates IgG along the epidermal side (roof) of the split

demonstrates circulating IgG antibodies to the basement membrane zone in 65–80% of the cases with active disease. Key microscopic and direct immunofluorescence features are summarized in Table 10.5.

Differential Diagnosis

The histologic pattern of an eosinophil-rich, subepidermal vesicular dermatitis most is quite characteristic of bullous pemphigoid. Occasionally, arthropod bite reactions can have prominent papillary dermal edema that histologically mimics a blister. In those cases, the depth of the infiltrate and clinical presentation should readily allow distinction.

There are two other pemphigoid diseases, cicatricial pemphigoid and pemphigoid gestationis, (also known as herpes gestationis) that figure into the differential diagnosis. In all three forms of pemphigoid, autoantibodies are directed against the same target basement membrane proteins. The three disorders share similar histologic features; however, they differ in their clinical presentations. Pemphigoid (herpes) gestationis is histologically indistinguishable from bullous

pemphigoid. Lesions of pemphigoid that demonstrate a mixture of eosinophils and neutrophils must be differentiated from inflammatory-rich epidermolysis bullosa acquisita. Neutrophil-predominant cases of bullous pemphigoid must be distinguished from dermatitis herpetiformis, bullous lupus erythematosus, and linear IgA disease. These entities are discussed in detail below.

Occasionally, bullous pemphigoid is relatively noninflammatory. In cases of cell-poor bullous pemphigoid, the differential diagnosis includes epidermolysis bullosa acquisita (see below). Although there are clinical differences between the two entities, the histologic and direct immunofluorescence features may be identical. Distinction between the two disorders requires the salt-split direct immunofluorescence technique to more precisely identify the location of the autoantibody. In this technique, the biopsy is placed in a sodium chloride solution that induces split within the basement membrane complex. The biopsy is then evaluated by direct immunofluorescence. With salt-split, clinically normal-appearing perilesional skin, the antibodies predominantly bind to the epidermal side (roof) of the blister in bullous pemphigoid and the dermal side (floor) of the blister in epidermolysis bullosa acquisita (Fig. 10.12). As in all bullous dermatoses, obtaining a proper biopsy for direct immunofluorescence examination is critical. With regard to bullous pemphigoid, false negative results may be seen in biopsies obtained from the lower extremities or lesional skin (see Table 10.6).

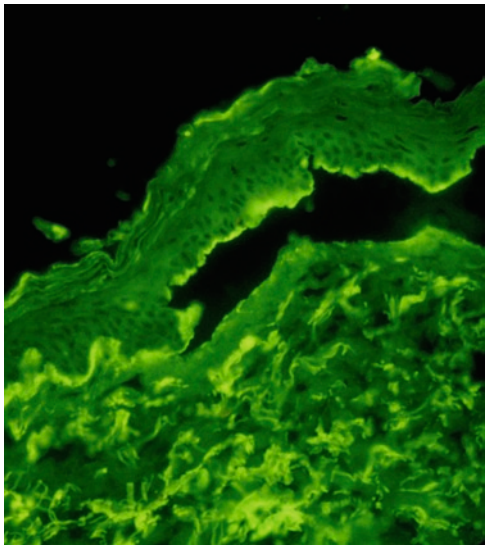

Fig. 10.12 *Salt-split direct immunofluorescence of bullous pemphigoid*. In a salt-split direct immunofluorescence of bullous pemphigoid, the deposits are (predominantly) on the roof of the blister

Table 10.6 Practical tips: bullous pemphigoid

- For accurate direct immunofluorescence examination, use perilesional skin
- False negative direct immunofluorescence results may be seen in biopsies from the lower extremities and lesional skin
- Always consider urticarial bullous pemphigoid when a biopsy from an elderly patient demonstrates eosinophilic spongiosis

Cicatricial Pemphigoid

Clinical Features

Cicatricial pemphigoid is a chronic blistering disorder involving mucous membranes including mouth, eye, nasopharynx, larynx, esophagus and genitalia. Lesions generally heal with scarring which can lead to decreased vision, blindness and supraglottic stenosis. Generalized skin lesions resembling bullous pemphigoid may occur, but are uncommon.

Microscopic Features

The two major antigens associated with cicatricial pemphigoid are BPAG2 and epiligrin (laminin-5). Intact mucosal lesions demonstrate separation of the epithelium from the basement membrane, accompanied by a slight number of inflammatory cells including eosinophils in the subepithelial stroma. A dermal scar may be evident if the biopsy is taken at the sight corresponding to previous blister formation (Fig. 10.13). The majority of lesions, however, are ruptured at the time of biopsy and therefore the subepithelial separation may be found just at the edge of an otherwise nonspecific ulcer (Table 10.7). In the majority of cases, direct immunofluorescence demonstrates linear IgG and C3 along the basement membrane zone. Indirect immunofluorescence demonstrates circulating autoimmune antibodies in more than half of patients.

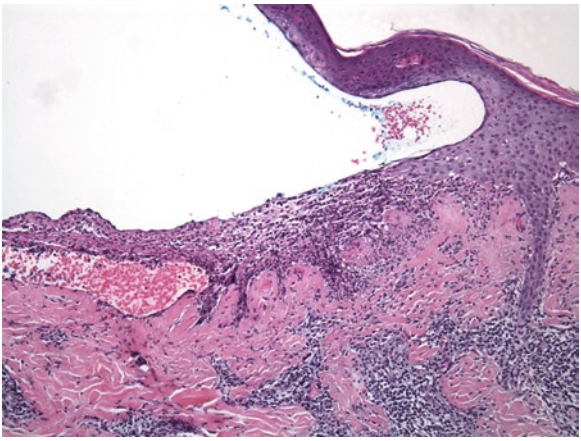

Fig. 10.13 *Cicatricial pemphigoid*. There is subepidermal separation of epidermis from dermis consistent with partial re-epithelialization. Also observed is a mixed inflammatory infiltrate in the papillary dermis composed of eosinophils, neutrophils, and lymphocytes. Note the fibrosis of the papillary dermis

Table 10.7 Key microscopic features: cicatricial pemphigoid

- Resembles bullous pemphigoid
- Scarring

Differential Diagnosis

As mentioned above, the differential diagnosis is bullous pemphigoid. Histologically, with the exception of the presence of scarring, the two diseases are indistinguishable. Clinical presentation of disease primarily restricted to mucous membranes is distinctive in cases where scarring is not histologically evident. In general, findings of pemphigoid (subepidermal blister with eosinophils with or without fibrosis) on a mucosal surface of an elderly individual should prompt consideration of the diagnosis (Table 10.8).

Table 10.8 Practical tips: cicatricial pemphigoid

- Involves mucosa
- Findings of pemphigoid on mucosal surface should prompt consideration of the diagnosis

Pemphigoid (Herpes) Gestationis

Clinical Features

Pemphigoid gestationis was originally named herpes gestationis on the basis of the morphologic similarity to herpetic blisters; however, this term is a misnomer as pemphigoid gestationis is not related to, or associated with any active or prior herpes virus infection. Pemphigoid gestationis is a pregnancy-associated autoimmune disease that occurs in 1 of 3,000 to 1 of 10,000 pregnancies. The eruption typically manifests during the second or third trimester of pregnancy and is characterized by an abrupt onset of severely pruritic papules and plaques. Blisters may develop and are often distributed in a herpetiform pattern. Lesions are distributed on the abdomen and trunk often in a characteristic periumbilical pattern. As the disease progresses, the eruption may spread peripherally, often sparing the face, palms and soles. Clinical course is variable. Exacerbation at delivery or immediately postpartum is classic, although it may resolve in the latter part of gestation with a flare at delivery. Most patients experience spontaneous regression over weeks to months postpartum. Complications that may be associated with the disorder include trophoblastic tumors, autoimmune diseases (e.g., Graves disease), transient skin eruptions in infants of affected mothers, and increased risk of prematurity and small-for-gestational age births.

Microscopic Features

The main antigenic target is the extracellular NC16A domain of the 180-kD BPAg2; however, autoantibodies also react (less frequently) with BP 230 (BPAg1). Pemphigoid gestationis is histologically indistinguishable from bullous

pemphigoid (Table 10.9). Direct immunofluorescence examination of perilesional skin demonstrates deposits of C3 (100% of cases) and IgG (27% of cases) at the basement membrane zone. Circulating complement-fixing autoantibodies ("HG factor") can be detected in most patients by indirect immunofluorescence on intact or salt-split skin.

Table 10.9 Key microscopic features: pemphigoid gestationis

- Microscopic features are histologically indistinguishable from bullous pemphigoid (both cell rich and urticarial forms)

Differential Diagnosis

As mentioned previously above, the histologic differential diagnosis is that of bullous pemphigoid. Clinical presentation generally allows distinction (Table 10.10). In rare cases, indirect immunofluorescence can be pursued, but this is rarely needed for diagnosis.

Table 10.10 Practical tips: pemphigoid gestationis

- Clinical presentation of periumbilical plaques in second or third trimester of pregnancy characteristic
- Common inflammatory disorders of pregnancy (atopic dermatitis, drug eruption) should be considered in the histologic differential of urticarial phase bullous pemphigoid

Subepidermal Vesicular Dermatitis with Predominantly Neutrophils

Dermatitis Herpetiformis

Clinical Features

Dermatitis herpetiformis is a rare, chronic subepidermal blistering disorder characterized by exquisitely pruritic, grouped urticarial plaques, papules and vesicles. Elbows, knees and shoulders are classically involved. The majority of patients have associated gluten sensitive enteropathy that is indistinguishable from celiac disease. Both dermatitis herpetiformis and celiac disease are associated with HLA-A1, HLA-B8, HLA-DR3, and HLA-DQ2. The majority of patients with dermatitis herpetiformis have no gastrointestinal symptoms, but greater than 90% have a gluten-sensitive enteropathy demonstrable on bowel biopsy. Although often difficult to accomplish due to compliance, 80% of

patients with dermatitis herpetiformis have improvement of skin disease when put on a gluten-free diet.

Microscopic Features

Recent studies suggest that epidermal transglutaminase (eTG) 3 is the predominant autoantigen of dermatitis herpetiformis. eTG is a cytosolic enzyme involved in cell envelope formation during keratinocyte differentiation. It has been demonstrated that sera from most patients with dermatitis herpetiformis demonstrate autoantibodies against eTG and tissue transglutaminase (TG2), which is found in the gut. IgA immune complexes containing eTG and IgA have been demonstrated in the papillary dermis in patients with dermatitis herpetiformis. These data suggest that development of this disorder is a complex, multifactorial process: a genetic predisposition to the disease, combined with a diet high in gluten, leads to formation of IgA antibodies to gluten-TG2 complexes. These antibodies cross-react with eTG, thus leading to papillary dermal deposition of IgA/eTG complexes and cutaneous lesions of DH.

In early lesions of dermatitis herpetiformis, neutrophils are observed at the tips of dermal papillae – so-called papillary microabscesses (Fig. 10.14). Fibrin may be present near the tips of dermal papillae giving a "necrotic" appearance. Subepidermal vesiculation with neutrophils is seen in older lesions (Fig. 10.15.). Blood vessels in the upper and mid dermis are surrounded by an infiltrate of lymphocytes, histiocytes, neutrophils and eosinophils. Direct immunofluoresence of perilesional skin demonstrates granular, thread-like deposits of IgA along the dermoepidermal junction with accentuation at the dermal papillary tips (Fig. 10.16). Complement C3 deposition may also be present. Key microscopic features and direct immunofluorescence profile are summarized in Table 10.11.

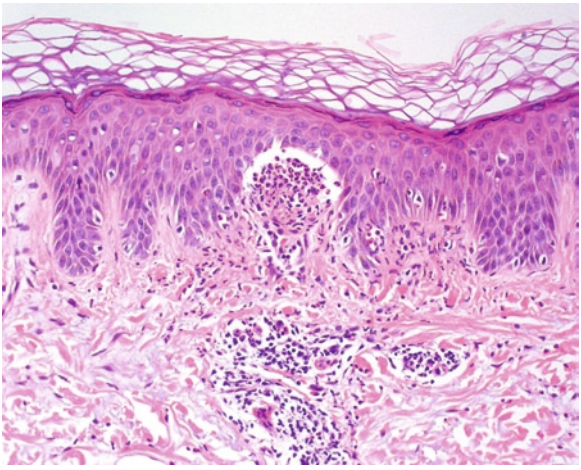

Fig. 10.14 *Dermatitis herpetiformis*. In early lesions of dermatitis herpetiformis there are neutrophilic microabscesses in the dermal papillae

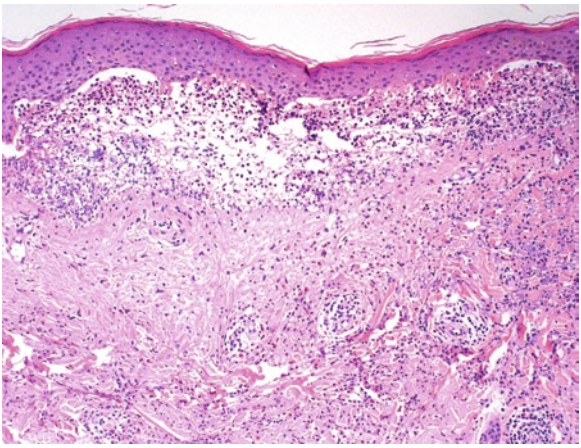

Fig. 10.15 *Dermatitis herpetiformis*. In established lesions there is subepidermal blister formation. Neutrophils are the predominant inflammatory cell in the blister cavity

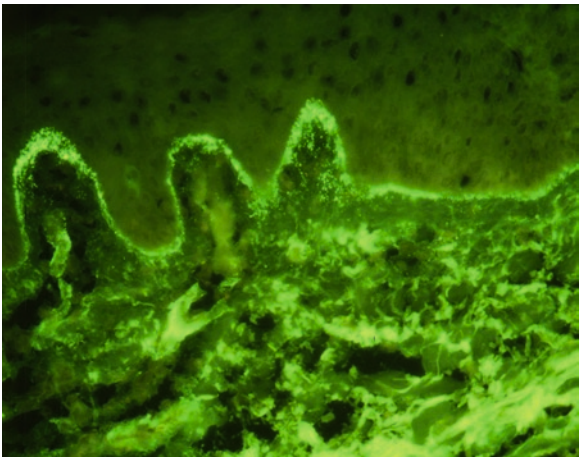

Fig. 10.16 *Dermatitis herpetiformis*. Direct immunofluorescence of perilesional skin demonstrate granular deposits of IgA along the dermoepidermal junction. Staining is frequently most intense in the tips of the dermal papillae

Table 10.11 Key microscopic features: dermatitis herpetiformis

- Early lesions: neutrophils at the tips of dermal papillae ("papillary microabscesses")
- Well-developed lesions: subepidermal vesiculation with neutrophils
- Direct immunofluorescence examination demonstrates IgA deposited in a granular fashion along the basement membrane
- IgA deposits often more prominent at the dermal papillary tips

Differential Diagnosis

The histologic differential diagnosis includes linear IgA disease and bullous lupus erythematosus (see below). The former is essentially indistinguishable from dermatitis herpetiformis. Bullous lupus erythematosus often has other histologic features of lupus erythematosus. Direct immunofluorescence allows distinction between these entities (see Table 10.12). Clinically, excoriated eczematous dermatitis

Table 10.12 Practical tips: dermatitis herpetiformis

- Significant overlap with bullous lupus erythematosus, linear IgA disease and inflammatory-rich cases of epidermolysis bullosa acquisita
- In the absence of direct immunofluorescence, sign out descriptively
- Clinically, dermatitis herpetiformis and excoriated eczematous dermatitis can look alike

(see Chap. 2) can resemble lesions of dermatitis herpetiformis. Histologically, this is spongiotic dermatitis, not a blistering disease.

Bullous Lupus Erythematosus

Clinical Features

Bullous lupus erythematosus is a rare variant of systemic lupus erythematosus that most commonly affects African-American women. Patients fulfill the American College of Rheumatology criteria for systemic lupus erythematosus and present with non-pruritic tense vesicles and bullae involving the upper trunk, proximal arms, face and neck. Mucosal involvement may be seen. Lesions respond dramatically to dapsone.

Microscopic Features

Indirect immunofluorescence assay demonstrates circulating IgG autoantibodies to the basement membrane zone. These autoantibodies target a 209-kDa protein which represents the NC1 domain of type VII collagen.

There is a subepidermal vesicle accompanied by a band-like neutrophilic inflammatory infiltrate in the upper dermis (Fig. 10.17). Leukocytoclasia and leukocytoclastic vasculitis may be present. Mucin deposition may also be observed.

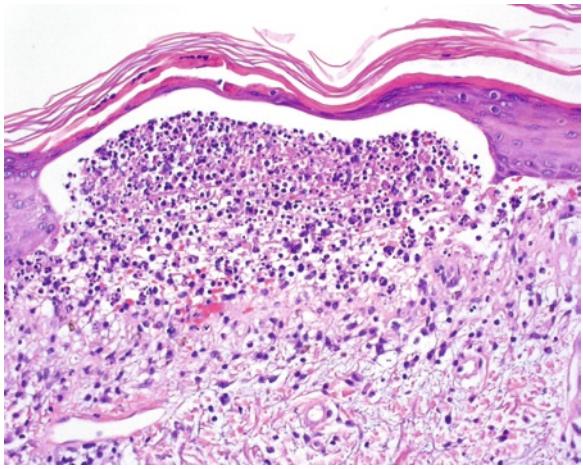

Fig. 10.17 *Bullous lupus erythematosus* is characterized by a subepidermal vesicle with a band-like neutrophilic infiltrate in the underlying dermis. Note the presence of dermal mucin between the collagen bundles, a clue to the diagnosis

Table 10.13 Bullous lupus erythematosus: key microscopic features

- Subepidermal vesicle associated with band-like neutrophilic infiltrate in the dermis
- Papillary neutrophilic microabscesses
- Leukocytoclasia
- Leukocytoclastic vasculitis may be present
- Mucin deposition
- DIF: IgG and C3 along the dermal-epidermal junction; IgM (50%) and IgA (60%)
- Salt-split: dermal side (floor) of the split

Direct immunofluorescence examination demonstrates granular and/or linear staining of IgG and C3 along the dermal-epidermal junction. IgM (50%) and IgA (60%) deposition may also be observed. Salt-split direct immunofluorescence demonstrates deposits on the dermal side of the split. See Table 10.13 for summary of key microscopic and direct immunofluorescence features.

Differential Diagnosis

The histologic differential diagnosis of bullous lupus erythematosus includes dermatitis herpetiformis, linear IgA bullous dermatosis, and inflammatory epidermolysis bullosa acquisita. Histologic evidence of other features of lupus erythematosus (e.g., mucin deposition) can allow for recognition. Clinical information is also very useful. For example, bullous lupus erythematosus is nonpruritic, unlike dermatitis herpetiformis which is intensely pruritic in essentially all cases. Direct immunofluorescence examination will also allow distinction. See Table 10.14 for clues to distinguishing bullous lupus from other neutrophil-rich subepidermal vesicular dermatoses.

Table 10.14 Practical tips: bullous lupus erythematosus

- Clinical presentation is characteristic
- There may be considerable histologic overlap with dermatitis herpetiformis. In bullous lupus, neutrophils tend to extend more deeply and in around vessels
- Presence of other histologic findings of lupus erythematosus (e.g. dermal mucin) can be a clue
- DIF allows distiniction between dermatitis herpetiformis, IgA bullous disease and epidermolysis bullosa acquisita

Linear IgA Disease

Clinical Features

Linear IgA dermatosis is a clinically heterogeneous disorder, with both adult and childhood forms described. Lesions may clinically simulate bullous pemphigoid, dermatitis herpetiformis, cicatricial pemphigoid and epidermolysis bullosa acquisita. Classic IgA disease presents as erythematous patches rimmed by tense blisters at the edges (“string of pearls”). There are a number of associated conditions that

have been described with linear IgA disease including inflammatory bowel disease (ulcerative colitis/Crohn's disease), lymphoproliferative disorders, and drugs (with vancomycin being the most common culprit).

Microscopic Features

Patients with linear IgA disease have circulating antibodies against components of the epidermal basement membrane including bullous pemphigoid antigen 1 and/or bullous pemphigoid antigen 2. Linear IgA is characterized by a subepidermal vesicle with neutrophils aligned along the dermal-epidermal junction (Fig. 10.18). Occasional eosinophils may be present. Later stage lesions may demonstrate basal vacuolization and papillary dermal edema. Direct immunofluorescence of perilesional skin demonstrates homogenous linear deposition of IgA along the dermoepidermal junction (Fig. 10.19). Table 10.15 summarizes key microscopic and direct immunfluorescence features.

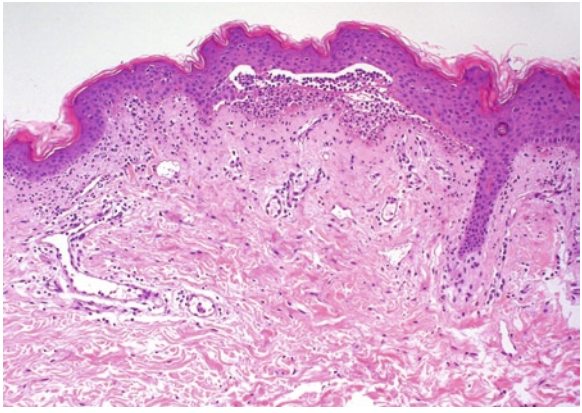

Fig. 10.18 *Linear IgA disease*. Subepidermal vesicle with neutrophils aligned upon the dermal-epidermal junction

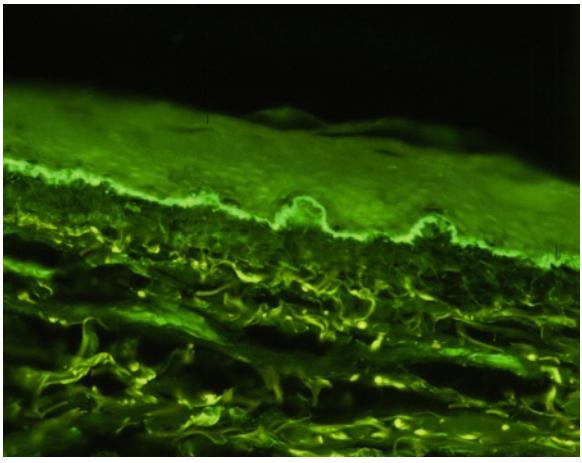

Fig. 10.19 *Linear IgA Disease*. Direct immunofluorescence of perilesional skin demonstrating linear IgA deposition along the dermal-epidermal junction

Table 10.15 Linear IgA disease: key microscopic features

- Subepidermal vesicle with neutrophils
- Papillary microabscesses may be seen (dermatitis herpetiformis-like)
- Direct immunofluorescence of perilesional skin demonstrates linear deposition of IgA along the basement membrane zone of non-lesional skin

Differential Diagnosis

The main differential diagnostic entity to consider is dermatitis herpetiformis. As discussed previously, classic lesions of dermatitis herpetiformis are characterized by fairly discrete papillary dermal microabscesses whereas the neutrophilic infiltrate in linear IgA is more diffuse in nature. In reality, however, there may be considerable histologic overlap between the two entities and direct immunofluorescence examination is required for definitive diagnosis. Other diagnostic considerations include bullous pemphigoid, inflammatory-rich epidermolysis bullosa acquisita, and bullous systemic lupus erythematosus. Non-autoimmune disorders that also fall into the differential diagnosis includes bullous arthropod bite reaction or bullous drug eruption. These are not typically neutrophil rich. Table 10.16 highlights clues in differentiating linear IgA disease from its closest histologic mimic, dermatitis herpetiformis.

Table 10.16 Practical tips: linear IgA disease

- Subepidermal neutrophilic infiltrate tends to be more dispersed in linear IgA vs. dermatitis herpetiformis
- Eosinophils may predominate in drug-associated cases of linear IgA
- Unequivocal distinction from dermatitis herpetiformis impossible without direct immunofluorescence examination

Subepidermal Vesicular Dermatitis with Little to No Inflammation

Epidermolysis Bullosa Acquisita

Clinical Features

Three different clinical forms of epidermolysis bullosa acquisita have been described. In the most common (noninflammatory) variant, patients present with trauma-induced acrally distributed blisters and erosions that heal with scarring. There may be associated nail dystrophy and alopecia. The inflammatory variant of epidermolysis bullosa acquisita presents as a generalized blistering eruption resembling bullous pemphigoid. The third form of epidermolysis bullosa acquisita predominantly involves mucous membranes and can result in significant scarring and dysfunction, similar to cicatricial pemphigoid.

Microscopic Features

Patients with epidermolysis bullosa aquisita have circulating IgG autoantibodies against the noncollagenous (NC1) domain of type VII collagen, the major component of anchoring fibrils that maintain the structural integrity of epidermal-dermal attachment. The histology of epidermolysis bullosa acquisita is that of a subepidermal blister with fibrin and only a few inflammatory cells in the lumen (Fig. 10.20). In non-inflammatory lesions, there is a sparse superficial lymphocytic infiltrate around the vessels of the superficial vascular plexus, while in inflammatory lesions, there is a heavy upper dermal inflammatory infiltrate composed of lymphocytes, neutrophils and eosinophils. In older lesions, there will be some dermal scarring and milia. Direct immunofluorescence of perilesional skin or mucosa demonstrates linear deposition of IgG along the basement membrane zone, similar to bullous pemphigoid. Salt-split perilesional skin demonstrates IgG along the dermal side (floor) of the split (Fig. 10.21). Approximately, 50% of patients have circulating IgG antibodies to the BMZ by indirect immunofluorescence assay. Table 10.17 highlights key microscopic features and direct immunofluorescence profile.

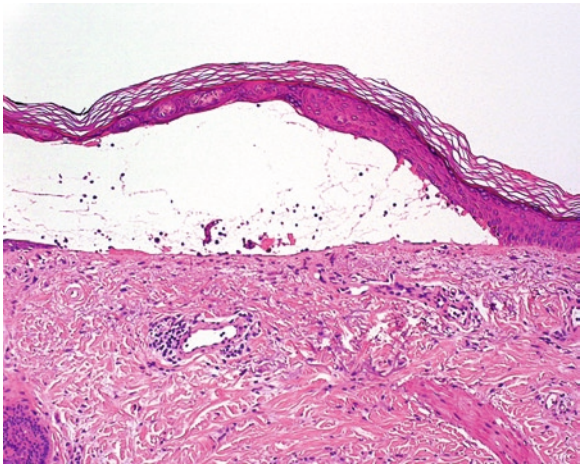

Fig. 10.20 *Epidermolysis bullosa acquisita* is characterized by an inflammatory-poor subepidermal vesicle

Differential Diagnosis

In classic, noninflammatory lesions, the differential diagnosis includes other cell-poor subepidermal blistering disorders including cell-poor bullous pemphigoid, porphyria cutanea tarda and pseudoporphyria. Cell poor bullous pemphigoid is differentiated by the location of the autoantibody on salt-split skin direct immunofluorescence as mentioned previously above. In epidermolysis bullosa acquisita, the autoantibodies are on the floor of the salt-split blister.

Porphyria cutanea tarda and pseudoporphyria are discussed in more detail below. Briefly, these entities have rigid dermal papillae protruding into the blister

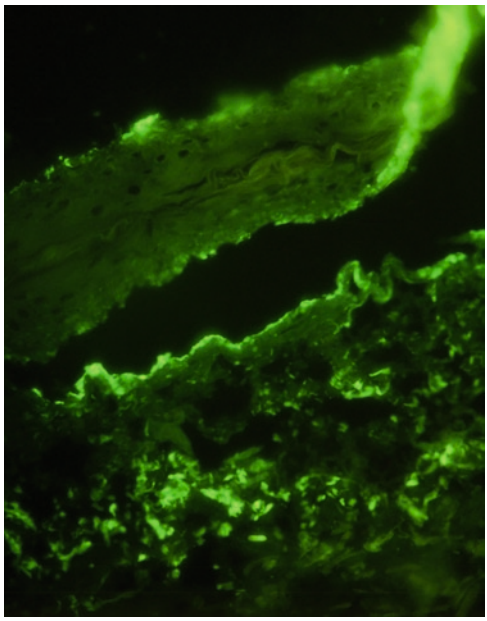

Fig. 10.21 *Salt-split direct immunofluorescence of epidermolysis bullosa acquisita*. Salt-split perilesional skin demonstrating linear IgG deposition along the dermal side (floor) of the split

Table 10.17 Key microscopic features: epidermolysis bullosa acquisita

- The most common pattern is that of a subepidermal blister with fibrin and only a few inflammatory cells in the lumen (non-inflammatory pattern)
- Occasional cases may demonstrate a heavy upper dermal inflammatory infiltrate composed of lymphocytes, neutrophils and eosinophils (inflammatory pattern)
- Older lesions may demonstrate dermal scarring and milia
- DIF profile: linear IgG and C3 at the dermal-epidermal junction; in salt-split skin examination, antibodies bind to the dermal side (vs. epidermal side for bullous pemphigoid)

cavity and thick-walled superficial dermal blood vessels. In addition to basement membrane deposits of antibodies, there are waxy vascular deposits seen on direct immunofluorescence that are not seen in epidermolysis bullosa acquisita. Inflammatory lesions of epidermolysis bullosa acquisita may overlap histologically with bullous lupus erythematosus and bullous pemphigoid. (see Table 10.18 for tips in distinguishing epidermolysis bullosa acquisita from other minimally inflammatory subepidermal blistering disorders).

Table 10.18 Practical tips: epidermolysis bullosa acquisita

- Noninflammatory subepidermal blister should prompt consideration
- Blisters tens to be on trauma prone areas
- No festooning of dermal papillae like in porphyria cutanea tarda

Porphyria Cutanea Tarda

Clinical Features

Porphyria cutanea tarda is a disease associated with underlying defects in porphyrin metabolism. It can be hereditary or acquired as a result of underlying liver disease. The latter is more common. Clinical manifestations include acral blisters and erosions, skin fragility, milia, scars, and hypertrichosis. Cutaneous manifestations are exacerbated by ultraviolet light. The dorsal hands are the most common locations for the blisters.

Microscopic Features

The blister of porphyria cutanea tarda is a pauci-inflammatory subepidermal blister, classically with festooning of the dermal papillae (Fig. 10.22). This latter feature presents as the dermal papillae sticking into the blister cavity as finger-like projections. Festooning of the dermal papillae is frequently but not invariably present. Eosinophilic, segmented collections of basement membrane material, referred to as caterpillar bodies, may be seen along the roof of the blister. The vascular changes in the underlying dermis are useful diagnostic features. The papillary dermal blood vessels have relatively thick walls due to deposition of glycoproteins. In some cases, the deposits are best appreciated with PAS stains.

Direct immunofluorescence demonstrates deposition of IgG, complement C3 and fibrinogen along the basement membrane zone. IgM deposition is also sometimes seen. Characteristic features are the waxy vascular deposits in the superficial dermal blood vessels. Table 10.19 for summarizes of key microscopic features for porphyria cutanea tarda and pseudoporphyria.

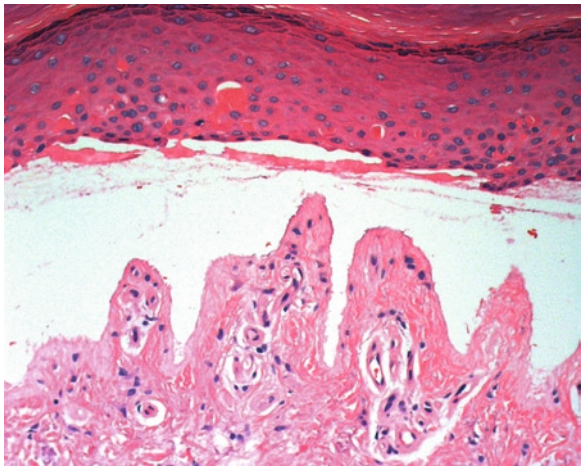

Fig. 10.22 *Porphyria cutanea tarda* (and pseudoporphyria) is characterized by a noninflammatory blister with festooning of the dermal papillae. Note the eosinophilic caterpillar bodies adjacent to the epidermis in the roof of the blister. The papillary dermal vessels have relatively thick walls

Table 10.19 Key microscopic features: porphyria cutanea tarda

- Noninflammatory subepidermal blister
- Festooning of dermal papillae
- Thick-walled papillary dermal blood vessels
- Caterpillar bodies
- Direct immunofluorescence demonstrates basement membrane and waxy vascular deposits (usually IgG)

Key microscopic features: pseudoporphyria

- Identical to porphyria cutanea tarda

Differential Diagnosis

The differential diagnosis includes epidermolysis bullosa acquisita and pseudoporphyria. Epidermolysis bullosa acquisita lacks the festooning of the dermal papillae and vascular deposits. On direct immunofluorescence, the presence of the vascular deposits seen in porphyria cutanea tarda is helpful. Pseudoporphyria is histologically indistinguishable form porphyria cutanea tarda. Differentiation is dependent on clinical factors (Table 10.20).

Table 10.20 Practical tips: porphyria cutanea tarda

- Most common on dorsal hands
- PAS stains can highlight glycoprotein deposits in vessel walls
- Acquired form associated with liver disease

Practical tips: pseudoporphyria

- Associated with renal disease
- Associated with NSAIDs and diuretics
- Discuss possibility with clinician

Pseudoporphyria

Clinical Features

Pseudoporphyria is clinically similar to porphyria cutanea tarda. It is associated with renal insufficiency or medications, especially nonsteroidal anti-inflammatory medications and diuretics. There is no underlying defect in porphyrin metabolism.

Microscopic Features

Pseudoporphyria is histologically indistinguishable from porphyria cutanea tarda.

Differential Diagnosis

The same comments regarding the differential diagnosis of porphyria cutanea tarda discussed above apply to pseudoporphyria.

Sample Reports

Sample Report: Pemphigus Vulgaris

Clinical history: Multiple vesicles and bullae on the groin of 75-year-old woman.
Diagnosis: Intraepidermal vesicular dermatitis, see comment.
Comment: There is prominent acantholysis with intraepidermal vesicle formation. Periadnexal extension of acantholysis is also observed. In the subjacent dermis, there is a slight superficial perivascular, predominantly lymphocytic inflammatory infiltrate with occasional eosinophils. Given the clinical presentation, the findings are strongly suspicious for pemphigus vulgaris. Recommend a biopsy of perilesional skin for direct immunofluorescence.
Note to reader: If the clinician suggests the possibility of pemphigus clinically, it would be acceptable to make the top line diagnosis as "pemphigus vulgaris" or "consistent with pemphigus vulgaris."

Sample Report: Transient Acantholytic Dermatosis

Example 1:
Clinical history: Pruritic papules on the chest; rule out folliculitis.
Diagnosis: Focal acantholytic dyskeratosis, see comment.
Comment: There are small, discrete foci of acantholytic dyskeratosis accompanied by a focal but brisk lymphocytic infiltrate in the underlying dermis. In this clinical setting, the findings are most compatible with Grover's disease (transient acantholytic dermatosis).

Example 2:
Clinical history: Keratotic lesion on the left arm; rule out basal cell carcinoma.
Diagnosis: Focal acantholytic dyskeratosis, see comment.
Comment: There is a solitary focus of acantholytic dyskeratosis. A slight superficial perivascular lymphocytic infiltrate is noted in the superficial dermis. Focal acantholytic dyskeratosis may be seen as an incidental finding in otherwise benign keratoses; however, in

the correct clinical setting (multiple lesions) the differential diagnosis includes Grover's disease. Clinical correlation is recommended.

Sample Report: Bullous Pemphigoid

Example 1: (fully developed lesion):
Clinical history: 70-year-old woman with vesicles and bullae on the lower abdomen.
Diagnosis: Eosinophil-rich subepidermal vesicular dermatitis, see comment.
Comment: Findings are strongly suspicious for bullous pemphigoid. A biopsy of perilesional skin for direct immunofluorescence is recommended for unequivocal diagnosis. The histologic differential diagnosis includes a bullous hypersensitivity reaction such as to drug or arthropod bite. Clinical correlation is recommended.
Note to reader: If the clinician suggests the diagnosis of bullous pemphigoid clinically, it would be acceptable to state the diagnosis as "consistent with bullous pemphigoid."

Example 2: (early urticarial lesion):
Clinical history: Urticarial papules and plaques on the thighs of a 65-year-old man.
Diagnosis: Eosinophil-rich spongiotic dermatitis, please see comment.
Comment: There is focal spongiosis of the epidermis accompanied by a perivascular and interstitial eosinophil-rich infiltrate. In foci, eosinophils are aligned along the dermal-epidermal junction. This histologic pattern may be seen with an eczematous hypersensitivity reaction such as to drug, contactant or arthropod bite. However, given the age of the patient, an urticarial/ non-bullous phase of bullous pemphigoid should be considered. If this is a clinical possibility, a biopsy of perilesional skin submitted in Michel's solution for direct immunofluorescence examination is recommended.

Sample Report: Pemphigoid Gestationis

Clinical history: 29-year-old woman in late second trimester of pregnancy presents with pruritic, urticarial papules on the abdomen, trunk and upper extremities.
Diagnosis: Eosinophil-rich spongiotic dermatitis, see comment.
Comment: There is slight spongiosis of the epidermis accompanied by an underlying mixed dermal inflammatory infiltrate composed of

lymphocytes and eosinophils surrounding the superficial vascular plexus. There is mild papillary dermal edema. These features may be seen with an eczematous hypersensitivity reaction such as to drug or contactant; however, in this clinical setting, pemphigoid gestationis must be excluded. Recommend punch biopsy of perilesional skin for direct immunofluorescence examination and unequivocal diagnosis.

Sample Report: Dermatitis Herpetiformis

Clinical history: Pruritic papules and vesicles around the elbows.
Diagnosis: Skin, punch biopsy: Subepidermal vesicle with neutrophils, see comment.
Comment: There is a subepidermal vesicle with papillary microabscesses in the dermal papillae. The clinical presentation in combination with the histologic features is strongly suggestive of dermatitis herpetiformis. The histologic differential diagnosis includes other autoimmune bullous disorders including bullous lupus erythematosus or linear IgA bullous dermatosis. Recommend punch biopsy of perilesional skin for direct immunofluorescence examination.

Sample Report: Linear IgA Disease

Clinical history: Bullae on the trunk.
Diagnosis: Subepidermal vesicle with neutrophils, see comment.
Comment: There is a subepidermal vesicle accompanied by a band-like neutrophilic infiltrate in the upper dermis. This histologic pattern raises consideration of linear IgA disease or, in the appropriate clinical setting, bullous lupus erythematosus. A biopsy of perilesional skin for direct immunofluorescence is recommended for unequivocal diagnosis.

Sample Report: Epidermolysis Bullosa Acquisita

Clinical history: Vesiculobullous lesions on the fingers of a 55-year-old man.
Diagnosis: Inflammatory poor subepidermal vesicular dermatitis, see comment.
Comment: There is a subepidermal vesicle with fibrin and few inflammatory cells in the lumen. The differential diagnosis includes

epidermolysis bullosa acquisita, cell-poor bullous pemphigoid or porphyria cutanea tarda/pseudoporphyria. Recommend biopsy for direct immunofluorescence evaluation.

Sample Report: Porphyria Cutanea Tarda/Pseudoporphyria

Clinical history: 45-year-old man with blisters on dorsal hands.
Diagnosis: Subepidermal vesicular dermatitis consistent porphyria cutanea tarda or pseudoporphyria, see comment.
Comment: Sections demonstrate a non-inflammatory subepidermal blister with festooning of the dermal papillae. The papillary dermal blood vessels have thick walls. The histologic features are consistent with porphyria cutanea tarda or pseudoporphyria. These entities are histologically indistinguishable. Distinction requires an appropriate clinical evaluation.

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Chapter 11
Panniculitis

Keywords Erythema nodosum • Nodular vasculitis • Erythema induratum • Lipodermatosclerosis • Lupus panniculitis • Factitial panniculitis

The panniculitides are a heterogenous group of inflammatory disorders involving the subcutaneous adipose tissue. Diagnosis remains a challenge to clinicians and pathologists alike for several reasons. First, clinical monotony is common among the diseases. Second, there are often sampling issues, including inadequate superficial biopsies, which preclude optimal evaluation of the fat. Finally, as in all cutaneous inflammatory diseases, the panniculitides are dynamic processes that may demonstrate different histologic features at different stages of development. For example, early lesions of erythema nodosum are characterized by neutrophils permeating the connective tissue septa; in contrast, late stage lesions demonstrate granulomatous inflammation with prominent septal fibrosis.

Although several classification schemes for evaluation of have been proposed, the most commonly used and useful classification scheme divides panniculitides into septal or lobular patterns. That being said, essentially all cases of panniculitis demonstrate a mixed pattern of septal and lobular involvement. It is therefore critical to decide which is the predominant pattern typically best appreciated at low power. One then must look for additional histological features (composition of the inflammatory infiltrate, presence or absence of vasculitis) for definitive diagnosis.

In summary, we suggest a stepwise approach when evaluating an inflammatory process in the subcutis:

- Determine the predominant location of the inflammatory cell infiltrate: septal (Fig. 11.1) vs. lobular (Fig. 11.2). This feature is best appreciated at scanning magnification
- Note the composition of the inflammatory infiltrate (neutrophilic, eosinophilic, granulomatous, or mixed)
- Examine blood vessels to determine whether there is vascular inflammation
- Note type of fat necrosis (lipophagic, enzymatic, hyaline, membranous, or ischemic)
- Finally, some diseases may require additional studies for definitive diagnosis (e.g., gene rearrangement studies to detect clonal T-cell or clonal B-cell populations)

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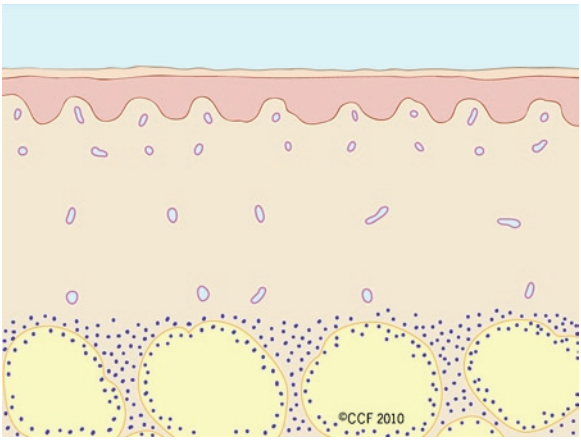

Fig. 11.1 *Schematic of septal panniculitis*. The pattern of panniculitis is characterized by inflammation and fibrosis that predominantly involves the septae that divided the subcutaneous lobules

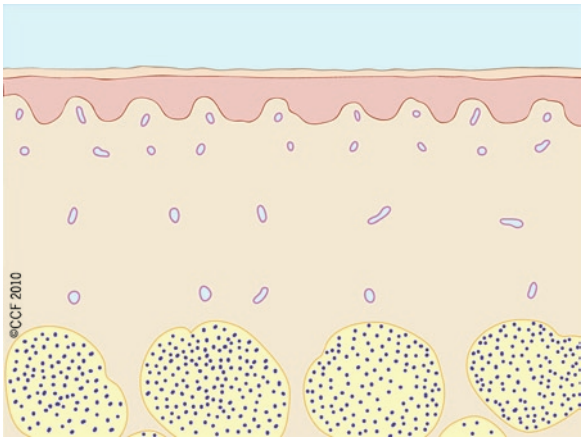

Fig. 11.2 *Schematic of lobular panniculitis*. The pattern of panniculitis is characterized by inflammation predominantly involving the fat lobules of the subcutis with relative sparing of the septae

Discussion of panniculitides in this chapter will highlight important clues to the diagnosis based on the histologic features outlined above.

Erythema Nodosum

Clinical Features

Erythema nodosum is the most common type of panniculitis, accounting for well over 80% of cases of panniculitis encountered in daily practice. It can occur at any age, with an incidence peak of 20–30 years of age. Erythema nodosum is characterized by the acute onset of tender, erythematous nodules or plaques most

commonly involving the shins. Lesions may be associated with fever, arthralgias and fatigue. The pathogenesis is unclear; it is probably a hypersensitivity response to underlying antigens, as it is associated with infections, drugs, malignancies and inflammatory disorders. In adults, the most frequent etiologic factors include drugs, sarcoidosis (Löfgren syndrome) and inflammatory bowel disease. In children, erythema nodosum is most often associated with streptococcal infections.

Microscopic Features

Erythema nodosum is the stereotypical example of a mostly septal panniculitis, with no vasculitis (Fig. 11.3). The composition of the inflammatory infiltrate varies with the stage of the lesions. In early lesions, the septal infiltrate is predominantly neutrophilic in nature (Fig. 11.4). Early lesions are less commonly biopsied and it is relatively uncommon to encounter the early phase of erythema nodosum. In later, well-developed lesions, there is septal fibrosis (Fig. 11.5) and the inflammatory region is composed of lymphocytes, histiocytes, eosinophils, and multinucleated giant cells (Fig. 11.6). There is usually some "spill over" of inflammatory cells into the periphery of the fat lobules. Sometimes, the central portion of the lobules may be involved, but the inflammation is still more prominent at the periphery. A histologic hallmark is the presence of so-called Miescher's radial granulomas. These consist of small, well-defined aggregates around a central stellate cleft. Miescher's granulomas appear in the septa sometimes surrounded by neutrophils (Fig. 11.7). These structures may be inconspicuous in some cases, seen only on examination of multiple levels. Diagnosis of erythema nodosum does not depend on the finding Miescher's granulomas; the diagnosis depends on recognition of the predominant septal pattern of panniculitis.

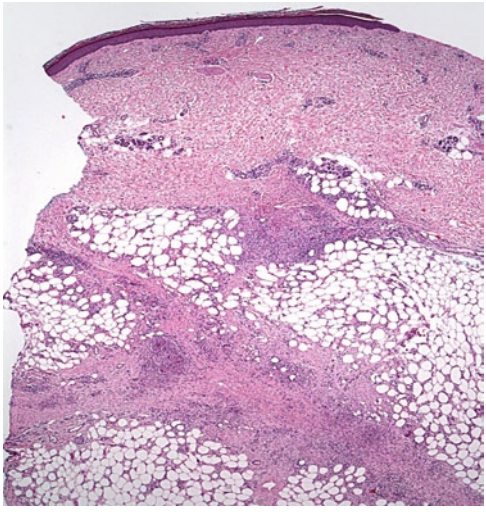

Fig. 11.3 *Erythema nodosum*. Evaluation of any panniculitis should start at scanning magnification, to determine whether the process is septal, lobular or mixed. Erythema nodosum is the prototypic example of a septal panniculitis. There is no evidence of a vasculitis

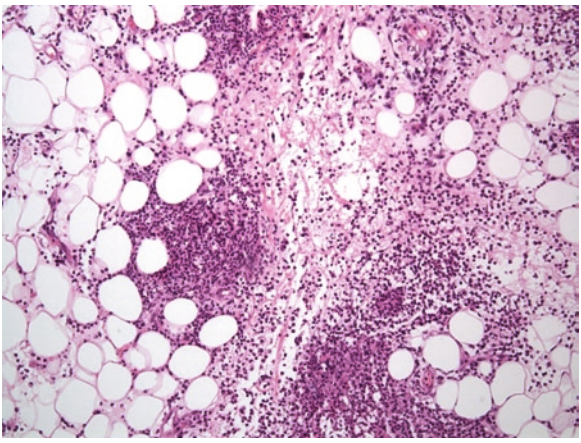

Fig. 11.4 *Erythema nodosum – early lesion*. Early lesions of erythema nodosum are characterized by a neutrophilic inflammatory infiltrate and edema of the septum more than fibrosis, prompting consideration of an infectious process

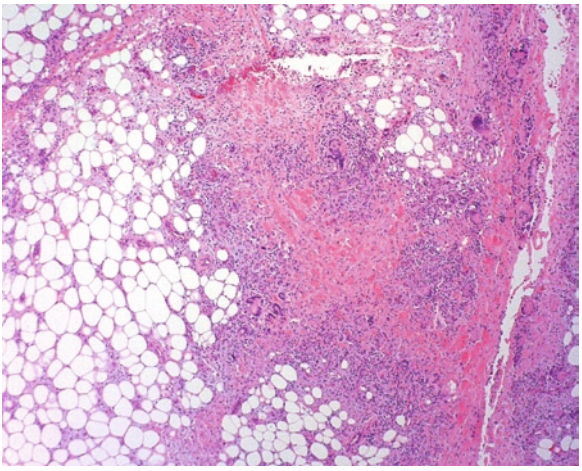

Fig. 11.5 *Erythema nodosum – well-developed lesion*. There is striking septal fibrosis accompanied by a brisk lymphohistiocytic infiltrate with multinucleated giant cells

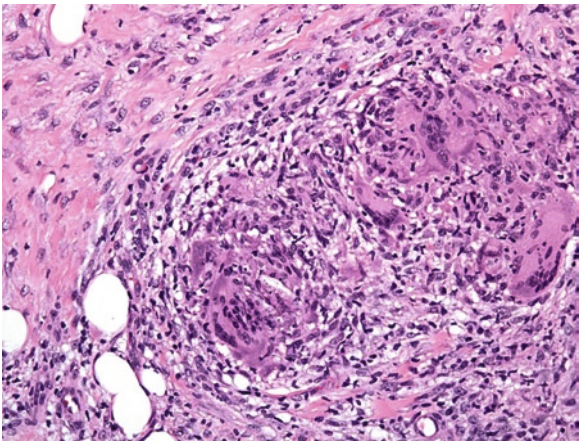

Fig. 11.6 *Erythema nodosum – well developed lesion*. Multinucleated giant cells within fibrotic septae are characteristic of well developed lesions of erythema nodosum

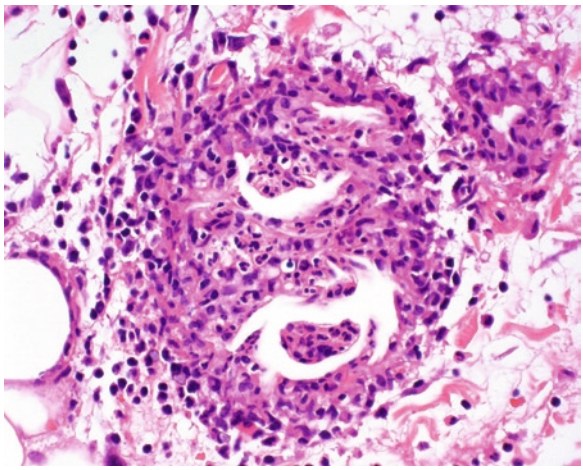

Fig. 11.7 *Miescher's granuloma of erythema nodosum*. Well-defined aggregates of histiocytes surrounding a central cleft, so-called Miescher's granulomas, are a histologic hallmark of erythema nodosum

Table 11.1 Erythema nodosum: key microscopic features

- Early lesions have more inflammation (neutrophils) and less fibrosis
- Later lesions demonstrate septal thickening, lymphocytes, histiocytes, eosinophils, and multinucleated giant cells
- Miescher's radial granulomas: aggregates of small histiocytes around central cleft
- No vasculitis

There may be a superficial deep perivascular lymphocytic infiltrate in the overlying dermis. Microscopic features are summarized in Table 11.1.

Differential Diagnosis

Well-established lesions of erythema nodosum are generally not a diagnostic problem. Infectious panniculitis may be a consideration, especially in earlier lesions, when neutrophils may be prominent. Sarcoidosis (discussed in Chap. 7) falls in the differential diagnosis of well-developed lesions of erythema nodosum. However, unlike erythema nodosum, in subcutaneous sarcoidosis, there are well defined, lobular-based naked granulomas with minimal or no septal involvement. Nodular vasculitis (erythema induratum), discussed below, is distinguished from erythema nodosum by the presence of vasculitis and a predominantly lobular panniculitis. Membranocystic change, a feature of lipodermatosclerosis (see below), may be seen in well-established lesions of erythema nodosum; however, lesions of lipodermatosclerosis usually demonstrate dermal changes of stasis, are less inflammatory, and occur in a distinctive clinical setting. Cutaneous polyarteritis nodosa, discussed in Chap. 6, may sometimes resemble a septal panniculitis, but is defined by a vasculitis. Practical tips for the diagnosis of erythema nodosum are summarized in Table 11.2.

Table 11.2 Erythema nodosum: practical tips

- Evaluation of all panniculitides requires an adequate biopsy (preferably a deep wedge) for optimal visualization of the inflammatory pattern and involvement of blood vessels
- Low power examination is crucial for dividing the inflammatory process into the septal or lobular patterns
- Erythema nodosum is the prototypic example of a septal panniculitis
- Remember erythema nodosum accounts for the >80% of all cases of panniculitis

Nodular Vasculitis (Erythema Induratum)

Clinical Features

Recent consensus opinion is that erythema induratum and nodular vasculitis are related entities. Differences are probably related to etiologic factors: the former is regarded as a tuberculin hypersensitivity reaction (a form of tuberculid occurring on the legs), whereas the latter represents the nontuberculous counterpart. Lesions are present as recurrent painful nodules most frequently on the calves.

Microscopic Features

Nodular vasculitis/erythema induratum are histologically identical. Nodular vasculitis is classically a lobular panniculitis, but secondary septal inflammation is commonly seen. Within the lobules, there is a granulomatous inflammation with some evidence of vasculitis (Fig. 11.8). Vascular inflammation may involve arteries, veins and venules. Vasculitic changes can show frank fibrinoid necrosis in early lesions (Fig. 11.9) to endothelial swelling and a mixed inflammatory infiltrate in the vessel walls in older lesions. In some cases, there is extensive necrosis of the panniculus with neutrophilic microabscesses. Special stains (AFB or Fite) do not demonstrate the presence of acid-fast bacilli (Table 11.3).

Differential Diagnosis

Late stage lesions of erythema nodosum may be considered in the histologic differential diagnosis. However, erythema nodosum is a septal panniculitis and does not demonstrate features of a vasculitis. Polyarteritis nodosa is also in the differential diagnosis (see Chap. 6). Briefly, in polyarteritis nodosa, the inflammation of fat lobules is more restricted to the immediate area around damaged vessels rather than the more diffuse pattern of nodular vasculitis. Obviously, an infectious etiology should be excluded in those lesions of nodular vasculitis that demonstrate areas of neutrophilic inflammation. Special stains and cultures should be considered. In most infections, vasculitis is not a feature. See Table 11.4.

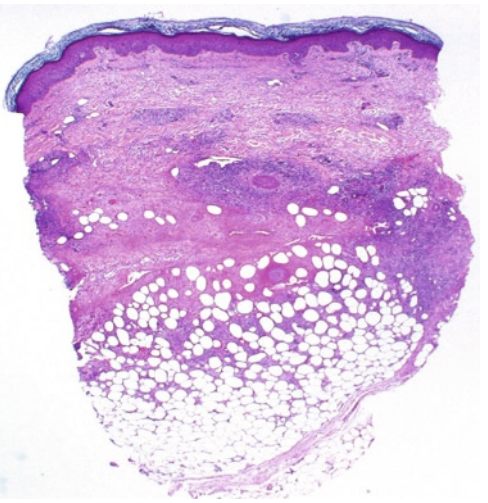

Fig. 11.8 *Nodular vasculitis*. Scanning magnification demonstrates a lobular panniculitis associated with medium vessel vasculitis. Note how the central portion of the lobule is involved but the septum is relatively spared

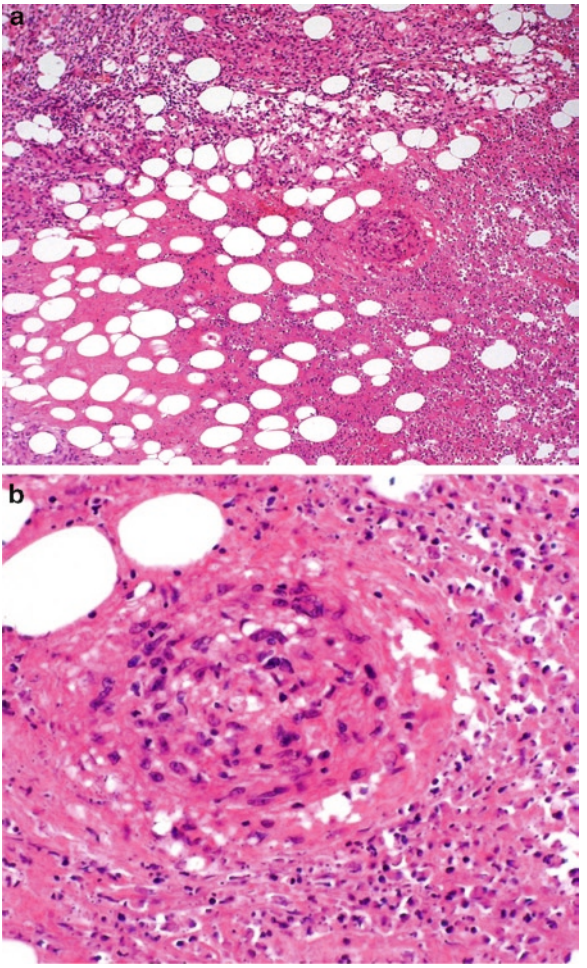

Fig. 11.9 *Nodular vasculitis*. (**a**) In this well-developed lesion of nodular vasculitis there is extensive necrosis of the subcutaneous fat throughout the lobule associated with vasculitis of medium-sized vessel. (**b**) There is fibrinoid necrosis of the affected vessel

Table 11.3 Nodular vasculitis/erythema induratum: key microscopic features

- Acute vasculitis in septae affecting artery and/or veins
- Adjacent lobular panniculitis with granulomas and fat necrosis
- Septae may be widened in older lesions

Table 11.4 Nodular vasculitis/erythema induratum: practical tips

- Low power examination crucial
- Inflammatory process involves the entire lobule (vs. polyarteritis nodosa in which inflammation is more restricted around vessels)
- Look for evidence of vascular damage
- Most common on calves

Lipodermatosclerosis (Sclerosing Panniculitis)

Clinical Features

Lipodermatosclerosis is a form of long-term chronic panniculitis that presents as indurated plaques involving the lower extremities. It usually develops in middle-aged or elderly women, often with a history of venous/arterial insufficiency and previous thrombophlebitis. There is woody, erythematous induration of the lower extremities. Long-standing lesions of lipodermatosclerosis can result in a deformity of the leg that resembles an inverted bottle.

Microscopic Features

Lesions are relatively noninflammatory, an important clue to the diagnosis. At scanning magnification, there is septal and lobular fibrosis (Fig. 11.10). Within the lobules, there is formation of fatty microcysts (Fig. 11.11) and lipomembranous fat necrosis. The latter feature is characterized by cystic cavities lined with a crenulated, hyaline membrane that is PAS-positive (Fig. 11.12). Changes of stasis dermatitis may be seen in the overlying dermis (see Chap. 2) (Table 11.5).

Differential Diagnosis

Membranocystic change is not unique to lipodermatosclerosis. It is considered to be a form of fat cell degeneration that has been described in a number of other panniculitides, wincluding erythema nodosum, and subcutaneous morphea. However, in the appropriate clinical setting (venous insufficiency and sclerosing plaques on lower extremities) the findings are fairly diagnostic (Table 11.6).

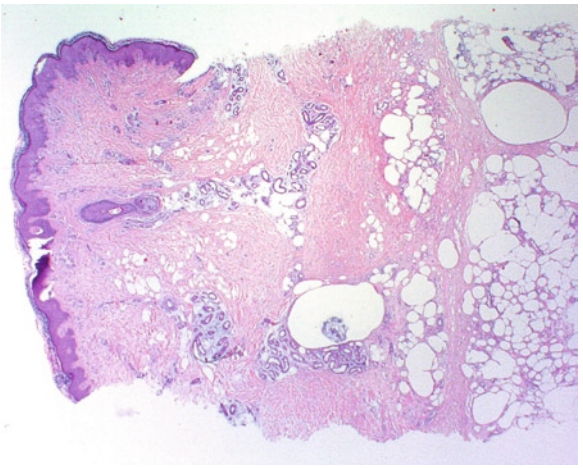

Fig. 11.10 *Lipodermatosclerosis* appears relatively non-inflammatory and is a mixed septal and lobular panniculitis with membranocystic change. The deep reticular dermis is fibrotic

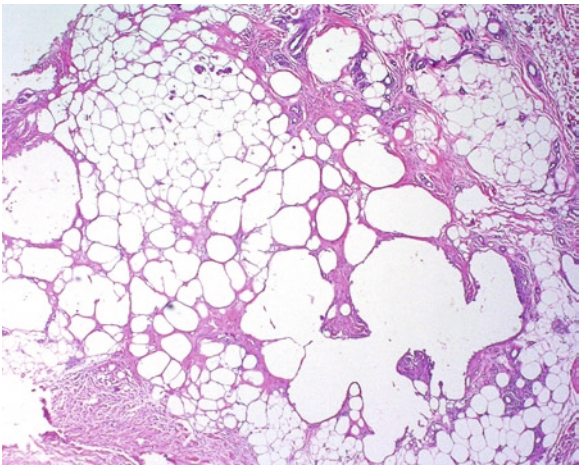

Fig. 11.11 *Lipodermatosclerosis*. Within the lobule there is microcyst formation in association lipomembranous change accompanied by septal and lobular fibrosis

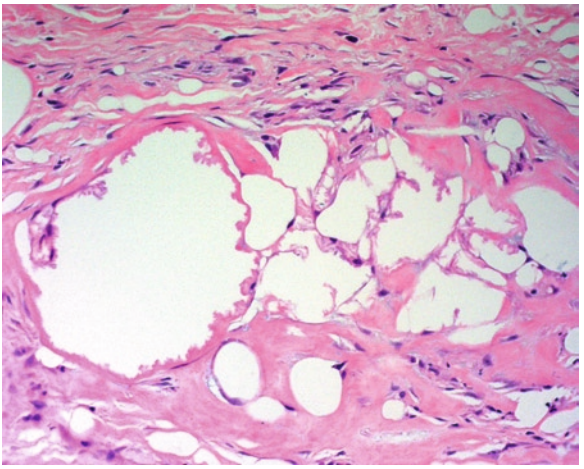

Fig. 11.12 *Lipodermatosclerosis*. Lipomembranous fat necrosis is characterized by cystic cavities lined by a crenulated hyaline membrane

Table 11.5 Lipodermatosclerosis: key microscopic features

- Septae widened by fibrosis
- Lipomembranous fat necrosis (cystic cavities lined by a crenulated hyaline membrane that is PAS-positive)
- Mild perivascular lymphocytic infiltrate
- Overlying features of stasis change in dermis and epidermis

Table 11.6 Lipodermatosclerosis: practical tips

- Relatively non-inflammatory
- Microcysts are the key diagnostic feature
- Stasis changes of dermis
- Clinical history of venous insufficiency

Lupus Panniculitis

Clinical Features

Lupus panniculitis, also called lupus profundus, is an unusual clinical variant of lupus erythematosus, which may occur as a separate entity in the lupus erythematosus spectrum, or be associated with discoid or systemic lupus erythematosus. Lupus panniculitis typically occurs in young to middle-aged women, and consists of deep nodules or plaques that may arise in crops. Usual involved sites are proximal extremities, particularly lateral arms and shoulders, buttocks, trunk, breast, face and scalp. The clinical presentation of a panniculitis in the upper half of the body should prompt consideration of lupus erythematosus panniculitis. Overlying erythema is commonly seen and, when clinical features of discoid lupus erythematosus are present, the skin surface may show scaling, follicular plugging, dyspigmentation or telangiectasia. Lipoatrophy may develop after resolution of the lesions. Patients with lupus panniculitis have a chronic and disabling course because of the scarring, pain and atrophy produced by the lesions.

Microscopic Features

Lupus panniculitis is considered a lobular panniculitis, but mixed septal and lobular involvement is common (Fig. 11.13). The inflammatory infiltrate is composed of lymphocytes accompanied by an admixture of histiocytes and plasma cells. Lymphoid aggregates, often with prominent germinal centers, are characteristic, but not pathognomonic. Perhaps, the most helpful diagnostic feature is the presence of hyaline fat necrosis, a form of fat necrosis in which fat cells undergo hyalinization resulting in a glassy eosinophilic appearance to the fat lobules (Fig. 11.14).

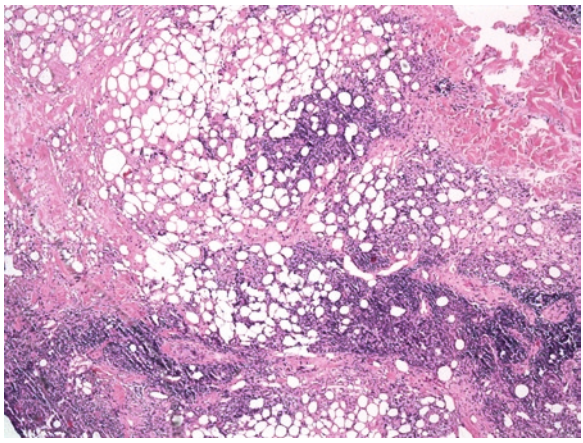

Fig. 11.13 *Lupus erythematosus panniculitis*. Lupus panniculitis is predominantly lobular panniculitis, but septal involvement is common. The inflammatory infiltrate is composed predominantly of lymphocytes and plasma cells and there is hyaline fat necrosis

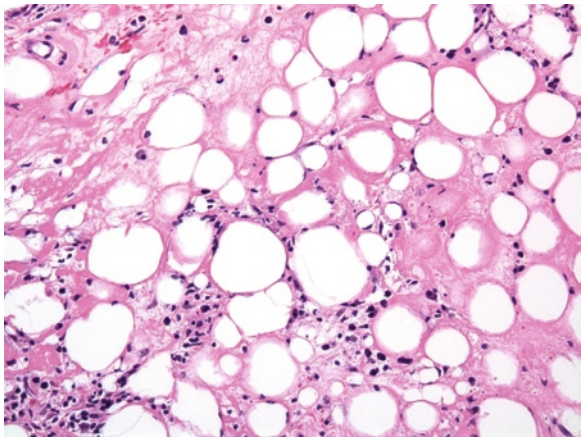

Fig. 11.14 *Lupus erythematosus panniculitis*. Hyaline fat necrosis is a characteristic feature of lupus panniculitis. Hyalinization of fat cells gives a glassy appearance to the fat lobules. There are also foci of karyorrhexis, a feature often observed in lupus panniculitis

Foci of karyorrhexis in areas of necrosis are often seen. There may be vascular changes in the form of lymphocytic vasculitis (Table 11.7). Overlying histologic features of discoid lupus erythematosus may be seen in some cases; when present, they are an important clue to the diagnosis (see Chap. 3).

Table 11.7 Lupus panniculitis: key microscopic features

- The two most important histologic features are lobular lymphoplasmacytic inflammation accompanied by hyaline necrosis and nuclear dust
- Lymphoid follicles in the subcutaneous fat are characteristic
- Lymphocytic vasculitis may be seen in LEP

Differential Diagnosis

Subcutaneous morphea may demonstrate lymphoid aggregates like those seen in lupus panniculitis; however, germinal center formation is neither usually seen nor is hyaline fat necrosis or karyorrhexis. The most challenging and important entity to consider in the differential diagnosis is subcutaneous panniculitic-like T-cell lymphoma (SPTCL). Indeed, lupus panniculitis may be exceedingly difficult to differentiate from SPTCL. In brief, SPTCL is a mature T-cell α/β lymphoma in which lymphomatous cells are positive for CD2, CD3, CD5, and negative for CD4 and CD56. Cytotoxic granular proteins TIA-1, perforin, and granzyme-B are present in almost all cases. Histologically, well-developed lesions of SPTCL are characterized by a brisk lobular infiltrate of pleomorphic, small-medium to medium-large atypical T lymphocytes. Rimming of individual fat cells by atypical lymphocytes, fat necrosis, and karyorrhexis of lymphocytes are characteristic features. Cytophagocytosis and erythrophagocytosis by macrophages (bean-bag cells) may be seen. Early cases of SPTCL may have minimal atypia; these are the cases that may be particularly difficult to differentiate from lupus panniculitis. The presence of hyaline fat necrosis, prominent mucin deposition, germinal center formation and vacuolar change at the dermal–epidermal junction all favor lupus panniculitis (Table 11.8). However, difficult cases may require a battery of immunohistochemical stains as well as gene rearrangement studies.

Table 11.8 Lupus panniculitis: practical tips

- Consider lupus panniculitis in cases of panniculitis presenting in the upper half of the body
- Unlike other forms of lupus erythematosus, ANA serology is typically negative to low titer positive; other autoantibodies are uncommon
- There is considerable clinical and histologic overlap with subcutaneous panniculitis-like T-cell lymphoma
  - Hyaline fat necrosis, mucin deposition, lymphoid follicle formation and interface change favor lupus panniculitis
  - Immunophenotypic and gene rearrangement studies may be needed to completely exclude lymphoma – borderline cases should be followed clinically!
- The presence of histopathologic features of discoid lupus erythematosus in the overlying epidermis and dermis are helpful clues to the diagnosis when present

Artifactual Panniculitis (Including Factitial, Traumatic, and Cold Panniculitis)

Clinical Features

Artifactual panniculitides can be produced by chemical (injection of foreign material), mechanical (traumatic) or physical (cold/heat) means. The inciting event may be accidental, purposeful, or iatrogenic.

Factitial panniculitis is often characterized by confounding clinical and histologic features that defy diagnosis until self-inoculation is suspected. Most patients with factitial panniculitis are in a health care field profession with access to syringes and needles, and it is more common in women. Lesions are often localized to areas that are accessible to the hands, including buttocks and thighs. Agents implicated in factitial panniculitis include oily materials (paraffin), tissue fillers, and therapeutic agents including phytonadione (vitamin K). Some patients inject biological material such as saliva or feces.

Traumatic panniculitis does not have a specific clinical presentation; however, in adults it is most commonly seen as breast masses in women. The lesions are often indurated, warm erythematous subcutaneous nodules.

Cold panniculitis is a form of traumatic panniculitis caused by direct exposure to the cold. Infants and children are more commonly affected than adults. In children, the cheeks and chin are the most common sites of involvement. In adults, cold panniculitis usually appears in women, associated with obesity or certain sports activities including cycling or horseback riding.

Microscopic Features

Factitial panniculitis usually shows a lobular panniculitis associated with prominent fat necrosis and a neutrophil-predominant inflammatory infiltrate. In some cases, polarization may identify birefringent material causing the panniculitis. In factitial panniculitis caused by injectable material, the substance may be seen in the overlying dermis, a feature that is not seen in other forms of panniculitis. Paraffinoma (mineral oil) is a classic example of factitial panniculitis characterized by the presence of empty spaces in the dermis and subcutaneous fat (Fig. 11.15), giving a so-called

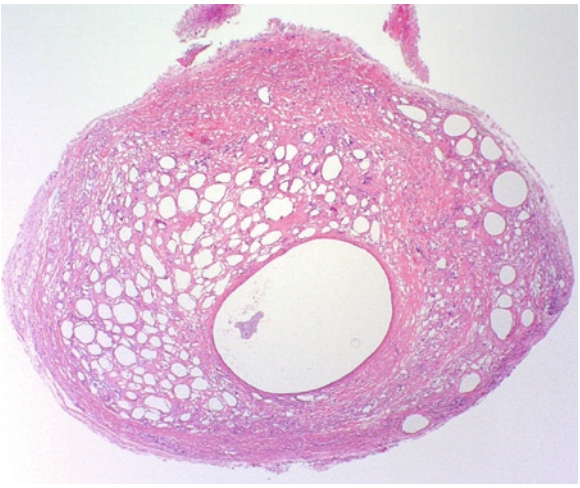

Fig. 11.15 *Paraffinoma*. A form of factitial panniculitis, paraffinoma is characterized by prominent empty spaces in the dermis and subcutaneous tissue

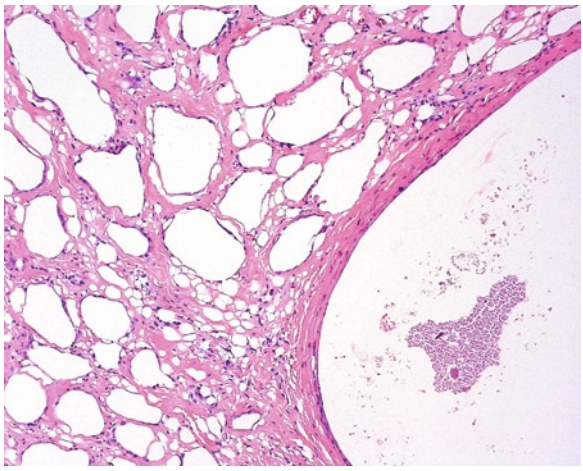

Fig. 11.16 *Paraffinoma*. Variably sized cystic spaces give the so called "swiss cheese" appearance of paraffinoma

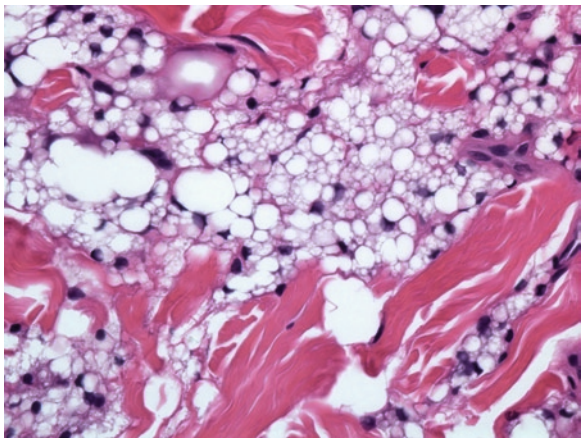

Fig. 11.17 *Silicone granuloma*. Histiocytes with multiple cytoplasmic vacuoles are characteristic of silicone granulomas

"Swiss cheese" appearance to the specimen (Fig. 11.16). The pattern of panniculitis secondary to esthetic implants varies with the material. For example, silicon granuloma is characterized by prominent foamy histiocytes with multiple vacuoles (Fig. 11.17). When biological material is injected, there is often a lobular panniculitis with abscess formation. Bacterial organisms may be identified, but their absence does not exclude the diagnosis, as cultures are more sensitive (Table 11.9).

The histological findings of traumatic and cold panniculitis are nonspecific and require some degree of clinical suspicion. Early lesions demonstrate a septal and lobular nonspecific inflammatory infiltrate of lymphocytes and macrophages (Fig. 11.18). In late lesions, there is lipoatrophy with variable pseudocystic change accompanied by macrophages, fibrosis, and foreign body giant cells.

Table 11.9 Artifactual panniculitis (factitial, traumatic/cold): key microscopic features

- Histologic features depend on the cause of the trauma. Self-inflicted injections with contaminated material produces an acute suppurative panniculitis, resembling an infection-induced panniculitis
- Paraffinoma (mineral oil) injection results in a classic "swiss cheese" appearance to the fat lobules (pseudocystic spaces surrounded by giant cells)
- Later stage lesions may demonstrate nonspecific fibrosis, lipomembranous changes, granulomas and hemorrhage
- Histologic findings of traumatic panniculitis are generally nonspecific (septal and lobular inflammation, fat necrosis, mixed inflammatory infiltrate)

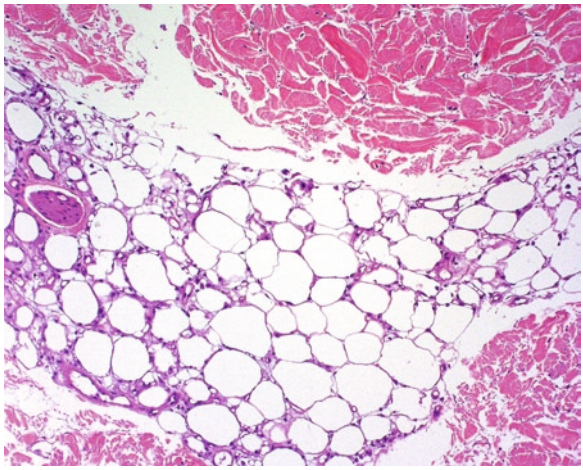

Fig. 11.18 *Traumatic fat necrosis*. The histologic features are relatively nondescript. There is often lipoatrophy with variable fat necrosis with foamy macrophages, chronic inflammation and fibrosis

Differential Diagnosis

The histological features of the artifactual panniculitides are not always specific. In cases demonstrating acute inflammation and necrosis, infection should be excluded by antimicrobial stains (Gram's, PAS, and Fite/AFB) and/or tissue culture. Positive cultures or the presence of microorganisms do not exclude a factitial process. In fact, cultures with more than one type of bacteria should prompt consideration of a factitial process due to injection of biologic material. Another important clue to the diagnosis is that the histologic findings do not match the clinical presentation. Frequently, the patient may have had multiple previously nonspecific biopsies. That should raise the suspicion of a factitial process (Table 11.10).

Table 11.10 Artifactual panniculitis: practical tips

- Consider factitial etiology when there are confounding clinical and histologic features
- When acute inflammation and necrosis, are present, the differential diagnosis includes an area adjacent to a ruptured follicle/cyst, or an infectious process. Special stains and/or tissue culture may be useful in these cases
- Polarization of the slide is a cheap and quick way to identify birefractile foreign material

Sample Reports: Erythema Nodosum

Example 1: (Early lesion of Erythema Nodosum)
Clinical history: Bilateral erythematous nodules on the legs of a 13-year-old boy.
Diagnosis: Septal panniculitis with neutrophils. See comment.
Comment: Initial and level sections were examined. The connective tissue septa of the subcutis are slightly thickened and expanded by an inflammatory infiltrate composed predominantly of neutrophils. Within the neutrophilic infiltrate, there are small, scattered aggregates of histiocytes around a central cleft (Miescher's radial granulomas). There is no evidence of vasculitis. The overlying dermis demonstrates a slight superficial and deep perivascular lymphocytic infiltrate. Epidermis is unremarkable. The histological findings are consistent with an early stage of erythema nodosum. If there is clinical suspicion of an infectious process, tissue culture is recommended.

Example 2: (Well established lesion of Erythema Nodosum)
Clinical history: Adult woman with ulcerative colitis presents with painful nodules on the legs. Rule out erythema nodosum.
Diagnosis: Erythema nodosum. See comment.
Comment: Scanning power demonstrates thickening of the connective tissue septa by an inflammatory infiltrate. In areas the inflammatory cells spill over into the fat lobules. At higher magnification, the infiltrate is composed of lymphocytes, histiocytes, and well-developed septal granulomas with prominent multinucleated giant cells. There is no evidence of vasculitis. These findings are compatible with erythema nodosum.
Note to reader: In cases where the clinical history is less precise, the diagnosis could be stated as "septal panniculitis consistent with erythema nodosum."

Sample Report: Nodular Vasculitis

Clinical history: Painful nodules on the calf of a middle-aged woman.
Diagnosis: Lobular panniculitis with vasculitis. See comment.
Comment: There is a diffuse lobular inflammatory infiltrate composed of lymphocytes and neutrophils accompanied by fat necrosis with foamy histiocytes and occasional giant cells. Large areas of necrosis are observed. Medium-sized vessels in the septa demonstrate fibrinoid necrosis and intramural inflammation. Stains for microorganisms (AFB, gram, PAS) are negative. The findings are consistent with nodular vasculitis/erythema induratum. Recommend complete clinical work-up to exclude an underlying infectious process.

Sample Report: Lipodermatosclerosis

Clinical history: Older woman with presenting with erythematous, indurated plaques on the lower extremities.

Diagnosis: Septal and lobular panniculitis with prominent membranocystic change and overlying dermal changes of stasis dermatitis. See comment.

Comment: There is a sparse inflammatory infiltrate of lymphocytes in the connective tissue septa, which are otherwise fibrotic. A mixed inflammatory infiltrate composed of lymphocytes, histiocytes and foamy macrophages is noted in the adjacent fat lobules. Fatty microcysts lined by amorphous eosinophilic material (membranocystic change) are a prominent feature. In the papillary and mid dermis, there is a lobular proliferation of capillaries accompanied by hemosiderin deposition and fibrosis, consistent with changes of stasis dermatitis. The clinical presentation together with the histologic pattern is consistent with lipodermatosclerosis.

Sample Report: Lupus Erythematosus Panniculitis

Clinical history: Young woman with poorly circumscribed breast nodule.

Diagnosis: Mixed septal and lobular panniculitis with extensive hyaline fat necrosis and lymphoid follicles. See comment.

Comment: There is a brisk, predominantly a lobular panniculitis composed of lymphocytes accompanied by extensive hyaline fat necrosis. Lymphoid follicles surrounded by plasma cells are observed in the connective tissue septa. Foci of karyorrhexis are noted in areas of hyaline necrosis. There is increased interstitial mucin in the dermis. No vasculitis is observed. Epidermis is unremarkable. The findings are most compatible with lupus panniculitis. Lupus panniculitis may demonstrate significant overlapping features with subcutaneous, panniculitis-like T-cell lymphoma. Recommend clinical correlation and follow-up.

Sample Reports: Artifactual Panniculitis

Example 1:

Clinical history: Nodule above upper lip in older woman.

Diagnosis: Lobular panniculitis with pseudocystic cavities and surrounding multinucleated giant cells. See comment.

Comment: The subcutaneous fat lobules are replaced by pseudocystic spaces surrounded by histiocytes and multinucleated giant cells. There is associated dense fibrosis. No polarizable material is seen. The findings are compatible with injection of some type of foreign material (paraffinoma). Clinical correlation recommended.

Example 2:

Clinical history: Nodule on thigh of a middle-aged woman.

Diagnosis: Mixed septal and lobular panniculitis. See comment.

Comment: There is a moderately brisk inflammatory infiltrate involving the septa and fat lobules with numerous neutrophils. There is also fat necrosis with coalesced fat cells forming pseudocysts lined by eosinophilic material. No vasculitis is observed. No polarizable material is demonstrated. Special stains for microorganisms (GMS, Fite, and gram stains) are negative. The findings do not fit into a traditional pattern of panniculitis. An infectious process could be considered despite negative stains. In the appropriate clinical context, the possibility of a factitial process could be considered. Clinical correlation is recommended.

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Chapter 12
Infections

Keywords Viral infection • Fungal infection • Dermatophyte • Scabies

This chapter discusses a collection of infectious entities that are relatively commonly encountered in dermatopathology specimens. This is an admittedly abbreviated listing of the various cutaneous infections encountered in the skin. It is meant to reflect common or uniquely important entities rather than an encyclopedic text on the subject. For example, certain esoteric infections (e.g., *Strongyloides*) will not be covered because it is beyond the spirit of this text. Some common entities, such as impetigo, will not be discussed because it is so rarely biopsied. As a rule, many of the entities do not neatly fall into a reaction pattern; therefore, they will be described according to the general class of infection. One exception is tinea versicolor, which will be described in Chap. 13.

Viral Infections

Molluscum contagiosum

Clinical Features

Molluscum contagiosum presents as solitary or multiple centrally umbilicated papules. It is most common in children and adolescents, but may present at any age. Lesions are most common on the head and neck, followed by genitalia, the latter is often the result of sexual transmission. Fomite transmission is the major route of infection, accounting for the frequency in young children. Immunosuppressed patients can have widespread lesions.

S.D. Billings and J. Cotton, *Inflammatory Dermatopathology: A Pathologist's Survival Guide*, 203
DOI 10.1007/978-1-60327-838-6_12,

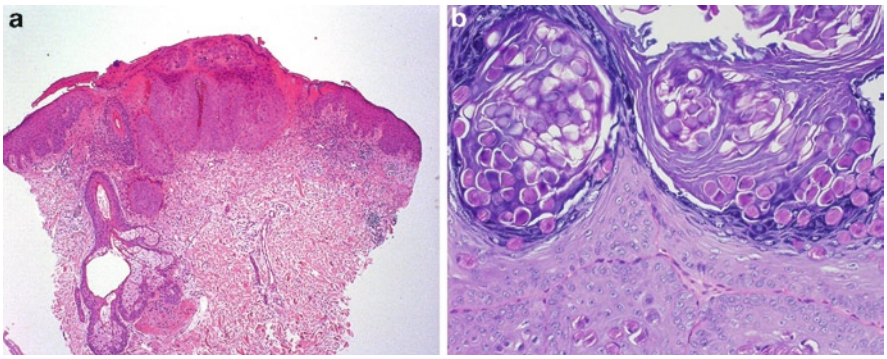

Fig. 12.1 *Molluscum contagiosum*. (**a**) In *Molluscum contagiosum* there is an endophytic proliferation of epidermis. (**b**) The infected keratinocytes have large intracytoplasmic eosinophilic viral inclusions

Microscopic Features

The lesions are characterized by an inverted proliferation of squamous epithelium that opens to the epidermal surface in the central portion. Within the cytoplasm of the keratinocytes, there are intracytoplasmic eosinophilic viral inclusions (Fig. 12.1) (Table 12.1). Occasionally, there can be rupture of the invaginated epithelium leading to a brisk inflammatory response mimicking a ruptured folliculitis. In such cases, deeper levels may reveal the characteristic viral inclusions.

Table 12.1 Key microscopic features: *Molluscum contagiosum*

- Endophytic proliferation of epidermis
- Intracytoplasmic eosinophilic viral inclusions

Differential Diagnosis

For typical cases, there is essentially nothing else in the differential diagnosis due to the distinctive appearance of *Molluscum contagiosum*. As noted above, some cases can be confused with a folliculitis (Table 12.2).

Table 12.2 Practical tips: *Molluscum contagiosum*

- If clinically suspected and not seen, get deeper levels on the block
- Can mimic folliculitis in cases where there is rupture; deeper levels usually reveal keratinocytes with viral inclusions

Herpesvirus Infections

Clinical Features

Herpesvirus infections are usually encountered in three settings: oral lesions of Herpes simplex 1 (HSV-1), genital lesions of Herpes simplex 2 (HSV-2), or reactivation of Varicella zoster in the form of herpes zoster (shingles). HSV-1 infection usually

initially presents in childhood and as vesicular crusted lesions around the mouth. Patients can have episodes of reactivation throughout life. HSV-2 is typically acquired in adult life and is generally the result of sexual transmission. Lesions are similar to HSV-1 but are most common on genital or perianal skin. For herpes zoster, there is a linear, painful vesicular eruption that follows a dermatomal distribution. It is more frequent in older adults but may be seen in a wide age range.

Microscopic Features

Essentially, all of these entities have the same histological features. Distinction between subtypes requires culture or other techniques (e.g., direct fluorescent antibody tests). Classically, there is in intraepidermal vesicle with acantholysis and degenerating keratinocytes. The diagnostic feature is the presence of keratinocytes with intranuclear viral inclusions (Fig. 12.2). The intranuclear inclusions have an eosinophilic to steel gray appearance with peripheral margination of the chromatin. Frequently, the affected keratinocytes fuse, resulting in multi-nucleation (Table 12.3). In older lesions, the epidermis may be necrotic and it is vital to look for evidence of viral inclusions in the necrotic epidermis. Follicles should also be examined, as it is sometimes possible to identify virally infected cells that are not recognizable in the necrotic epidermis, or because the epidermal surface is ulcerated. Finally, in some resolving lesions, no viral inclusions are evident and the histological features are a nonspecific granulomatous dermatitis (Fig. 12.3).

Differential Diagnosis

The diagnosis is generally quite straight forward. For more subtle cases, entities such as pemphigus or even acute spongiotic dermatitis can be considered. Neither of these has intranuclear viral inclusions. Once the epidermis is completely ulcerated,

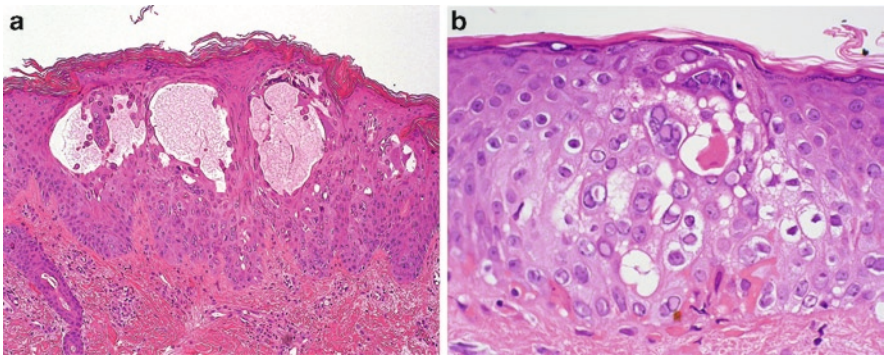

Fig. 12.2 *Herpesvirus*. (**a**) Intraepidermal vesicles with acantholysis are the classic lesion of herpesvirus infection. (**b**) The virally infected cells have intranuclear steel gray inclusions with peripheral condensation of the native chromatin. Multinucleation is common

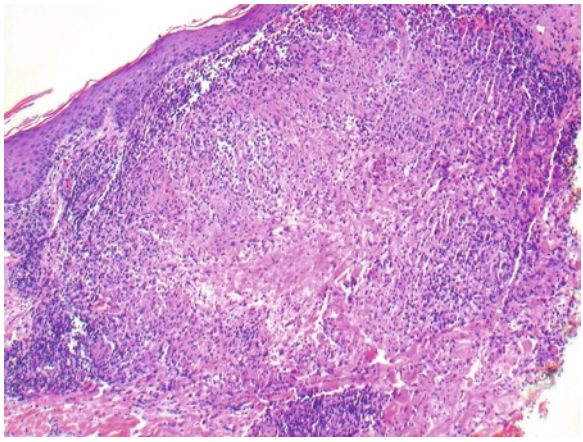

Fig. 12.3 *Post-Zoster granulomatous inflammation*. In some case, after the viral infection has histologically resolved, there is a granulomatous inflammatory infiltrate. This is nonspecific, but suggestive in a clinical setting where zoster is suspected clinically. (Courtesy of Dr. Soon Bahrami)

Table 12.3 Key microscopic features: herpesvirus infections

- Intraepidermal vesicle with ballooning degeneration, acantholysis
- Multinucleated keratinocytes
- Intranuclear viral inclusions with steel gray color and peripheral condensation of chromatin
- Follicular involvement common

it may be more difficult to recognize the presence of the virus. If there is still some necrotic epidermis present, it may be possible to recognize the remnants of viral nuclear inclusions. Failing that, close examination of follicles will often reveal presence of the virus (Table 12.4).

Table 12.4 Practical tips: herpesvirus infections

- Look for evidence of viral infection in necrotic keratinocytes
- Examine follicles when epidermis is ulcerated

Human Papillomavirus Infections

The most common entities encountered in dermatopathology caused by human papilloma virus (HPV) include verruca vulgaris, verruca plantaris, verruca plana, and condyloma acuminatum.

Clinical Features

Verruca vulgaris, caused by HPV-1, 2, 3, and 4, is the most common HPV related lesion in dermatopathology. They present as papules or plaques with a rough,

hyperkeratotic surface. They are most commonly encountered on the fingers and hands but may be encountered in a variety of locations. Verruca plantaris (and palmaris) is caused by HPV-2 and presents most frequently on the sole of the foot and less commonly on the palm. They are solitary or multiple hyperkeratotic but less elevated lesions. Verruca plana, caused by HPV-3, presents as small skin-colored to brown minimally elevated papules. They are usually multiple and present on the face or extremities. Condyloma acuminatum, caused by HPV-6, 8, 11, 16, and 18, most commonly, are dome-shaped papules presenting on the genitalia, perianal skin or groin.

Microscopic Features

Verruca vulgaris has papillomatosis, hyperkeratosis, and variable parakeratosis. The peripheral edges of the lesion claw toward the center in a buttressed fashion (Fig. 12.4). The koilocytes are most easily seen in the granular layer. They are

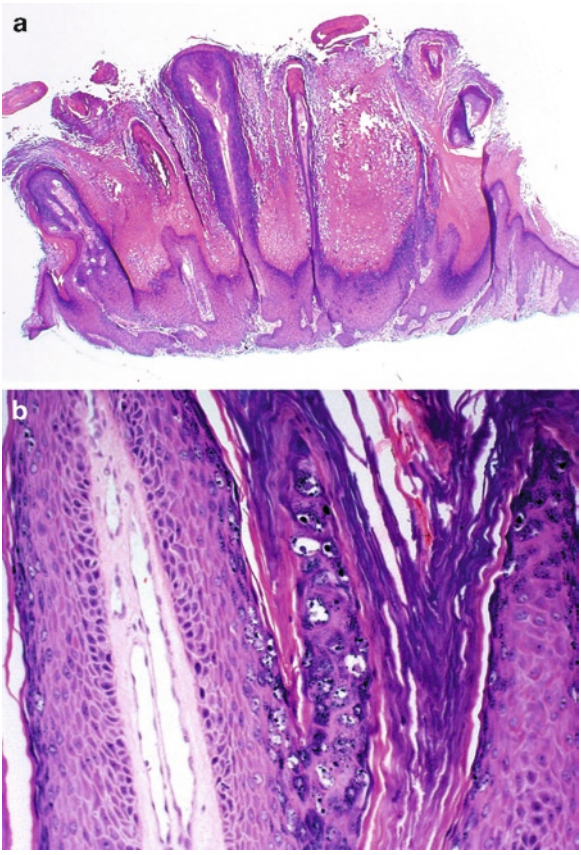

Fig. 12.4 *Verruca vulgaris*. (**a**) There is a papillomatous surface and the peripheral edges of the lesion claw in toward the center resembling a buttress. (**b**) The papillary dermal blood vessels are dilated. The koilocytes have irregular nuclei and coarse keratohyaline granules

characterized by vacuolated keratinocytes with coarse keratohyaline granules. The papillary dermal blood vessels in the tips of the papillations are dilated, and there is often hemorrhage in the overlying stratum corneum (Table 12.5).

Verruca plantaris has a thick hyperkeratotic surface. A papillomatous architecture may be less apparent, and the lesion is frequently partly endophytic (Fig. 12.5). Koilocytes are present and may be quite prominent.

Table 12.5 Key microscopic features: human papilloma virus (HPV) infections

- Verruca vulgaris
  - Papillomatous surface
  - Hemorrhage in stratum corneum overlying tips of the papillations
  - Dilated blood vessels in tips of papillations
  - Buttressed edges
  - Koilocytes with coarse keratohyaline granules
- Verruca plantaris
  - Endophytic growth
  - Buttressed edges
  - Koilocytes
- Verruca plana
  - Less prominent papillomatosus
  - Lacks buttressed edges
  - Koilocytes
- Condyloma acuminatum
  - Polypoid silhouette
  - Subtle koilocytes

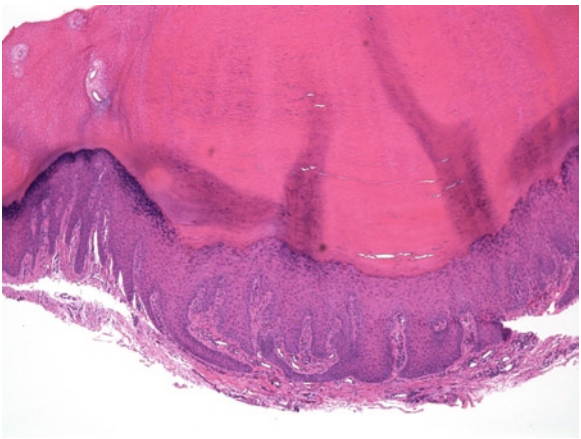

Fig. 12.5 *Verruca plantaris*. Verruca on the sole have an endophytic growth pattern, but otherwise features typical of a verruca

Verruca plana is acanthotic, but lacks pronounced papillomatosis and the buttressed edges (Fig. 12.6). The granular layer is thickened and koilocytes are present, but they may be less prominent than verruca vulgaris or plantaris.

Condyloma acuminatum usually has a polypoid, dome-shaped silhouette, lacking the papillomatous surface (Fig. 12.7). Koilocytes are frequently and maddeningly subtle. In such cases, it may be necessary to pursue extra testing to confirm the presence of HPV. In our experience, chromogenic in situ hybridization is superior to routine immunohistochemical stains.

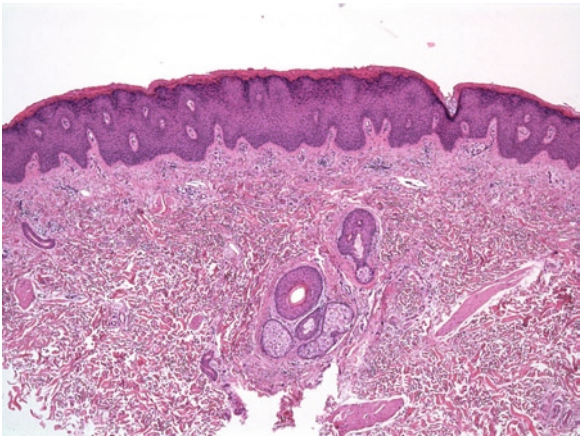

Fig. 12.6 *Verruca plana*. Flat warts have less pronounced papillomatosis and do not have the prominent peripheral buttressing

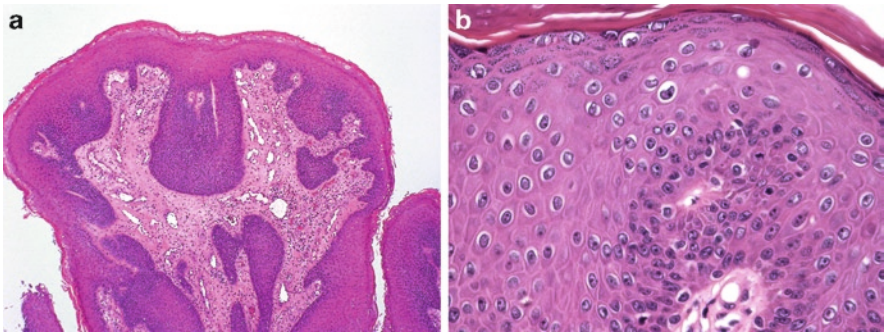

Fig. 12.7 *Condyloma acuminatum*. (**a**) Condyloma acuminatum frequently has a polypoid growth pattern. (**b**) Koilocytotic change is often subtle

Differential Diagnosis

For verruca vulgaris, the differential diagnosis is usually not difficult. In irritated or inflamed lesions, koilocytes may not be as evident. This situation can cause

confusion with an irritated seborrheic keratosis, or possibly a squamous cell carcinoma. The papillomatous surface with hemorrhage in the stratum corneum, dilated papillary dermal blood vessels and buttressed edges are keys to the diagnosis. It should be pointed out that the overlap between some cases of verruca vulgaris and irritated seborrheic keratosis can be so significant that it is not always possible to unequivocally distinguish them. Some use the term "verrucal keratosis" in this situation. Some reactive atypia is allowed in irritated or inflamed verruca vulgaris, but prominent pleomorphism or a desmoplastic stroma are clues to the diagnosis of squamous cell carcinoma. It should be remembered that malignancy can arise in cutaneous warts, especially in older patients or organ transplant patients.

Verruca plantaris is not a difficult diagnosis provided there is an adequate specimen. Too often, only the hyperkeratotic surface is biopsied with little or no underlying dermis. In such a situation, it is important to look for evidence of a papillomatous architecture that can be revealed by the pattern of hyperkeratosis and for evidence of hemorrhage in the stratum corneum that can lead the pathologist to suggest the possibility of a verruca (Fig. 12.8). Verruca plana frequently comes submitted with a clinical diagnosis of entities such as actinic keratosis, squamous cell carcinoma, basal cell carcinoma, etc. Recognizing the thickened granular layer with koilocytes is crucial to the diagnosis. Verruca plana does not show significant atypia.

Condyloma acuminatum can be a frustrating diagnosis. It closely resembles seborrheic keratosis. In fact, a clue to the diagnosis is that it resembles a dome-shaped seborrheic keratosis on genital skin. Careful examination usually reveals some koilocytes, though they are not as numerous as in other warts. In cases where there is any doubt, special studies such as chromogenic in situ hybridization should be pursued, as this diagnosis carries important implications. I have heard stories, perhaps apocryphal, about pathologists being successfully sued for over diagnosis of this entity (See sample report for dealing with ambiguous cases) (see Table 12.6).

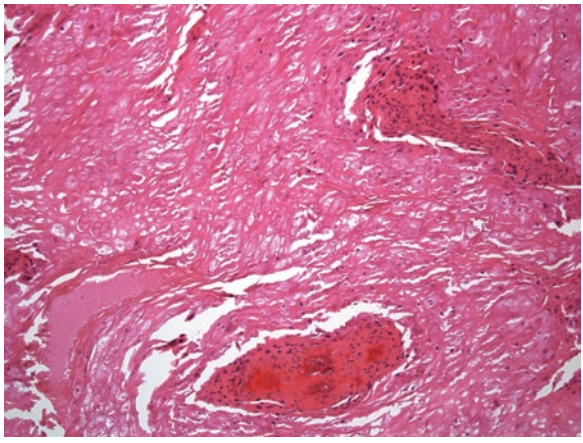

Fig. 12.8 *Superficially sampled verruca plantaris*. Frequently, only the keratotic surface of a verruca plantaris is sampled. The keratotic surface shows remnants of the dermal papillae with parakeratosis and hemorrhage

Table 12.6 Practical tips: HPV infections

- Verruca vulgaris
  - Koilocytes in irritated/inflamed warts not always apparent
  - Buttressed edges often a key feature
  - Hemorrhage in stratum corneum and underlying dilated vessels a clue
  - Do not over interpret thickened granular layer as koilocytes in conditions like prurigo nodularis
- Verruca plantaris
  - Biopsies often superficial due to endophytic growth
  - Multiple levels may be needed
  - May see evidence of papillomatous pattern in stratum corneum
- Verruca plana
  - Frequently not suspected clinically
  - Look for koilocytes when histologic features do not match clinical diagnosis, especially in lesions from face
- Condyloma acuminatum
  - Looks like a seborrheic keratosis on low power
  - Koilocytes often subtle
  - Review medical record for evidence of HPV infections (e.g., previous diagnosis of condyloma acuminatum or positive Pap tests)
  - Consider special testing if histology is subtle and the patient has no prior history

Fungal Infections

The most common fungal infections encountered are dermatophyte infection, tinea versicolor, and candidiasis. Other important fungal infections to be aware of include blastomycosis, cryptococcosis, sporotrichosis, zygomycosis and aspergillosis. Tinea versicolor in discussed in Chap. 13.

Dermatophyte Infection (Dermatophytosis or Tinea)

Clinical Features

Superficial fungal infections caused by a dermatophyte (species of fungi belonging to the genera *Trichophyton, Microsporum,* or *Epidermophyton*) are referred to as "tinea." These infections are relatively common, and can involve scalp hair and skin of the scalp (tinea capitis), general body surfaces (tinea corporis), feet (tinea pedis) and nail plate (tinea unguium/onychomycosis). Clinical presentation depends on the body site. Features of tinea capitis include localized alopecia, scaling, follicular papules and pustules. Tinea corporis presents as annular, growing crusted areas with central clearing ("ringworm"). Dermatophyte infections of the feet, one of the most common forms of dermatophyte encountered, can present as macerated areas or as vesiculobullous lesions. Onychomycosis, or

tinea unguium, usually presents in older patients and is characterized by yellowish nail discoloration, thickening and separation of the nail plate by the nail bed (onycholysis) and crumbly nails.

Microscopic Features

The quintessential feature of dermatophyte infection is the presence of neutrophils in the stratum corneum (Fig. 12.9). The epidermis shows varying amounts of hyperkeratosis, parakeratosis, spongiosis and acanthosis. In some cases, psoriasiform hyperplasia may be prominent (Fig. 12.10). Within the dermis, there is usually a perivascular mixed inflammatory infiltrate of lymphocytes and eosinophils. The fungal hyphae are often difficult to see on routine H&E stained sections. It is often necessary to perform special stains such as PAS or GMS stains (Fig. 12.11). The

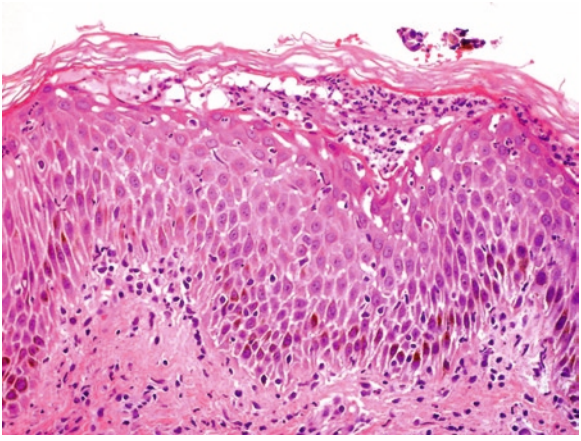

Fig. 12.9 *Dermatophyte infection*. The classic histologic feature of dermatophyte infection seen on routine microscopy is the presence of collections of neutrophils in the stratum corneum

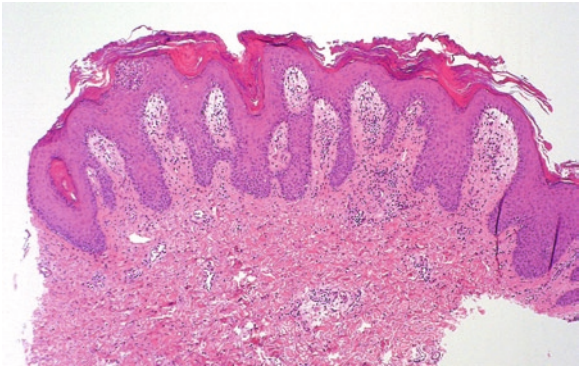

Fig. 12.10 *Dermatophyte infection*. The epidermis may have prominent psoriasiform hyperplasia

hyphae may not be visible in the most heavily inflamed areas of the stratum corneum. Examination of adjacent areas of the stratum corneum usually has a higher yield. Cases may also exhibit the so-called "sandwich sign" in which there is normal stratum corneum overlying an area of parakeratosis/compact hyperkeratosis. The organisms are sandwiched between the normal stratum corneum and altered cornified layer (Fig. 12.12). In tinea capitis, there is frequent involvement of the hair shafts within the follicles (Fig. 12.13); the organism may not be seen in the overlying stratum corneum. The hair shaft may be invaded (endothrix) or surrounded (ectothrix) by the organism, though differentiating between the patterns is not critical. There is an associated acute folliculitis with neutrophils in the follicular epithelium. In tinea capitis, the dermal infiltrate is often more brisk and extends to the mid

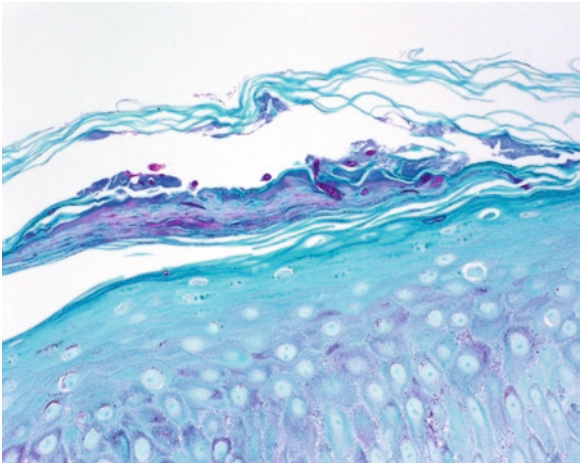

Fig. 12.11 *Dermatophyte infection*. Fungal hyphae in the stratum corneum are highlighted by a PAS stain. The use of a light green counterstain makes visualization of the organisms easier

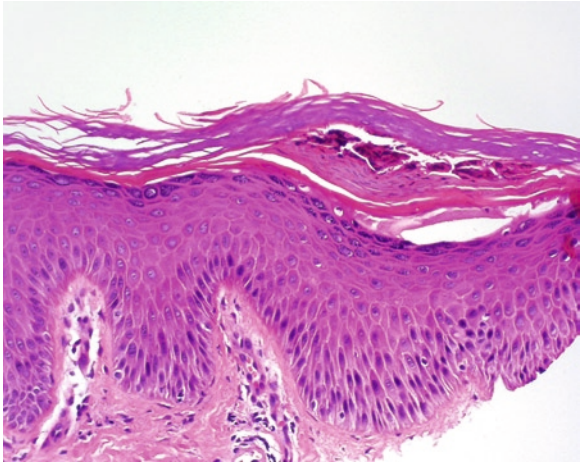

Fig. 12.12 *Dermatophyte sandwich sign*. This is a biopsy from a foot that shows normal stratum corneum overlying a focus of parakeratosis/hyperkeratosis. This pattern, referred to as the sandwich sign is a clue to a possible dermatophyte infection

to deep dermis. Biopsies for the diagnosis of onychomycosis are typically submitted as nail clippings. Therefore, the biopsy only consists of compact nail keratin. Fungal hyphae are usually not evident on routine examination, but require either a PAS or GMS stain (Fig. 12.14). See Table 12.7.

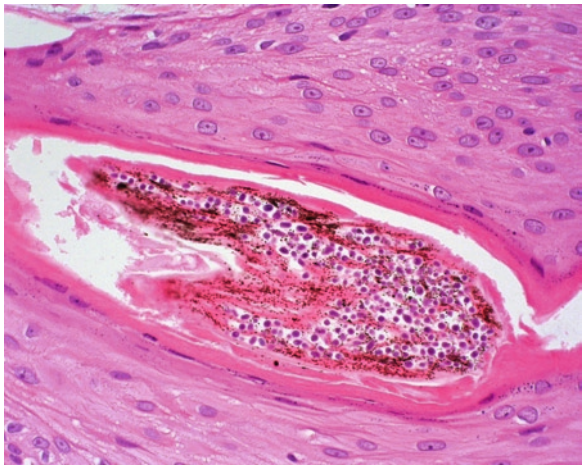

Fig. 12.13 *Tinea capitis*. Numerous fungal organisms are present in the follicle

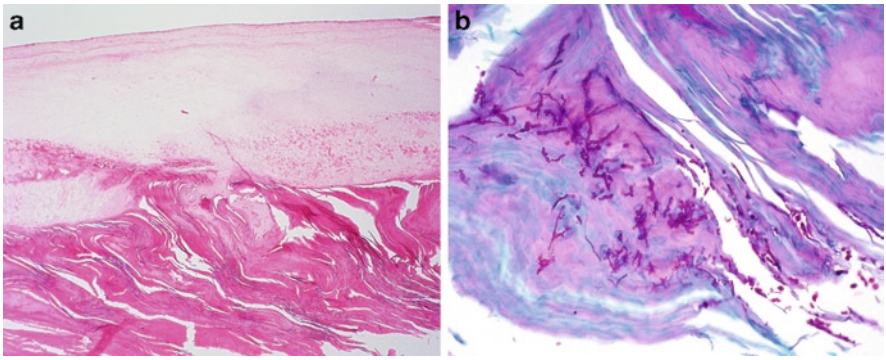

Fig. 12.14 *Onychomycosis*. (**a**) The hyphae are usually not apparent with routine H&E stains. (**b**) A PAS stain demonstrates the hyphae in the nail keratin

Table 12.7 Key microscopic features: dermatophyte infection

- Neutrophils in stratum corneum
- Acanthosis, sometimes psoriasiform
- Superficial perivascular infiltrate usually contains eosinophils

Differential Diagnosis

The differential diagnosis of most dermatophyte infections includes spongiotic dermatitis and psoriasis (Chaps. 2 and 3). Requisite for distinction is recognition of the fungus. If neutrophils are present in the stratum corneum of spongiotic dermatitis, it is prudent to consider fungal stains. Similarly, in a biopsy resembling psoriasis, a fungal stain should be considered, especially if the dermal infiltrate contains eosinophils. In many cases, patients may have been treated with topical steroids prior to biopsy. In this situation, some of the typical features, especially epidermal neutrophils, may be absent (Fig. 12.15). It is always important to consider the possibility of dermatophyte infection even when not considered clinically in at least two distinct situations: (1) a rash that has had a poor response to topical steroids and (2) a clinically annular lesion that does not fit another diagnosis (e.g., granuloma annulare, lupus erythematosus). It should be remembered that other annular rashes do occur such as erythema annulare centrifugum.

Candidiasis can be considered in the differential diagnosis. Candidiasis usually presents in intertriginous areas. There are yeast cells as well as pseudohyphae. See below for more details.

In tinea capitis, Pityrosporum folliculitis could be considered. Normally, this fungus exists as a normal commensal organism. Occasionally, it will cause a true folliculitis. It can look similar, but there are typically abundant yeast forms in the affected follicle. The yeasts are less intimately associated with the hair shaft. Bacterial folliculitis or other forms of acute folliculitis are in the differential diagnosis as well.

The differential diagnosis of onychomycosis includes other causes of dystrophic nails. If there are collections of neutrophils in the nail keratin and no evidence of fungi, the possibility of psoriasis should be considered. Lichen planus is another cause of dystrophic nail. Often it is not possible to make an unequivocal diagnosis

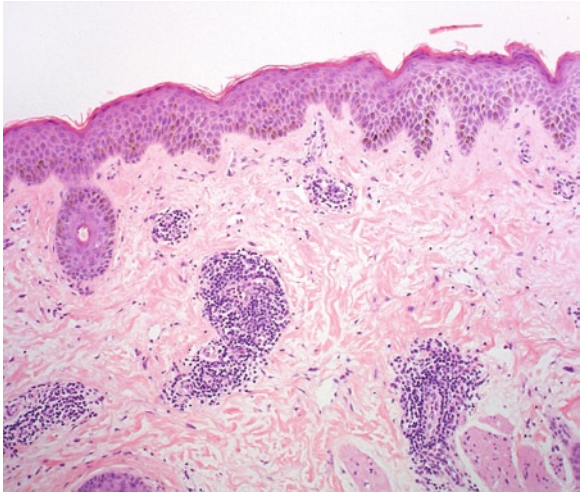

Fig. 12.15 *Dermatophyte infection treated with topical steroids*. Dermatophyte infections treated with topical steroids often lack classic histologic features. Important clues to the diagnosis is history of poor response to steroids or the clinical description of an annular lesion

in the absence of identification of fungal hyphae. The most important role for the pathologist in this setting is to document the absence of fungal hyphae, not to establish a different cause of nail dystrophy. It should be noted that yeast and bacteria are frequently seen in association with nail keratin. Typically, these are commensal organisms, not pathogens, but their presence should be mentioned on the report. Practical tips are summarized in Table 12.8.

Table 12.8 Practical tips: dermatophyte infection

- It is important to keep a high index of suspicion for dermatophytosis
- If neutrophils are in the stratum corneum, consider special stains for fungi
- If lesion is clinically annular, consider special stains for fungi
- Always suspect dermatophyte infection when there is a history of a poor response to topical steroids even in the absence of characteristic histologic features

Candidiasis

Clinical Features

Candidiasis typically presents as papules and pustules in intertriginous areas and along skin folds. Lesions frequently become confluent and there is often associated erosion.

Microscopic Features

The epidermis has overlying parakeratotic scale that contains the small budding yeast and pseudohyphae (Fig. 12.16). Pseudohyphae are often more numerous than yeast forms. The organisms are usually more apparent on routine sections than dermatophytes, and have a light purple color on H&E stained sections. The epidermis is spongiotic, often with subcorneal pustules (Fig. 12.16). The organism may not be as evident within the pustules. Within the dermis, there is a superficial perivascular mixed infiltrate that usually has eosinophils (Table 12.9). GMS or PAS stains are still useful for highlighting the organisms and may make recognition of yeast forms easier.

Differential Diagnosis

The differential diagnosis includes dermatophyte infection, inverse psoriasis, contact dermatitis, acute generalized exanthematous pustulosis (AGEP), and scabies. Dermatophyte infection usually has a different clinical distribution. Dermatophyte organisms do not have the same light purple color on H&E stained sections and lack yeast. Of course, if you can't distinguish between the two, there is no harm done as both are treated with antifungals.

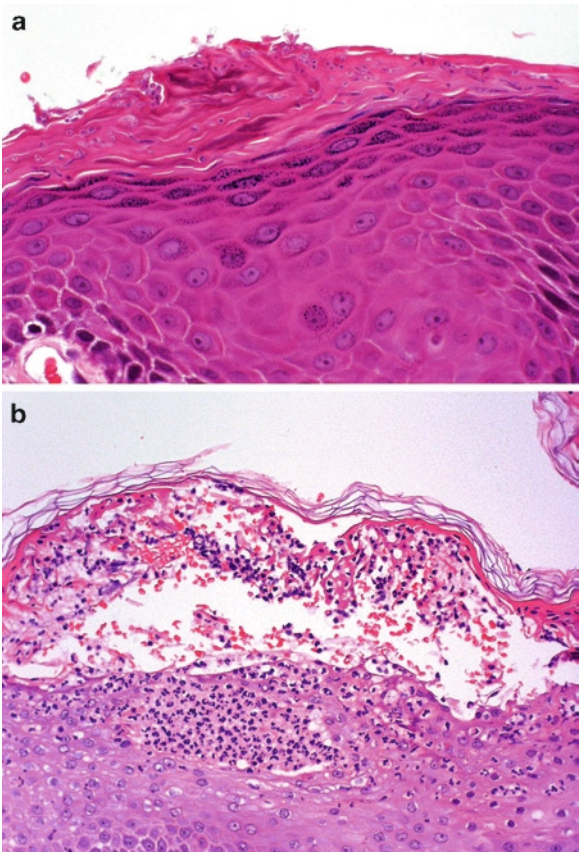

Fig. 12.16 *Candidiasis*. (**a**) The yeast and pseudohyphae in the stratum corneum have a light purple color on H&E stained sections. (**b**) Frequently the epidermis has neutrophilic pustules

Table 12.9 Key microscopic features: candidiasis

- Neutrophilic pustules
- Spongiosis
- Yeast and pseudohyphae in stratum corneum/superficial epidermis
- Mixed dermal infiltrate with eosinophils

Inverse psoriasis is a form of psoriasis that present in intertriginous zones and may resemble candidiasis. It lacks yeast or pseudohyphae and does not have eosinophils in the dermal infiltrate.

Contact dermatitis, a form of eczematous dermatitis discussed in Chap. 2, frequently presents in the axillae like candidiasis. In this location, it is usually a reaction to substances

in deodorant. It resembles other forms of spongiotic dermatitis. It lacks fungal organisms and may have Langerhans cell microabscesses in the epidermis.

AGEP is a widespread pustular drug eruption. The histological features may resemble candidiasis, but the distribution is different and again, there are no fungal organisms.

Scabies infestation can clinically present in intertriginous zones, especially the groin. It will be discussed in more detail below. Recognition of the mite and absence of fungal organisms allows for distinction. See Table 12.10.

Table 12.10 Practical tips: candidiasis

- Pseudohyphae may greatly outnumber yeast forms
- Light purple color of organisms on H&E stain is a clue
- Occurs in skin folds (e.g., groin, axilla)

Blastomycosis

Clinical Features

Cutaneous blastomycosis, caused by *Blastomyces dermatitidis*, is usually the result of disseminated systemic infection, but may rarely be the result of direct inoculation of the skin. The cutaneous lesions present as violaceous verrucal plaques. Frequently, a neoplasm such as squamous cell carcinoma is suspected.

Microscopic Features

There is prominent pseudoepitheliomatous hyperplasia of the epidermis in association with a brisk neutrophilic infiltrate (Fig. 12.17). Scattered multinucleated giant cells are present in the dermis. Within the infiltrate and within the multinucleated cells, there are large budding yeasts between 8 and 15 μm in size. The yeasts have thick refractile walls on H&E stained sections (Fig. 12.17). Budding forms have a characteristic broad base. They may be rare, and special stains (PAS, GMS) may help unveil their presence (Table 12.11).

Differential Diagnosis

The most important differential diagnosis is squamous cell carcinoma. The pseudoepitheliomatous proliferation can bear a striking resemblance to malignancy. Given that a neoplasm is often suspected clinically, it is no surprise that cases are misdiagnosed. I have personally reviewed cases of “recurrent squamous cell carcinoma” that were in fact blastomycosis. Obviously, recognition of the organism is the key to diagnosis. Whenever a squamous proliferation is seen in conjunction

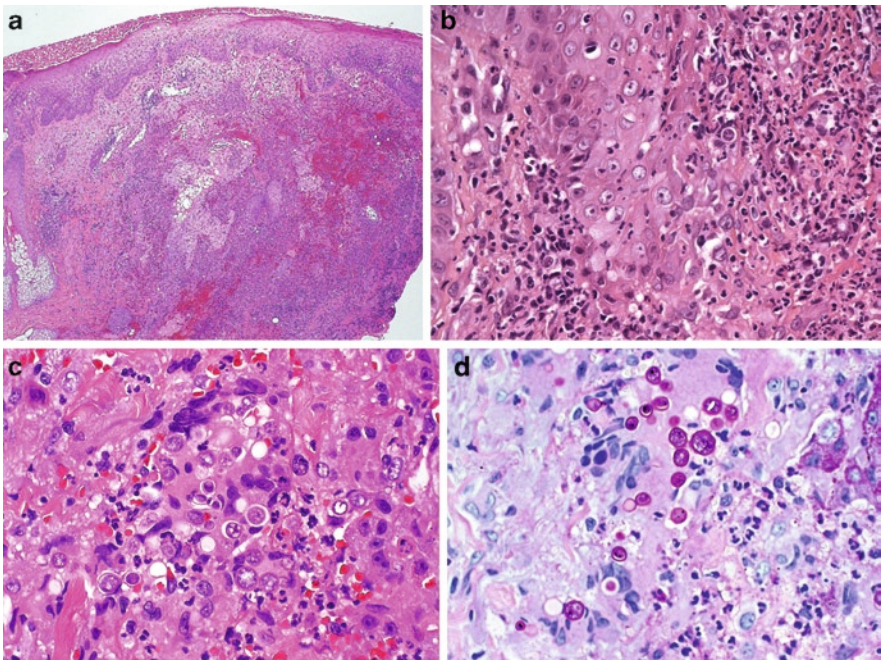

Fig. 12.17 *Blastomycosis*. (**a**) Pseudoepitheliomatous hyperplasia of the epidermis is common in blastomycosis. (**b**) In this higher power picture the pseudoepitheliomatous hyperplasia with reactive squamous atypia in association with blastomycosis is appreciated. (**c**) The yeast of blastomycosis have thick refractile walls. (**d**) Broad-based budding is characteristic

Table 12.11 Key microscopic features: blastomycosis

- Pseudoepitheliomatous epidermal hyperplasia
- Neutrophil rich infiltrate
- Scattered multinucleated histiocytes
- Large yeast (8–15 μm) with broad-based buds

with a brisk dermal neutrophilic infiltrate, the possibility of blastomycosis should be considered.

The other entity in the differential diagnosis is coccidioidomycosis, caused by *Coccidioides immitis*. Like blastomycosis, it is associated with pseudoepitheliomatous epidermal hyperplasia and a suppurative infiltrate. The organism in the cutaneous lesions is a large thick-walled spherule with numerous endospores. The spherule is much larger than the yeast of blastomycosis (20–80 μm). This disease is endemic in the Southwestern United States and rare to see in patients outside this geographic area. See Table 12.12.

Table 12.12 Practical tips: blastomycosis

- If the biopsy looks like squamous cell carcinoma but there are numerous neutrophils, consider blastomycosis
  - If you practice in the Southwestern United States, this pattern should trigger the search for coccidioidomycosis
- Size matters: the size range of the yeast in blastomycosis is an important clue to avoid confusion with cryptococcosis and coccidioidomycosis

Cryptococcosis

Clinical Features

Cryptococcosis is caused by *Cryptococcus neoformans*. Cutaneous disease is the result of secondary skin involvement by an underlying systemic infection and presents in immunocompromised patients as multiple small ulcerating papules.

Microscopic Features

There are two basic patterns: granulomatous and gelatinous. In the former, there is a granulomatous inflammatory infiltrate in association with the organism. In the latter, there are sheets of the yeast with little inflammatory response (Fig. 12.18). The yeasts are variable in size ranging from 4 to 12 μm and usually have a thick clear capsule (Fig. 12.19). The thick capsule can give the appearance of drops of water within the dermis. Some narrow-based budding may be seen. The organisms can be highlighted by PAS or GMS stains. The capsules can be stained with a mucicarmine stain. A Fontana–Masson stain will also highlight the organism. This is useful in identifying variant organisms lacking capsules (Table 12.13).

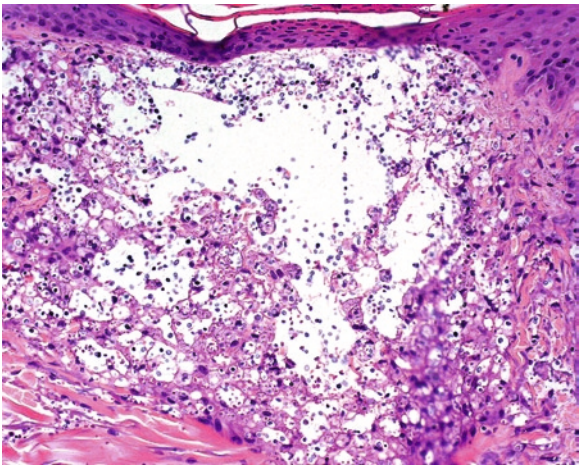

Fig. 12.18 *Cryptococcosis*. The gelatinous pattern is characterized by sheets of organisms in the dermis

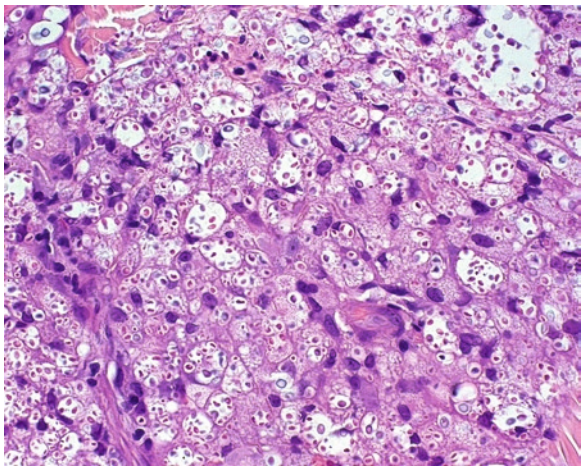

Fig. 12.19 *Cryptococcosis*. The yeast have thick capsules and are quite variable in size

Table 12.13 Key microscopic features: cryptococcosis

- Yeast with thick clear capsule
- Capsule highlighted with mucicarmine stain
- Narrow based budding
- Variable in size: 4–12 μm

Differential Diagnosis

Cryptococcosis can be confused with blastomycosis because of the overlap in size of the organism. *Cryptococcus neoformans* is more variable in size with smaller forms than is seen in blastomycosis. The thick capsule usually allows easy distinction. In selected cases, mucicarmine stains to highlight the capsule or Fontana–Masson stains will allow recognition of cryptococcosis (Table 12.14).

Table 12.14 Practical tips: cryptococcosis

- Size overlap with blastomycosis, but smaller yeast forms too small for blastomycosis
- Water drop appearance on H&E is a clue
- Consider mucicarmine or Fontana-Masson stains

Coccidioidomycosis

Clinical Features

This infection caused by *Coccidioides immitis* is endemic to the Southwestern United States. Cutaneous involvement is rare, occurring in 1% of patients developing

systemic disease. Cutaneous lesion in systemic disease present as verrucal plaques. Interestingly, a subset of patients' with coccidioidomycosis also develop other cutaneous diseases: erythema nodosum and erythema multiforme.

Microscopic Features

The epidermis exhibits pseudoepitheliomatous hyperplasia. Within the dermis, there is suppurative granulomatous inflammation and large spherules containing endospores (Fig. 12.20). The spherules are variable in size, generally ranging from approximately 20 to 80 μm (Table 12.15).

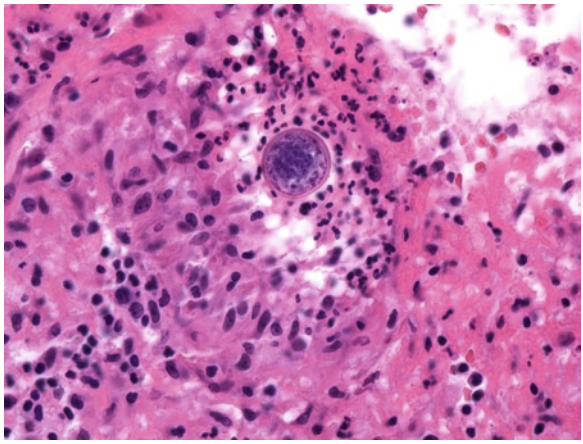

Fig. 12.20 *Coccidioidomycosis*. The characteristic feature is the spherule that contains numerous endospores

Table 12.15 Key microscopic features: coccidioidomycosis

- Large spherules (20–80 μm) with endospores
- Pseudoepitheliomatous hyperplasia
- Neutrophil-rich granulomatous infiltrate

Differential Diagnosis

The primary differential diagnosis is blastomycosis, which is discussed in detail above (Table 12.16).

Table 12.16 Practical tips: coccidioidomycosis

- Spherules may appear smaller that they truly are depending on plane of section
- Ruptures spherule may be devoid of endospores and appear as empty sacs
- Spherules do not bud; absence of budding helps distinguish from blastomycosis

Sporotrichosis

Clinical Features

Sporotrichosis is caused by *Sporothrix schenckii*. It is a primary cutaneous infection caused by trauma, typically a splinter or rose thorn. It presents an erythematous ulcerated nodule that can progress up the affected extremity following the lymphatics.

Microscopic Features

There is epitheliomatous hyperplasia and suppurative granulomatous inflammation. Small microabscesses are common. Identification of the fungus is often difficult, and special stains (GMS) are almost always required. The organism consists of elongated cigar-shaped budding yeast ranging in size from 2 to 8 μm (Fig. 12.21) (Table 12.17). Rarely asteroid forms, characterized by yeast with numerous radiating spikes, are seen.

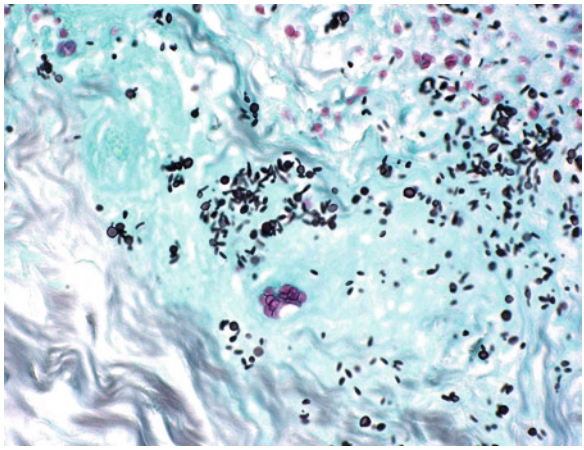

Fig. 12.21 *Sporotrichosis*. The GMS stain highlights the yeast of sporotrichosis which are variable in size and often cigar-shaped

Table 12.17 Key microscopic features: sporotrichosis

- Suppurative granulomatous inflammation with microabscesses
- Cigar-shaped yeast 2–8 μm in size
- Asteroid bodies (rarely seen)

Differential Diagnosis

Because of the clinical presentation of lymphangitic spread, epithelioid sarcoma should be considered because of potential overlapping clinical presentation. Epithelioid

sarcoma can have a pseudogranulomatous pattern, but typically has atypia and a less suppurative appearance. Otherwise other infectious processes should be considered in the differential diagnosis. Diagnosis requires identification of the organism by microscopy or, more frequently, culture (see sample report) (Table 12.18).

Table 12.18 Practical tips: sporotrichosis

- Organisms are rare; multiple levels often necessary
- Clinical history important
- Don't miss epithelioid sarcoma

Mucormycosis

Clinical Features

Mucormycosis is caused by *Rhizopus*, *Mucor* and *Absidia* fungi. Identifying the specific organism requires cultures. This infection is seen in immunocompromised patients, diabetics, and patients with an underlying hematologic malignancy. Cutaneous lesions are usually the result of disseminated spread, but primary skin infections can be seen as the result of infected burns or trauma. The lesions present as dusky, necrotic plaques. This is a serious infection with a high rate of mortality.

Microscopic Features

The fungi are characterized by broad, ribbon-like relatively non-septate hyphae that branch at right angles (Fig. 12.22). The fungi are frequently angioinvasive and may result in ischemic necrosis in surrounding tissue. The inflammatory infiltrate may be quite mild in nature, owing to the underlying immunosuppression (Table 12.19). The fungi are often more evident with PAS or GMS stains.

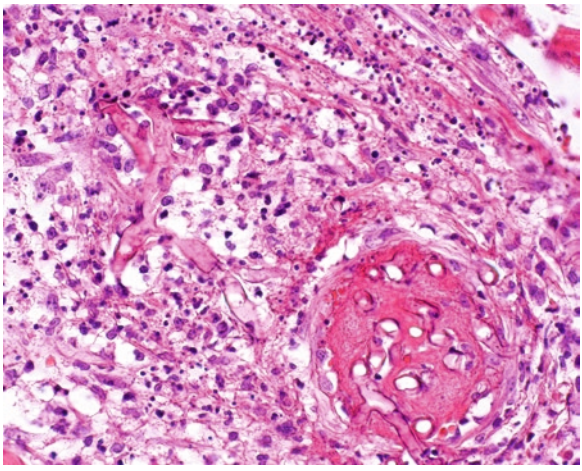

Fig. 12.22 *Mucormycosis*. The hyphae are broad and ribbon-like and relatively nonseptate. Angioinvasion is commonly seen

Table 12.19 Key microscopic features: mucormycosis

- Broad relatively nonseptate, ribbon-like hyphae with right angle branches
- Angioinvasion common
- Inflammatory infiltrate can be sparse

Differential Diagnosis

As a result of the vaso-occlusive nature of the angioinvasion, mucormycosis can be confused with thrombotic disease or vasculitis on low power examination. Higher power examination reveals the presence of fungal hyphae and special stains can be helpful. Other forms of angioinvasive fungal infections, notably aspergillosis, are in the differential diagnosis. *Aspergillus* organisms have narrower hyphae, more regular septations and acute angle branching. As a practical matter, distinction can be difficult as it may be difficult to see the hyphae in the proper orientation in tissue sections or due to degenerative features that can be present in the fungal hyphae (Table 12.20). Correlation with culture results is recommended. In cases where the type of fungal infection is uncertain, a descriptive diagnosis can be useful (see sample reports).

Table 12.20 Practical tips: mucormycosis

- Immunocompromised and diabetic patients
- Some septae often present; their presence does not rule out the diagnosis
- Broad hyphae helps distinguish from aspergillosis
- If biopsy resembles vaso-occlusive disease on low power in an immunocompromised patient, consider an angioinvasive fungal infection
- Degenerative changes in hyphae may preclude definitive diagnosis
  - Consider descriptive diagnosis if necessary (see sample reports)

Aspergillosis

Clinical Features

Aspergillosis is caused by *Aspergillus* species. It occurs in the same patient population as mucormycosis and lesions are clinically similar.

Microscopic Features

Classically, the hyphae of *Aspergillus* are regular with septation and acute angle branching, but fine detail may not be apparent in tissue sections. There may be a

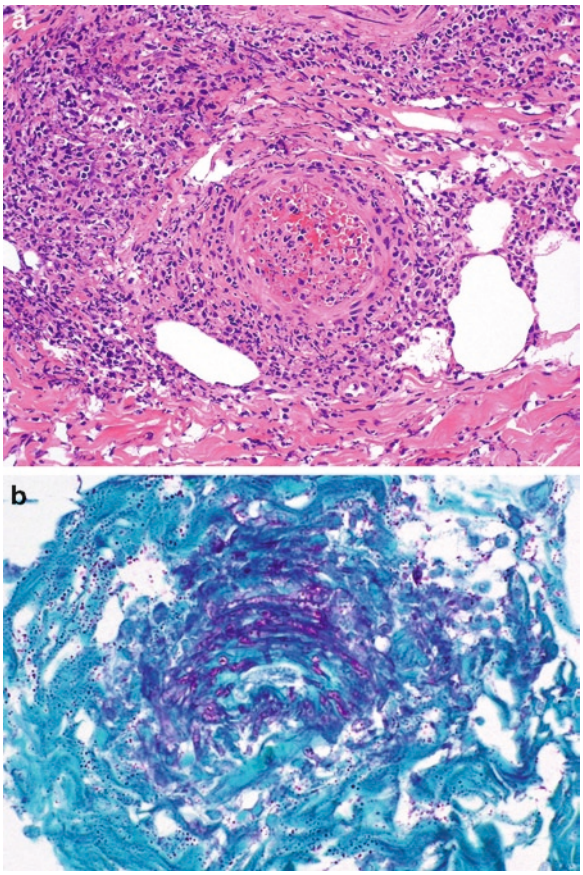

Fig. 12.23 *Aspergillosis*. (**a**) This case of aspergillosis mimicked vasculitis. (**b**) The PAS stain highlights the fungal hyphae

Table 12.21 Key microscopic features: aspergillosis

- Regular septate hyphae with acute angle branching
- Angioinvasion
- Inflammatory infiltrate can be sparse

granulomatous response or there may be little inflammation as result of immunosuppression. Angioinvasion and vascular occlusion is common (Fig. 12.23) (Table 12.21), and there is frequent tissue ischemic necrosis.

Differential Diagnosis

The differential diagnosis includes mucormycosis, which is discussed in detail in the preceding section. *Fusarium* infection can have a similar appearance, but the

hyphae of *Fusarium* branch at right angles and pinch in at branch points (Fig. 12.24). Distinction can be very difficult on tissue sections and correlation with culture results is always recommended. Like mucormycosis, confusion with a thrombotic process or vasculitis is possible on cursory examination. Definitive diagnosis of fungal type is often dependent on culture (see sample reports) (Table 12.22).

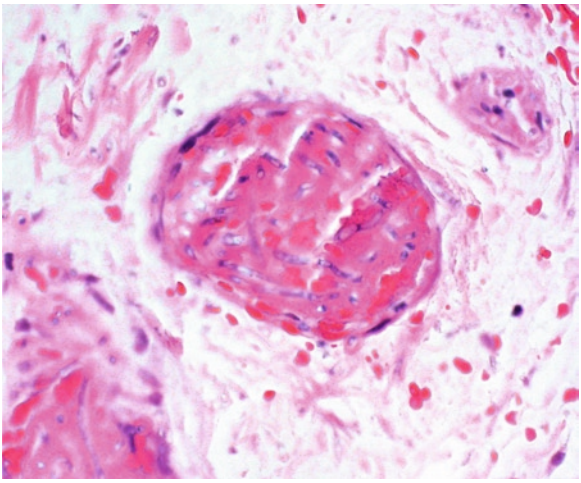

Fig. 12.24 *Fusarosis*. The vessel is occluded by fungal hyphae. There is subtle pinching of the hyphae at septations typical of *Fusarium*

Table 12.22 Practical tips: aspergillosis

- Immunocompromised patients
- If biopsy resembles vaso-occlusive disease on low power in an immunocompromised patient, consider an angioinvasive fungal infection
- Degenerative changes in hyphae may preclude definitive diagnosis
  - Consider descriptive diagnosis if necessary (see sample reports)
- Regular pattern of septation favors aspergillosis over mucormycosis
- Correlation with culture results essential

Leishmaniasis

Clinical Features

Leishmaniasis is caused by the parasite *Leishmania*. There has been a resurgence of this diagnosis in the United States and is seen in military personnel and others returning from the Middle East where this disease is endemic. It has a variety of colloquial names including Baghdad boil. Infection is acquired via sandfly bites. Acute lesions present as single pruritic papules that eventuate into ulcerated nodules. Mucocutaneous forms involve mucous membranes as well as the skin and can

cause significant disfigurement as a result of mucous membrane involvement. Chronic forms present as multiple persistent plaques.

Microscopic Features

There is a brisk dermal infiltrate of histiocytes admixed with lymphocytes, plasma cells, neutrophils and eosinophils. The organisms are seen in the cytoplasm of the histiocytes, typically at the periphery of the cell. They are small (3 μm) with a basophilic nucleus on one side and a kinetoplast on the other imparting a safety pin appearance (Table 12.23). The organisms may be better visualized with Giemsa stains (Fig. 12.25).

Table 12.23 Key microscopic features: leishmaniasis

- Mixed infiltrate with histiocytes
- Intracellular organisms in histiocytes
- Organisms have nucleus on one end and kinetoplast on other

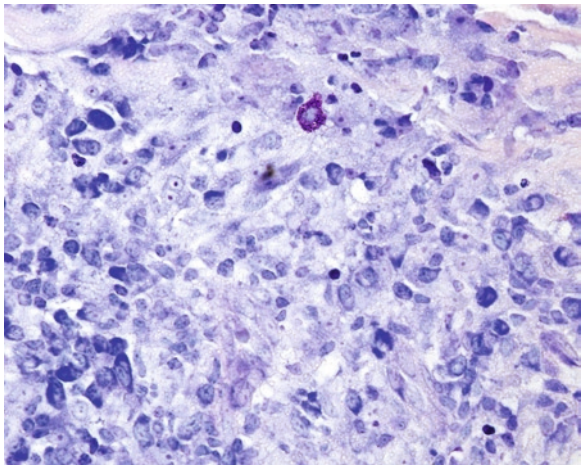

Fig. 12.25 *Leishmaniasis*. Giemsa stain highlighting intracellular organisms

Differential Diagnosis

The organisms are difficult to see because of their small size. They may be overlooked and the infiltrate can be considered a form of granulomatous dermatitis (I have made this painful mistake only to realize the diagnosis on a repeat biopsy). The size of the organism and intracellular location can cause confusion with histoplasmosis. GMS stains and the lack of kinetoplasts can help recognize histoplasmosis (Table 12.24).

Table 12.24 Practical tips: leishmaniasis

- High index of suspicion in patients who are in the military
- Careful examination of histiocytes at high power
- Giemsa stain can help identify organisms

Scabies

Clinical Features

Scabies is caused by cutaneous infestation with the mite *Sarcoptes scabei.* It is highly contagious and is transmitted by prolonged close contact. The classic clinical lesion is the burrow tract that presents as fine, wavy brown lines between the fingers. Lesions may also be papular, nodular vesicular or eczematous in appearance. Other common locations include the palms, wrists, nipples, inframammary folds, waist, and penis. Immunosuppressed patients may develop widespread, crusted lesions with numerous mites. This is also referred to as Norwegian scabies.

Microscopic Features

The diagnostic finding is the presence of the mite, mite feces, or eggs in the stratum corneum (Fig. 12.26). Findings can be focal and many levels may be necessary. In cases where the mite itself is not seen, egg case remnants described as having the appearance of "pigtails" may be a clue to the diagnosis (Fig. 12.27). Within, the dermis there is a mixed infiltrate with numerous eosinophils (Table 12.25).

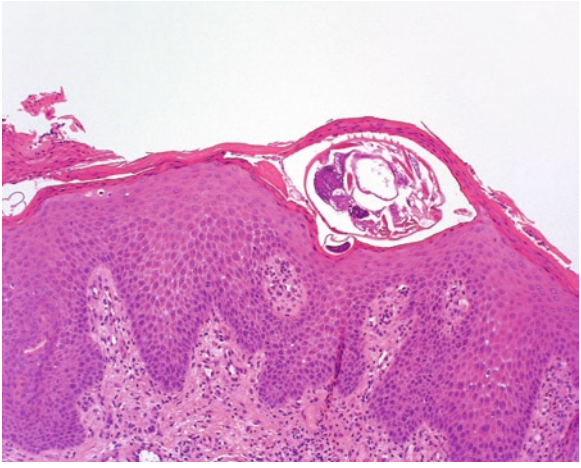

Fig. 12.26 *Scabies*. The sections demonstrates a scabetic mite in the stratum corneum

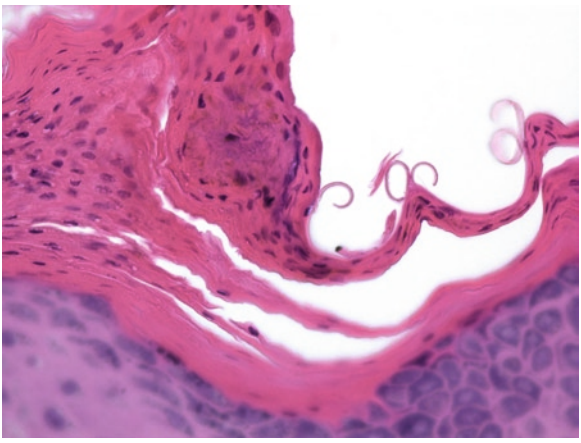

Fig. 12.27 *Scabies*. In this section only remnants of egg casings are seen. Their appearance has been likened to pigtails

Table 12.25 Key microscopic features: scabies

- Evidence of mites in stratum corneum
- Mixed dermal infiltrate with numerous eosinophils

Differential Diagnosis

If the mite is seen, there is really nothing else in the differential diagnosis. The dermal infiltrate can be confused with dermal hypersensitivity reactions such as urticaria or drug eruptions if there is no histological evidence of scabies infestation. See Table 12.26 for practical tips.

Table 12.26 Practical tips: scabies

- Obtain multiple deeper levels if initial slides are negative
- Evidence of infestation may be subtle: look for "pink pigtails"

Sample Reports

Since some of the entities in this chapter are so distinctive, sample reports will not be provided for each entity. The sample reports that follow will concentrate on entities that can be ambiguous.

Sample Report: Verruca Plantaris

In this case the lesion is superficially sampled.

Clinical history: Rule out verruca plantaris.

Diagnosis: Hyperkeratosis and parakeratosis consistent with surface of verruca, see comment.

Comment: There is compact hyperkeratosis and parakeratosis with evidence of hemorrhage. Only a limited amount of epidermis is present and it is superficially sampled. There are focal koilocytes present. The findings are consistent with the surface of a verruca. If there is a clinical suspicion of a possible malignancy, a repeat, deeper biopsy would be recommended. Clinicopathologic correlation is recommended.

Sample Report: Condyloma Acuminatum

In this case, unequivocal koilocytotic change is not evident.

Clinical history: Condyloma vs. other.

Diagnosis: Benign keratosis, see comment.

Comment: Sections demonstrate a benign squamous proliferation with a polypoid silhouette. The growth pattern is reminiscent of a condyloma acuminatum, but unequivocal koilocytotic change is not seen. In the appropriate clinical context, the histologic features would be consistent with that diagnosis. Additional testing for HPV can be performed on request. Clinicopathologic correlation is recommended. (Note to reader: if your laboratory has the capacity for assaying for HPV in ambiguous cases, I recommend pursuing additional tests in difficult cases.)

Sample Report: Sporotrichosis

In this case, organisms were not identified.

Clinical history: Rule out sporotrichosis.

Diagnosis: Granulomatous dermatitis, see comment.

Comment: Within the dermis, there is a prominent granulomatous infiltrate with focal microabscess formation. Special stains for fungi (GMS) are negative. The possibility of sporotrichosis cannot be excluded despite negative stains. Identification of the fungal organism is relatively uncommon on histologic examination. Correlation with cultures is recommended.

Sample Report: Mucormycosis

Clinical history: Ulcerated nodule, rule out infection.
Diagnosis: Angioinvasive fungal infection consistent with mucormycosis, see comment.
Comment: Within the dermis, there are numerous fungal hyphae with angioinvasion and vascular occlusion. In order to visualize the hyphae better, a PAS stain was performed. The hyphae are broad and ribbon-like with infrequent septae. The histologic features are most consistent with mucormycosis, but correlation with culture results is recommended.

Sample Report: Aspergillosis

Clinical history: Bone marrow transplant patient, rule out infection.
Diagnosis: Angioinvasive fungal infection suspicious for aspergillosis, see comment.
Comment: Within the dermis, there is an angioinvasive fungal infection with vascular occlusion by numerous fungal hyphae. A PAS stain demonstrates that the hyphae are relatively uniform with frequent septation. Acute angle branching is seen. The histological features are highly suspicious for aspergillosis, but correlation with culture results is essential.

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Chapter 13
Miscellaneous Dermatoses: Invisible Dermatoses and Inflammatory Processes that Clinically Mimic Tumors

Keywords Tinea versicolor • Erythrasma • Post inflammatory pigment alteration • Vitiligo • Rosacea • Chondrodermatitis nodularis helicis

Sometimes when viewing a biopsy, there are no obvious abnormalities noted at low magnification. This situation is referred by some authors as the "nothing lesion." Such a specimen warrants careful scrutiny beginning at the stratum corneum and working down to the subcutis, looking for subtle changes in the keratin layer (fungal infection), basal layer (melanocytes, melanin deposition,and basal vacuolization), papillary dermis (vascular wall thickening, amyloid deposition, mast cell infiltrates), dermis and adnexae (changes in collagen, elastic tissue, mucin deposition,and alterations in adnexae). Depending on the clinical question being asked, special stains may be very helpful in detecting organisms or deposited material.

This discussion will focus on entities that fall into this category of "invisible" dermatoses. By being aware of the clinical presentation, subtle histologic changes that characterize these lesions, and liberal use of special stains, a specific diagnosis can usually be rendered. This section of the chapter will also briefly discuss entities that occur elsewhere in the book. And the reader is referred to those chapters for more complete coverage.

Tinea Versicolor

Clinical Features

Tinea versicolor is caused by dimorphic, lipophilic organisms in the genus *Malassezia,* formerly known as *Pityrosporum*. It is characterized by hyperpigmented to hypopigmented macules with variable scale, typically located on the trunk. Patients often present toward the end of summer because their tan is uneven.

S.D. Billings and J. Cotton, *Inflammatory Dermatopathology: A Pathologist's Survival Guide*, 233
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Microscopic Features

The scale is typically a normal basket weave configuration with occasional parakeratosis. The epidermis is usually normal. A slight superficial perivascular infiltrate of lymphocytes may be seen or appear entirely normal. Hyphal and yeast forms (spaghetti and meatballs pattern) may be visible on routine histologic examination (Fig. 13.1) (Table 13.1) or highlighted with PAS or GMS stains. Sometimes, the organisms create empty spaces in the stratum corneum that can be detected on H&E slides. When cut at right angles, the hyphae appear like donuts.

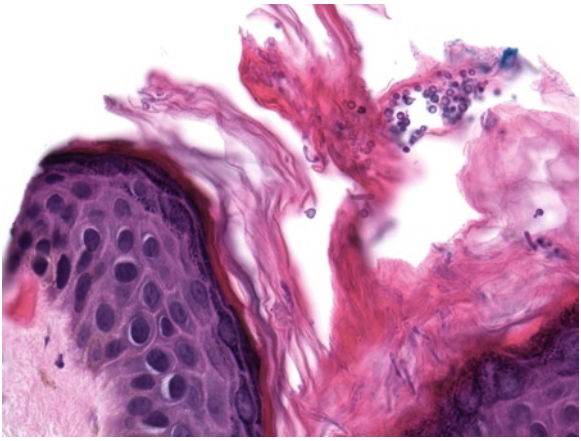

Fig. 13.1 *Tinea versicolor* is characterized by the presence of yeast and hyphae in otherwise normal looking skin

Table 13.1 Key microscopic features: tinea versicolor

- Hyphae and yeast in stratum corneum (spaghetti and meatballs pattern)
- Epidermis is usually normal
- Relatively noninflammatory

Differential Diagnosis

Dermatophyte infection is considered in the differential diagnosis histologically. The absence of neutrophils in the stratum corneum and normal epidermis are clues to tinea versicolor. Pigment disorders such as vitiligo or post inflammatory hypopigmentation may be a clinical consideration, and that history should always prompt consideration of tinea versicolor (Table 13.2).

Table 13.2 Practical tips: tinea versicolor

- Clinically can present as pigment disorder (e.g., vitiligo)
- Consider PAS stain

Corynebacterial Infection

Clinical Features

Corynebacterium overgrowth is seen in both erythrasma and pitted keratolysis. Erythrasma is the most common cause of interdigital foot infection. It may also involve intertriginous areas. The infection is found frequently in patients who are overweight or have diabetes mellitus. Lesions typically present as well-defined red-brown fine scaly patches. Pitted keratolysis presents as often malodorous, discrete pits on the plantar surfaces. Both infections demonstrate characteristic coral-red fluorescence by Wood's lamp examination.

Microscopic Features

Both erythrasma and pitted keratolysis are characterized by filamentous bacteria in the cornified layer (Fig. 13.2) (Table 13.3). A PAS stain or Gram stain highlights small, round coccobacilli.

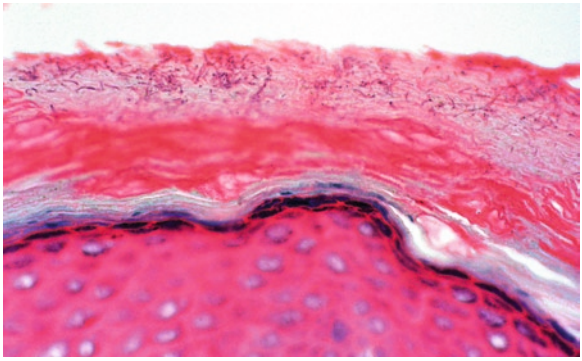

Fig. 13.2 *Erythrasma* (and pitted keratolysis) is characterized by filamentous bacteria in the stratum corneum

Table 13.3 Key microscopic features: erythrasma and pitted keratolysis (cornybacterial infection)

- Normal appearing axillary or acral skin
- Filamentous bacteria in stratum corneum

Differential Diagnosis

The differential diagnosis clinically is usually candidiasis for intertriginous cases and dermatophyte for foot infections. Erythrasma and pitted keratolysis lack the inflammatory changes and the organisms are much smaller (Table 13.4).

Table 13.4 Practical tips: erythrasma and pitted keratolysis

- Consider these diagnoses in biopsies of normal appearing axillary or acral skin
- Gram or PAS stains helpful

Post Inflammatory Pigment Alteration

Clinical Features

Post inflammatory pigment alteration usually presents as hyperpigmented or hypopigmented macules. It is the result of a previous, resolving inflammatory process. Clinically, it may still have some features resembling the disease and biopsies may be submitted with a clinical diagnosis of an inflammatory skin disease.

Microscopic Features

The epidermis is usually normal in appearance or may exhibit subtle alterations (e.g., minimal spongiosis or acanthosis). Within the dermis, there is a scant to mild perivascular lymphocytic infiltrate with scattered melanophages (Fig. 13.3; Table 13.5).

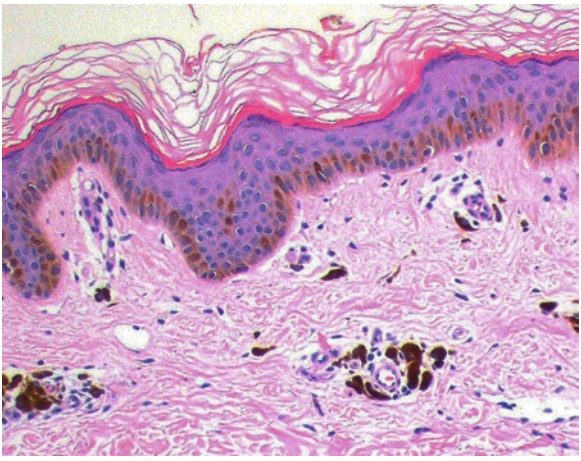

Fig. 13.3 *Post inflammatory pigment alteration*. The epidermis is unremarkable and there are perivascular melanophages

Table 13.5 Key microscopic features: post inflammatory pigment alteration

- Unremarkable epidermis
- Mild perivascular lymphocytic infiltrate with melanophages

Differential Diagnosis

The histologic differential diagnosis includes other vitiligo. Melanophages are more prominent in post inflammatory pigment alteration and there is no reduction in the number of melanocytes in post inflammatory pigment alteration. Ashy dermatosis, also called erythema dyschromicum perstans, is in the histologic differential diagnosis. It is a widespread dermatitis that presents as ash-colored or brown hyperpigmented macules that is most common in Latin America or in patients with Hispanic ancestry. It is a mild interface dermatitis that has a component of post inflammatory pigment alteration. Active lesions will demonstrate interface change in addition to dermal melanophages and a mild perivascular lymphocytic infiltrate. The interface change may be subtle and multiple levels may be needed. In biopsies submitted as solitary lesions, the possibility of a regressed melanocytic lesion or resolved benign lichenoid keratosis should be considered. In this situation, additional levels are recommended to help exclude these possibilities. Immunohistochemical stains for melanocytic markers can also be considered to help exclude an occult residual melanocytic tumor (Table 13.6).

Table 13.6 Practical tips: post inflammatory pigment alteration

- Clinically may be hyperpigmented or hypopigmented
- Consider immunostains to rule out vitiligo
- Consider PAS stains to rule out tinea versicolor
- If patient is of Hispanic descent, consider ashy dermatosis and look for evidence of interface change
- If lesion is solitary, consider regressed melanocytic lesion
  - Get deeper levels
  - Consider immunostains to evaluate for occult melanocytic tumor

Vitiligo

Clinical Features

Vitiligo is an acquired condition where melanocytes are absent from affected skin. Lesions are characterized by circumscribed, hypopigmented round or oval macules or patches. Vitiligo is a progressive disorder in which some or all of the melanocytes in the affected skin are selectively destroyed. Average age of onset is 20 years; face, neck and scalp are most commonly affected. Vitiligo is a complex disorder. Pathophysiologic hypotheses to explain this pathology include autocytotoxic, neural, and immunologic mechanisms, the details of which are beyond the scope of this book.

Microscopic Features

Ideally, the biopsy should include both lesional and nonlesional skin. In normal skin, melanocytes are distributed as one per approximately seven keratinocytes. In contrast to keratinocytes, basilar melanocytes often have halos surrounding the nucleus with some cytoplasm still clinging to the nucleus. Vitiligo is defined as a greatly reduced or absence of melanocytes and melanin. Practically speaking, it may be very difficult to recognize and distinguish melanocytes from basal keratinocytes on routine examination. For this reason, it is advisable to order a panel of special stains when evaluating for this possibility. Masson–Fontana stain demonstrates loss of melanin pigment in the basilar epithelium of vitiliginous skin. Immunohistochemical stains are the preferable means for evaluation, as they are more sensitive. Immunohistochemical staining with Melan-A or Mart-1 stains are better than S100 protein stains because of their relative specificity for melanocytes (Fig. 13.4). Immunostains for S100 protein will also highlight intraepidermal Langerhans cells. However, there are some potential interpretation pitfalls with Melan-A or Mart-1. In inflammatory process with active interface change, there may be false positivity of non-melanocytes with these stains. An immunohistochemical stain for microphthalmia transcription factor (MITF) can be useful, as it is a fairly specific nuclear marker of melanocytes. Early lesions of vitiligo can show superficial perivascular lymphocytes (inflammatory vitiligo); however, dermal melanophages favor nonspecific postinflammatory alteration over vitiligo (Table 13.7).

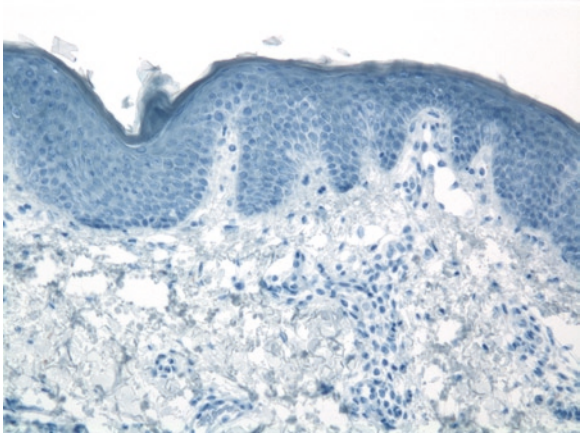

Fig. 13.4 *Vitiligo*. An immunohistochemical stain for Melan-A demonstrates an absence of melanocytes

Table 13.7 Key microscopic features: vitiligo

- Absence of melanocytes on H&E
- Immunostains ideal to prove reduction/absence of melanocytes

Differential Diagnosis

The primary differential diagnosis is postinflammatory pigment alteration. Tinea versicolor could also be considered. Neither of these entities has reduced numbers of melanocytes in the epidermis (Table 13.8).

Table 13.8 Practical tips: vitiligo

- Normal skin has ~1 melanocyte per 7 keratinocytes
- Exclude tinea versicolor with PAS or GMS stains
- Melan-A or Mart-1 immunostains superior to S100 protein immunostains

Macular Amyloidosis and Lichen Amyloidosis

Clinical Features

Macular amyloidosis presents most commonly as an intensely pruritic, dusky brown pigmented papules distributed over the upper back or arms. Approximately 50% of patients have a reticulated or rippled pattern of pigmentation. Lichen amyloidosis presents as pruritic waxy papules usually on the lower legs.

Microscopic Features

Both forms are essentially the same microscopically with deposition of amyloid within the dermal papillae. The homogenous, dull-pink deposits are associated with widened dermal papillae and dermal melanophages (Fig. 13.5). In our experience, the diagnosis is best made on H&E, as often classic amyloid stains (Congo-red) are

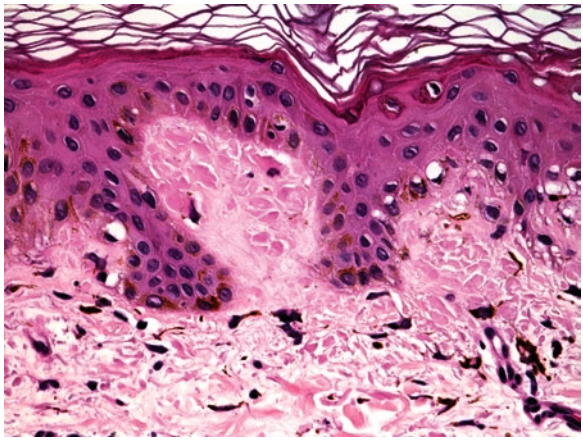

Fig. 13.5 *Macular amyloidosis*. The amyloid deposition is characterized by eosinophilic globules in the papillary dermis. Melanophages are present around the blood vessels

negative (Table 13.9). Reactive epidermal changes related to excoriation (hyperkeratosis, thickened granular layer) may be present.

Table 13.9 Key microscopic features: macular and lichenoid amyloidosis

- Homogenous dull pink papillary dermal deposits of amyloid
- Widened dermal papillae
- Melanophages

Differential Diagnosis

Distinguishing macular and lichen amyloidosis requires knowledge of the clinical presentation (Table 13.10). Systemic amyloidosis can look similar, but the deposits are usually more prominent and not just in the papillary dermis. They are more likely to be birefringent under polarized light with a Congo-red stain. Colloid milium can look identical histologically. Colloid milium is characterized by numerous yellow-brown papules on heavily sun-damaged skin.

Table 13.10 Practical tips: macular and lichenoid amyloidosis

- This form of amyloid often not birefringent on Congo red stains
- Best considered an H&E diagnosis

Other Inflammatory Diseases that Can Present as Nothing Lesions

In this section there is brief mention of other entities in the nothing lesion differential diagnosis that have been previously discussed in other chapters.

Dermatophyte Infections

Dermatophyte infections are discussed in detail in Chap. 12. Occasionally, dermatophyte infections are histologically quite subtle. Often, it is the result of prior treatment with topical steroids. Clues to occult dermatophyte infection include clinical history of poor response to topical steroids, history of an annular lesion and the sandwich sign as discussed in the previous chapter.

Cutaneous Mastocytosis

As discussed in Chap. 5, cutaneous mast cell disease is characterized by clinical heterogeneity. Urticaria pigmentosa and telangiectasia macularis eruptiva perstans

can be quite subtle histologically. Special stains are instrumental in recognizing subtle forms. Special stains such as Giemsa can be used, but an immunohistochemical stain for tryptase or CD117 are more sensitive as they also detect degranulated mast cells. See Chap. 5 for a more complete discussion.

Morphea

Clinical and histologic features of morphea are more completely discussed in Chap. 9. On scanning magnification, the "square" biopsy (as opposed to normal tapered or cone shape that occurs post-fixation) is a helpful clue to the diagnosis.

Dermal Hypersensitivity Reaction (Urticaria or Drug Eruption)

The entities have been previously discussed in more detail in Chaps. 4 and 5. For the purposes of this chapter, it is important to remember that the dermal infiltrate can appear sparse on scanning magnification, and therefore appear as a "nothing lesion." High power examination will reveal some perivascular eosinophils that are key to recognizing these dermal hypersensitivity reactions. Intravascular neutrophils may also be seen especially in the setting of urticaria.

Inflammatory Disorders Clinically Mistaken for Neoplasms

Inflammatory dermatoses can sometimes mimic cutaneous neoplasms. In our practices, the two most common inflammatory dermatoses that are frequently submitted with a clinical diagnosis of a cutaneous malignancy are rosacea and chondrodermatitis nodularis helicis. Knowledge of this is helpful in arriving at the proper diagnosis in this setting.

Rosacea (Acne Rosacea)

Clinical Features

Rosacea begins as an erythematous eruption on the central face, especially the cheeks and around the nose. Over the time, patients may develop papules and/or pustules. The papules may have surrounding telangiectasia. Occasionally, the appearance may cause a clinician to consider the possibility of a basal cell carcinoma.

Microscopic Features

The histologic findings of rosacea are variable. Fairly constant is the presence of a perivascular and perifollicular lymphocytic infiltrate (Fig. 13.6). An associated acute folliculitis may be present in occasional cases. Some cases have a relatively prominent granulomatous inflammatory infiltrate and are termed granulomatous rosacea (Fig. 13.7; Table 13.11).

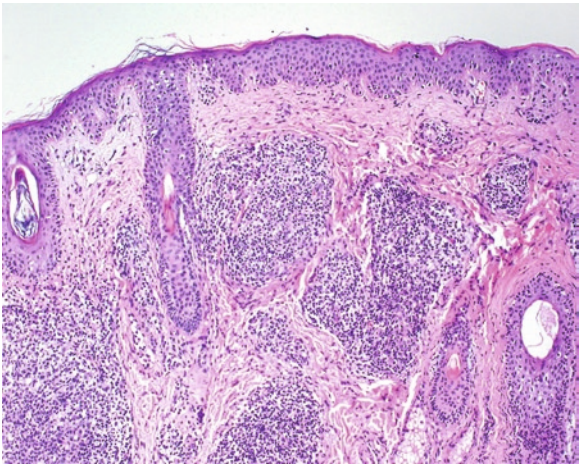

Fig. 13.6 *Rosacea* is characterized by a perifollicular and perivascular lymphohistiocytic infiltrate

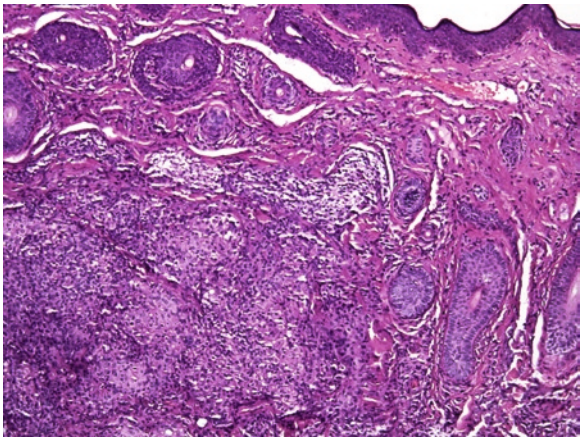

Fig. 13.7 *Granulomatous rosacea*. Within the dermis there is a brisk granulomatous infiltrate centered on follicles. The papillary dermal blood vessels are ectatic, a common finding in rosacea

Table 13.11 Key microscopic features: rosacea

- Perivascular and perifollicular lymphohistiocytic infiltrate
- Telangiectatic vessels
- May be granulomatous

Differential Diagnosis

The histologic features are often nonspecific. Rosacea is rarely biopsied except when basal cell carcinoma is a clinical concern. In such cases, it is prudent to obtain deeper levels to exclude that possibility. In granulomatous rosacea, sarcoidosis or infection could be considered. Usually the granulomas of granulomatous rosacea have a more developed lymphocytic cuff. The clinical concern for basal cell carcinoma is also a clue that suggests rosacea over sarcoidosis (Table 13.12).

Table 13.12 Practical tips: rosacea

- Occurs on central face, especially around nose
- May be submitted with clinical diagnosis of basal cell carcinoma
- Multiple levels recommended if clinical concern is basal cell carcinoma

Chondrodermatitis Nodularis Helicis

Clinical Features

Chondrodermatitis nodularis helicis, also referred to as chondrodermatitis nodularis chronica helicis, has a very specific clinical presentation. It is more common in middle aged to older patients. In men, it presents almost exclusively on the helix. In women, the antihelix is the most common location. It presents as a crusted or ulcerated nodule. Clinically, it can be confused with squamous cell carcinoma or, less frequently, basal cell carcinoma. The etiology of this process is thought to be related to chronic trauma. Some consider it a localized pressure ulcer. Supporting this are cases attributable to persistent headphone use in telephone operators in days of yore and the increased incidence on the dominant sleep side.

Microscopic Features

The epidermis is usually, but not always, ulcerated. Adjacent to the ulcer, the epidermis shows pseudoepitheliomatous hyperplasia. Immediately beneath the ulcer, there is the characteristic fibrinoid degeneration of the collagen (Fig. 13.8). Beneath the fibrinoid material is a reactive vascular proliferation, but with relatively little inflammation. Depending on how deep the process goes, a reactive proliferation of perichondrial fibroblasts and degenerative changes of the collagen may be seen (Table 13.13).

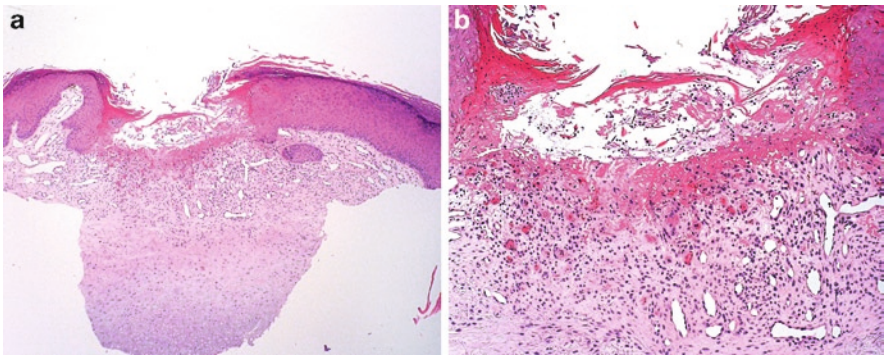

Fig. 13.8 *Chondrodermatitis nodularis helicis*. (**a**) At scanning magnification there is an epidermal ulcer overlying the cartilage. (**b**) Beneath the ulcer there is the characteristic fibrinoid change in the dermal collagen that is surrounded by a reactive vascular proliferation

Table 13.13 Key microscopic features: chondrodermatitis nodularis helicis

- Ulcerated epidermis with adjacent reactive epidermal hyperplasia
- Fibrinoid degeneration of dermal collagen
- Reactive vascular proliferation under degenerated collagen

Differential Diagnosis

The most common entity in the differential diagnosis is squamous cell carcinoma. The pseudoepitheliomatous hyperplasia must not be mistaken for squamous cell carcinoma. There may be some reactive atypia, but hyperchromasia and atypical mitotic figures are not seen. One must be careful not to over interpret the presence of adjacent actinic keratosis. As this lesion tends to occur in sun-damaged skin of older patients, adjacent actinic keratosis may be an incidental finding. The fibrinoid degeneration of the dermal collagen is the key histologic feature. Often, the biopsy is relatively shallow and does not demonstrate the underlying cartilage. The histologic findings are actually quite distinctive, and misdiagnosis is rare when one is aware of the features (Table 13.14).

Table 13.14 Practical tips: chondrodermatitis nodularis helicis

- High index of suspicion on biopsies from ear
  - Helix and antihelix almost exclusively involved
- Fibrinoid degeneration of collagen is the key microscopic feature

Sample Reports: Post Inflammatory Pigment Alteration

Example 1:

Clinical history: Hypopigmented macules, rule out vitiligo.

Diagnosis: Mild perivascular lymphocytic infiltrate with melanophages consistent with post inflammatory pigment alteration, see comment.

Comment: The epidermis is unremarkable. Within the dermis, there is a mild superficial perivascular lymphocytic infiltrate with scattered melanophages. Because of the clinical suspicion for possible vitiligo, an immunohistochemical stain for Melan-A was performed and compared to appropriate controls to assess for the number and distribution of melanocytes. There is a normal number and distribution of melanocytes. The histologic features are consistent with post inflammatory pigment alteration, which can clinically present as hypopigmented or hyperpigmented macules.

Example 2:

Clinical history: Pigmented lesion.

Diagnosis: Mild perivascular lymphocytic infiltrate with melanophages consistent with post inflammatory pigment alteration, see comment.

Comment: The epidermis is unremarkable. Within the dermis, there is a mild superficial perivascular lymphocytic infiltrate with scattered melanophages. Because of the clinical suspicion for a pigmented neoplasm, multiple deeper levels and an immunohistochemical stain for Melan-A was performed and compared to appropriate controls. No evidence of a melanocytic neoplasm is seen. The histologic features are consistent with post inflammatory pigment alteration, which can clinically present as hypopigmented or hyperpigmented macules. The possibility of a completely regressed melanocytic neoplasm or resolved benign lichenoid keratosis cannot be excluded. Clinicopathologic correlation and continued clinical follow-up is recommended.

Sample Report: Rosacea

Clinical history: Rule out basal cell carcinoma.

Diagnosis: Perivascular and perifollicular lymphohistiocytic infiltrate suggestive of rosacea, see comment.

Comment: Multiple levels were examined. Within the dermis, there is a perivascular and perifollicular lymphohistiocytic infiltrate. No evidence of malignancy is seen. The histologic features are consistent with rosacea in the appropriate clinical context. Clinicopathologic correlation is recommended.

Sample Report: Chondrodermatitis Nodularis Helicis

Clinical history: Squamous cell carcinoma.

Diagnosis: Consistent with chondrodermatitis nodularis helicis, see comment.

Comment: The epidermis is ulcerated. Beneath the ulcer, there is fibrinoid degeneration of the collagen, which is surrounded by a reactive vascular proliferation. Given the clinical presentation on the ear, the histologic features are consistent with the diagnosis of chondrodermatitis nodularis chronic helicis. Clinicopathologic correlation is recommended.

Selected References

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