Marisa R. Nucci
Carlos Parra-Herran

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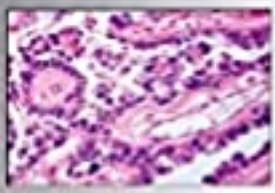
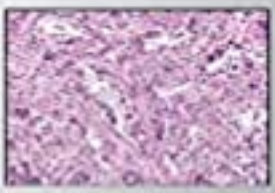
Gynecologic Pathology

SECOND EDITION





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Preface

All disciplines in the field of surgical pathology are constantly evolving, and female genital tract pathology is no exception. The last decade has brought remarkable progress in terms of our understanding of gynecologic disease and the role of tissue-based morphologic and molecular testing in its diagnosis. This second edition of *Gynecologic Pathology*, a volume in the *Foundations in Diagnostic Pathology* series, incorporates these advances using a schematic and simplified layout. In keeping with the highly successful format of the series, information is presented in both paragraph and bullet-point forms, and complemented by more than 1150 high-quality photographs. Each topic contains relevant clinical aspects including management and prognostic factors. The pathology information is organized in a systematic fashion: in addition to the key *macroscopic* and *histopathologic features*, emphasis is given to the role of *ancillary testing* (histochemistry, immunohistochemistry, and/or molecular diagnostics). As a major element, the section of *differential diagnosis* discusses pitfalls and distinguishing characteristics helpful in the diagnostic work-up. The information contained in this volume aims to be practical and applicable to most practice settings. We also incorporate emerging evidence and practice recommendations that, while still in the process of being validated and implemented, are likely to become standard of care in the future. Prime examples of this are the molecular-based classification of endometrial carcinoma and the role of molecular testing in the classification of uterine sarcomas.

This book is the product of the scholarly work of experts in the fields of gynecologic pathology, dermatopathology, and cytopathology. Each author has not only extensive knowledge in their areas of practice, but also great passion for education. Their expertise and dedication is reflected in the high quality and educational value of the chapters. As editors, we were honored and educated by their contributions, for which we are deeply grateful.

New to this second edition is the expansion to 21 chapters (from 17 in the first edition), including two new chapters on *non-neoplastic lesions of the cervix* and *cytology in the practice of gynecologic pathology*. We also cover the role of immunohistochemistry *and* molecular testing throughout the text and in a chapter fully devoted to this topic. We hope that the reader, whether a student or an experienced pathologist, finds in this reference a simple yet comprehensive tool to navigate through the practice of gynecologic pathology.

Marisa R. Nucci, MD and
Carlos Parra-Herran, MD, FASCP

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Marisa R. Nucci, MD and
Carlos Parra-Herran, MD, FASCP

To my family—my loving husband Branch, my two beautiful sons Julian and Cole, and our rambunctious but adorable cattle dog Rusty.

Marisa R. Nucci, MD

To my mom for her endless love, sacrifice, and insuperable example; to my dad, my brothers, and their families for being a continuous source of support and inspiration; and to Chris for being the best part of my day and the brightest part of my future, today and always.

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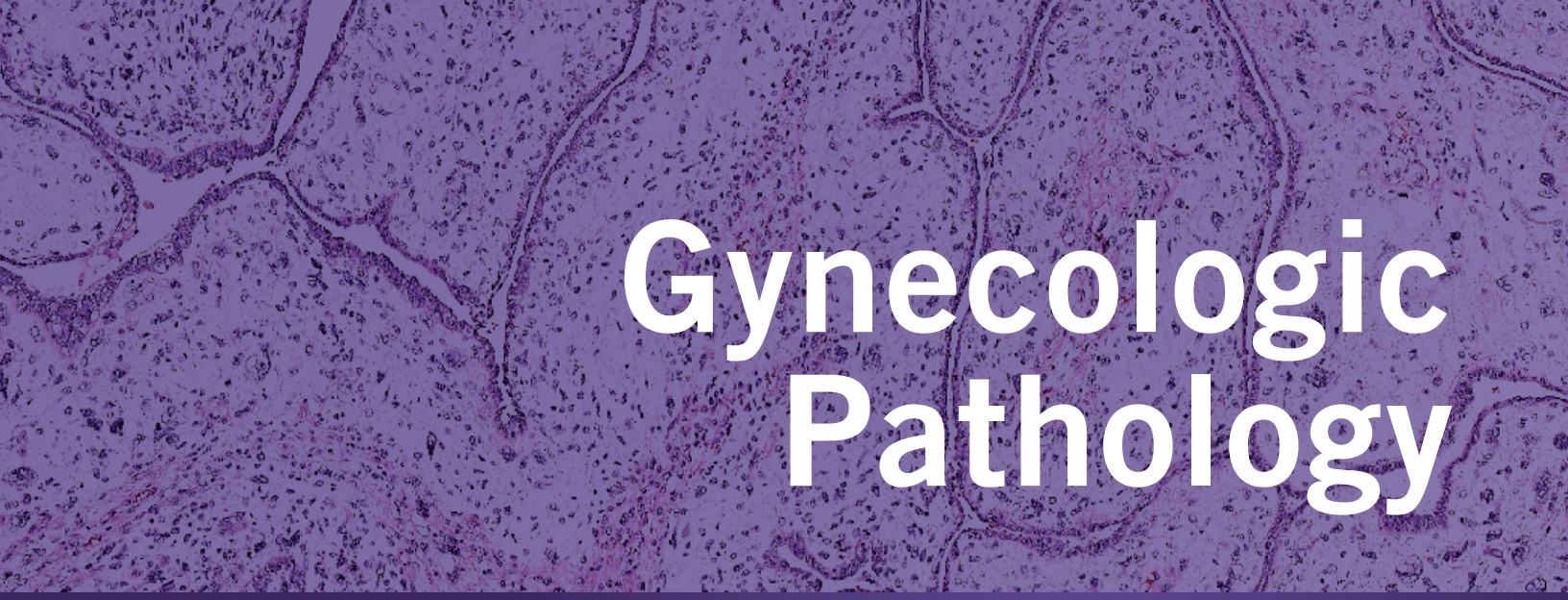

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1

Inflammatory Diseases of the Vulva

Lynn N. Hoang and Mary Kinloch

INTRODUCTION

Almost any inflammatory dermatological condition occurring on nongenital skin can afflict the vulva. Histopathologic diagnosis in the vulva, however, is often complicated by its unique anatomy (where there is increased occlusion, friction, and moisture, causing a variety of secondary changes), delayed seeking of medical attention due to patient embarrassment, and the use of self-treatment regimens which may not be readily divulged to the treating clinician. Moreover, vulvar dermatoses exhibit varying histologic features depending on the course of the disease and when the biopsy was taken. A patient may have endured multiple trials of recalcitrant treatments before a biopsy is eventually obtained. In the setting of vulvar inflammatory dermatoses, it must be emphasized that clinical information is of utmost importance to arrive at an accurate diagnosis.

The initial histologic approach to any inflammatory disorder of the skin or mucosa requires knowledge of the precise anatomic location and an appreciation of the alterations in the regional mucocutaneous anatomy. The mons pubis and labia majora closely resemble skin from other anatomic regions of the body and are composed of a slightly rugose, keratinizing, stratified epithelium containing all of the cutaneous adnexal structures and a richly vascular dermis. Areas of compact stratum corneum, in addition to the conventional basket-weave stratum corneum, are a normal finding in the mons pubis/labia majora. The labia minora, in contrast, have a stratified, glycogen-rich squamous epithelium. Adnexal structures are absent. On each side, the mucocutaneous junction between the labium majus and labium minus (also known as Hart's line) may exhibit a focal zone of parakeratosis and should not be mistaken for a pathologic abnormality. The subjacent dermis is highly vascular and contains erectile tissue.

The next step in evaluating an inflammatory process is the identification at low power of the *major tissue reaction pattern*, followed by the *pattern of inflammation*. Detailed descriptions of this approach, championed initially in the teachings of Wallace Clark, have been further popularized and refined by Ackerman, Weedon, and LeBoit. The *tissue reaction pattern* is a distinctive group of morphologic findings which allows the observer to place a biopsy within a specific group of cutaneous diseases. This rational framework was also adopted by the 2006 International Society for the Study of Vulvovaginal Disease (ISSVD) classification of vulvar dermatoses (Table 1.1). The *pattern of inflammation* refers to the distribution of the inflammatory infiltrate within the dermis and subcutis (Box 1.1). Once the *major tissue reaction pattern* and *pattern of inflammation* are identified, the pathologist can generate a working differential diagnosis (Table 1.1). In 2011, the ISSVD published a separate clinically oriented framework to classify vulvar dermatoses, allowing the clinician to generate a differential diagnosis based on macroscopic features (Table 1.2). This 2011 ISSVD framework serves as an adjunct tool to aid in diagnosis and was meant to supplement, not supplant, the 2006 classification scheme.

The above approach can be applied to the most common inflammatory disorders of the vulva, which should allow the pathologist to categorize lesions and generate a rational differential diagnosis. This, in turn, will allow the clinician to develop a meaningful treatment plan.

SPONGIOTIC (ECZEMATOUS) REACTION PATTERN

The terms "eczema" and "eczematous dermatidities" are clinical terms used to describe a variety of lesions that share similar clinical and histologic features (spongiotic dermatitis), but often are etiologically unrelated. Eczematous dermatitis can be due to intrinsic factors (atopic dermatitis and seborrheic dermatitis) or be triggered by extrinsic agents (irritant contact dermatitis [ICD]).

All eczematous dermatidities demonstrate epidermal spongiosis during their evolution, clinically seen as crusted patches and plaques, papules and vesicles, and, at the far end of the spectrum, frank bullous lesions and, rarely, ulceration. The histologic changes of spongiotic dermatitis typically affect the epidermis and sometimes upper dermis, while the lower dermis, follicular infundibula, and acrosyringia are spared. The cardinal histologic feature of the spongiotic (eczematous) epidermal reaction pattern is spongiosis, seen histologically as an increase in

TABLE 1.1

Adapted 2006 ISSVD Classification of Vulvar Dermatoses: Pathologic Subsets and Clinicopathologic Correlation[a]

Pattern	Characteristic Morphologic Feature	Clinical Correlation
Spongiotic (Eczematous) Pattern	Epidermal edema	Atopic dermatitis Allergic dermatitis Irritant contact dermatitis
Acanthotic Pattern	Epidermal hyperplasia	Psoriasis Lichen simplex chronicus - Primary/idiopathic - Secondary (superimposed on lichen sclerosus, lichen planus, or other)
Lichenoid Pattern	Band-like lymphocytic infiltrate at dermal–epidermal junction with basal keratinocyte damage	Lichen sclerosus Lichen planus Erythema multiforme
Dermal Homogenization/ Sclerosis Pattern	Dermal sclerosis	Lichen sclerosus
Vesiculobullous Pattern	Subepidermal or intraepidermal blister formation	Pemphigoid, cicatricial type Linear IgA disease
Acantholytic Pattern	Clefting of epithelial cells due to breakage of intercellular junctions	Hailey-Hailey disease Darier disease Papular genitocrural acantholysis
Granulomatous Pattern	Granulomas	Crohn disease Melkersson-Rosenthal syndrome Tuberculosis
Vasculopathic Pattern	Vascular injury	Aphthous ulcers (Non-sexually related acute genital ulcers, aka Lipschutz ulcer) Behcet disease Plasma cell vulvitis

ISSVD, International Society for the Study of Vulvovaginal Disease.
[a]The ISSVD excludes vulvar infections.

BOX 1.1

Patterns of Inflammation

Superficial perivascular inflammation
Superficial and deep perivascular inflammation
Folliculitis and perifolliculitis
Panniculitis

TABLE 1.2

2011 ISSVD Classification of Vulvar Dermatological Disorders

Skin-colored lesions
Red lesions: patches and plaques
Red lesions: papules and nodules
White lesions
Dark-colored (brown, blue, gray, or black) lesions
Blisters
Erosions and ulcers
Edema (diffuse genital swelling)

ISSVD, International Society for the Study of Vulvovaginal Disease.

the intercellular space between keratinocytes, due to the accumulation of edema fluid within the epidermis. As the vulvar skin is often confined by clothing, secondary changes such as crusting are also frequently found. If the severity of the response increases, there is widening of the intercellular space, eventuating in desmosomal rupture, followed by formation of vesicles within the epidermis. These vesicles may contain fluid, lymphocytes, Langerhans cells, and acantholytic or ruptured keratinocytes. Due to the laxity of the vulvar skin, vesicle formation is generally less common than in other parts of the body. In very severe cases, erosions and ulceration may occur. Chronic lesions can become progressively lichenified and evolve into lesions that resemble lichen simplex chronicus (LSC). At this stage, changes related to the inciting event will likely have dissipated.

Although absolute histologic distinction between the various categories of spongiotic dermatitis is not possible, there are some features that may be utilized to favor a

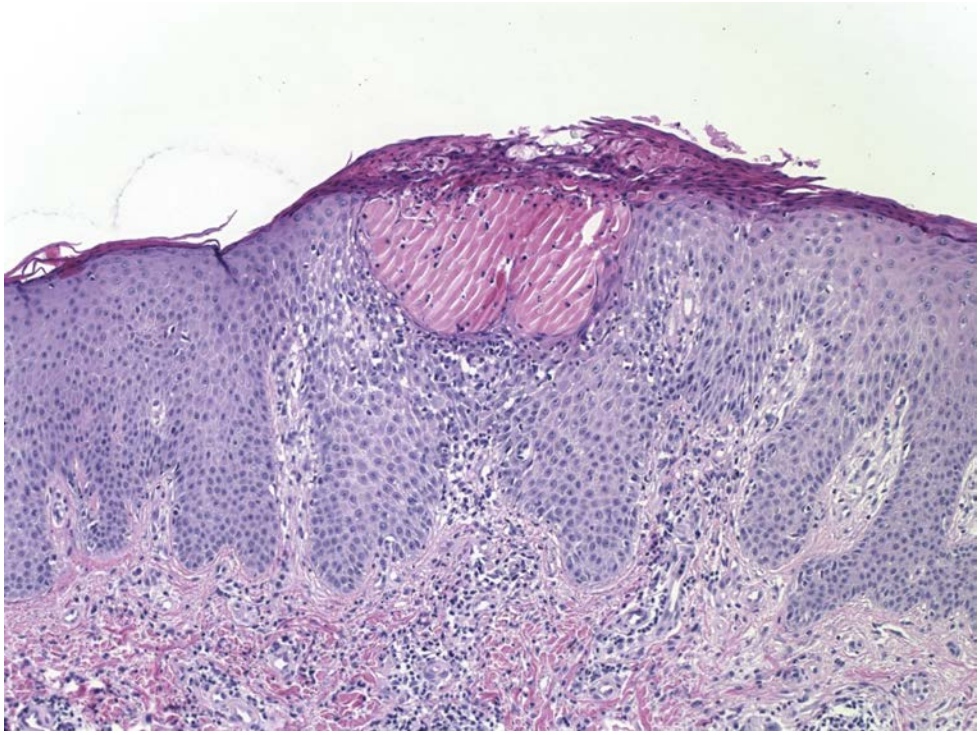

FIG. 1.1
Atopic dermatitis. Psoriasiform epidermal hyperplasia is associated with parakeratosis and spongiotic microvesicles. There is also lymphocyte exocytosis and a perivascular lymphohistiocytic infiltrate.

more specific clinical-pathologic correlate. In many cases, arrival at the correct diagnosis is contingent on the clinical history. The most important differential considerations in genital skin will be discussed.

ATOPIC DERMATITIS

Clinical Features

Atopic dermatitis is a chronic, pruritic process which occurs in individuals (more often men) with a personal or family history of atopic diathesis (including asthma, allergic rhinitis, allergic conjunctivitis). The disease usually first manifests during childhood as an erythematous papulovesicular rash involving the flexural and extensor surfaces of the extremities. The lesions evolve towards scaly lichenified patches and plaques over time. The vulva is infrequently involved.

Microscopic Features

Atopic dermatitis features the classic histologic changes of spongiotic dermatoses. In acute lesions, there is intercellular, and to some extent, intracellular edema of the lower epidermis with epidermal and perivascular infiltration by lymphocytes. Perivascular eosinophils are rare. Subacute lesions exhibit increasing psoriasiform epidermal hyperplasia with parakeratosis (Fig. 1.1), and a decrease in the extent of spongiosis. Chronic lesions display more marked psoriasiform epidermal hyperplasia and lichenification with very mild to absent spongiosis. Further lichenification produces prominent hyperkeratosis with "vertical streaking" of collagen in the papillary dermis, leading ultimately to LSC.

Differential Diagnosis

The distinction between atopic dermatitis, *allergic contact dermatitis* (ACD), and *ICD* (drug, ingestant, scabetic infestation, others) is difficult without clinicopathologic correlation. Direct immunofluorescence can be performed if there is a vesiculobullous lesion associated with eosinophils, to rule out *pemphigus vegetans* or *bullous pemphigoid*. Chronic lesions can resemble *psoriasis* histologically. Unlike the regular pattern of epidermal hyperplasia found in psoriasis, the rete ridges in advanced stages of a chronic eczematous dermatitis are generally irregular in both length and width.

Prognosis and Treatment

Most cases of atopic dermatitis resolve spontaneously by the age of 30. Treatment is aimed towards hydration of the skin, minimizing triggering factors and symptoms, and decreasing inflammation. The latter is usually achieved

with topical steroids. Nonsteroidal immunosuppressive agents such as tacrolimus are also considered as they have fewer disadvantages compared with chronic steroid use.

ATOPIC DERMATITIS—FACT SHEET

Definition
- Chronic pruritic dermatitis in individuals with personal or family history of atopic diathesis (atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis)

Incidence
- Common
- ~20% of infants and young children symptomatic, 90% before age 5

Morbidity
- Predisposition to infection due to compromised cutaneous barrier

Gender and Race
- Increased risk in males
- Increased risk in people of African or Asian descent

Clinical Features
- Erythematous papulovesicular rash in flexural and extensor surfaces of arms and legs
- Sometimes vulvar involvement, particularly in children
- Scaly lichenified patches and plaques
- Secondary infection may occur

Prognosis and Treatment
- Generally spontaneous remission throughout childhood
- Few cases persist over age 30
- Treatment includes hydration of skin, minimizing trigger factors, relief of pruritus, and decreasing inflammation
- Topical steroids and nonsteroidal immune modulators

ATOPIC DERMATITIS—PATHOLOGIC FEATURES

Microscopic Findings

Acute Lesion
- Intercellular edema of lower epidermis
- Exocytosis of lymphocytes
- Perivascular lymphohistiocytic infiltrate with occasional eosinophils and rarely neutrophils
- Epidermis of normal thickness with normal basket-weave stratum corneum
- Can have edema of papillary dermis

Subacute Lesion
- Psoriasiform epidermal hyperplasia with parakeratosis
- Serum crust can form, made of proteinaceous debris, neutrophils, and parakeratotic cells
- Variable lymphocyte exocytosis

Chronic Lesion
- Marked psoriasiform epidermal hyperplasia
- Compact hyperkeratosis, hypergranulosis, and less parakeratosis
- Mild to absent spongiosis and lymphocyte exocytosis
- Can resemble lichen simplex chronicus

Differential Diagnosis
- Contact dermatitis
- Spongiotic hypersensitivity reaction
- Pemphigus vegetans or bullous pemphigoid

TABLE 1.3

Potential Causes of Allergic Contact and Irritant Contact Dermatitis in the Vulva.

Endogenous	Urine, feces, sperm
Exogenous	Detergents, soaps/shampoos, perfume/deodorants, fabrics/wools, textile dyes, sanitary napkins, antiseptics/disinfectants, spermicides, latex, nickel, cosmetic fillers (silicone, hyaluronic acid)
Drugs	Antibiotics/Neosporin, corticosteroids, anesthetics (benzocaine in Vagisil), imiquimod, podophyllin

ALLERGIC CONTACT DERMATITIS

ACD is a type IV hypersensitivity reaction initiated by contact with an allergen to which an individual has been previously exposed and sensitized. Lesions typically develop within 12–48 hours following exposure to the allergen. Numerous chemical, biological, and physical agents can elicit this reaction pattern (Table 1.3). Exposure to the offending agent may be related to the patient's occupation or daily hygiene routines. Topical medications, fragrances, and preservatives are the most common causes of ACD. Patch testing with an allergist can be helpful to identify the offending agent.

Clinical Features

ACD is more frequent in females and in white persons. Common findings include a pruritic papulovesicular eruption, discretely patterned crusted plaques, or, occasionally, bizarre-appearing patterns, depending on the extent of contact with the agent.

Microscopic Features

In acute episodes, the spongiosis is limited to the lower epithelium, and the stratum corneum remains uninvolved. With persistent allergen exposure, there is formation of coalescing vesicles at various levels of the epidermis, imparting a "Swiss-cheese" appearance (Fig. 1.2). Intraepithelial inflammatory cells are usually lymphocytes (rarely eosinophils). Chronic forms feature progression from a spongiotic to a lichenoid pattern like in atopic dermatitis.

Differential Diagnosis

See atopic dermatitis section.

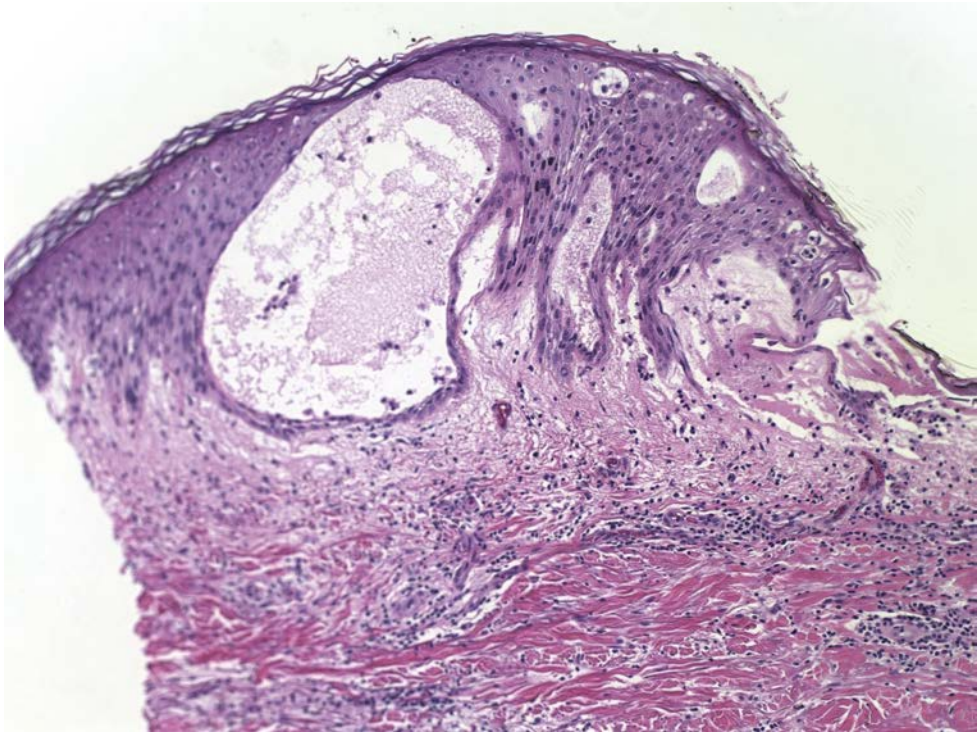

FIG. 1.2

Allergic contact dermatitis. Spongiosis leads to the formation of microvesicles within the epithelium imparting a "Swiss-cheese" appearance. There is associated lymphocyte exocytosis. The stratum corneum remains unchanged, in keeping with the acute nature of the insult.

Prognosis and Treatment

Removal of, or protection from the offending agent is paramount. Without it, the disease will persist, leading to longer and more severe episodes, and to complications such as infection. In addition, treatment includes short-term topical corticosteroid therapy to reduce inflammation, and emollients to allow the reestablishment of the barrier function of the skin.

ALLERGIC CONTACT DERMATITIS—FACT SHEET

Definition

- Type IV hypersensitivity reaction initiated by contact with allergen to which an individual has been previously sensitized

Incidence

- Common (4%–7% of all dermatologic consultations)

Morbidity

- Relapse and chronicity from reexposure to offending antigen, particularly occupational exposure
- May impact individual occupational choices

Gender and Race

- Approximately twice as common in females as in males
- More frequent in whites than in other racial groups

Clinical Features

- Pruritic papulovesicular eruption
- Circumscribed crusted plaques
- Occasionally bizarre-appearing patterns

Prognosis and Treatment

- Excellent prognosis if removal or protection from offending agent
- Emollients and short-term topical steroid therapy

ALLERGIC CONTACT DERMATITIS—PATHOLOGIC FEATURES

Microscopic Findings

- Spongiotic microvesicles within various levels of epidermis ("Swiss-cheese" appearance)
- Exocytosis of lymphocytes and eosinophils (eosinophilic spongiosis)
- Unchanged stratum corneum in acute reaction
- Epidermal hyperplasia and diminution of spongiosis if persistent allergen

Differential Diagnosis

- Atopic dermatitis
- Eczematous hypersensitivity reaction
- Pemphigus vegetans or bullous pemphigoid

IRRITANT CONTACT DERMATITIS

In contrast to ACD, ICD is caused by the direct effect of an irritant compound on an epithelial surface, and therefore occurs rapidly (minutes to hours) after exposure to the agent, not requiring prior sensitization. Offending agents can be similar to that seen with ACD (Table 1.3).

Clinical Features

Females are more frequently affected than males, with no particular genetic predisposition. A large range of clinical appearances may be seen, including erythema, eczematous

changes, vesiculobullous lesions, and epidermal necrosis. Lesions tend to be confined to the areas of contact with the offending agent, thus often sparing the genitocrural folds.

Microscopic Features

In contrast to ACD, the agent responsible for ICD produces direct injury to the epidermis. The degree and severity of the epidermal injury varies based on the nature, potency, and concentration of the irritant. Histologically, common changes include ballooning degeneration of the surface keratinocytes with subsequent necrosis and surrounding epidermal spongiosis. Neutrophil infiltration is seen in areas of epidermal necrosis (Fig. 1.3). The underlying superficial dermis contains perivascular inflammation composed of lymphocytes, macrophages and, frequently, neutrophils. Interstitial edema and vasodilatation are also present (Fig. 1.4).

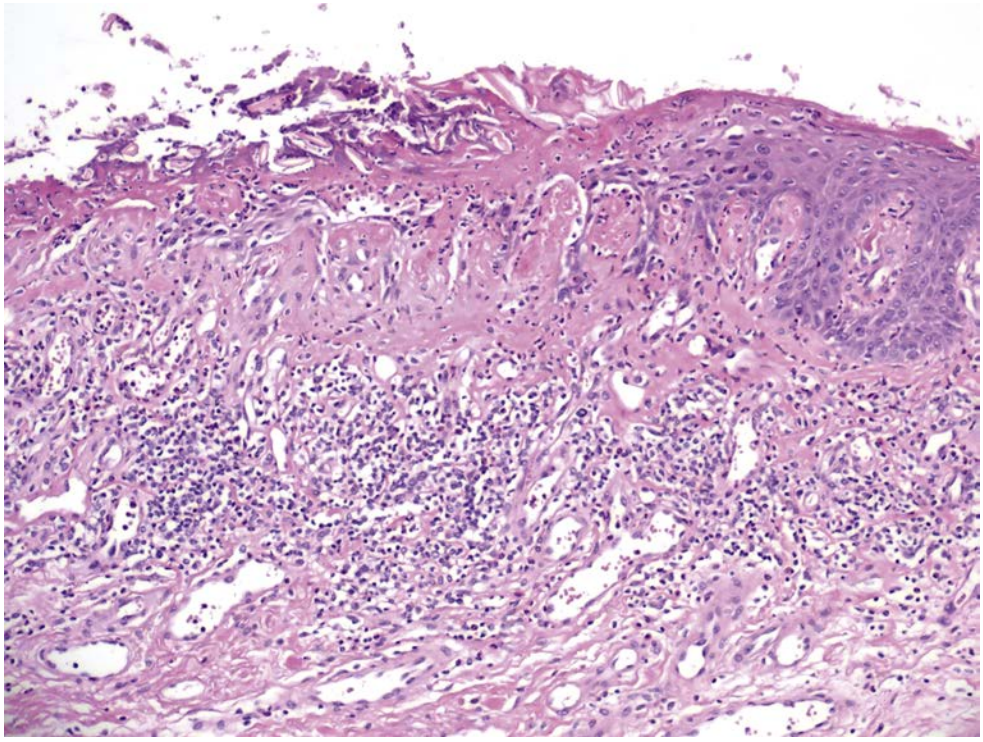

FIG. 1.3

Irritant contact dermatitis. Direct injury to the epidermis manifests acutely with necrosis and epithelial denudation. Adjacent remaining epithelium shows spongiosis and infiltration by neutrophils, which also infiltrate the superficial dermis along with lymphocytes and macrophages.

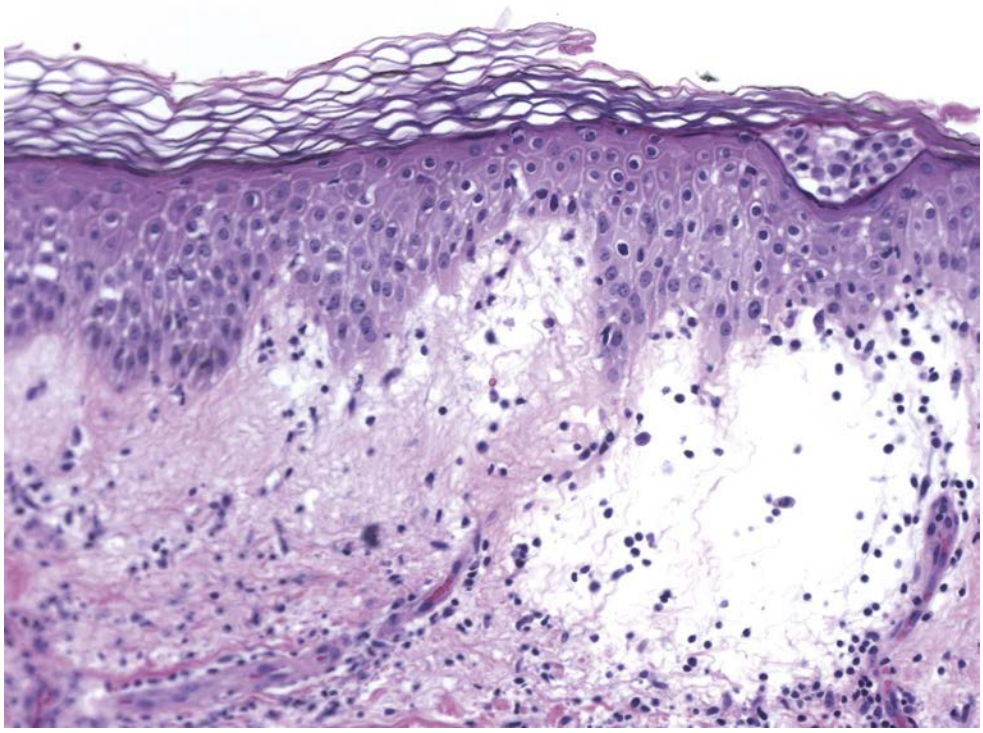

FIG. 1.4

Irritant contact dermatitis. This example has only mild spongiosis with accumulation of Langerhans cells within the spaces. The superficial dermis is edematous.

Differential Diagnosis

See atopic dermatitis section.

Prognosis and Treatment

Removal of, or protection from, the offending agent is paramount to prevent recurrences. Management aims to restore the skin's barrier function. Topical applications containing ceramides may be particularly helpful. Corticosteroids and immune modulators are in general not recommended.

IRRITANT CONTACT DERMATITIS—FACT SHEET

Definition
- Dermatitis initiated by direct effect of an irritant compound on epithelial surface

Incidence
- Common

Morbidity
- Significant long-term sequelae possible if chronic exposure

Gender, Race, and Age Distribution
- More common in women than men, secondary to environmental rather than genetic factors
- No age or racial predilection

Clinical Features
- Wide range of clinical appearances, including erythema, eczematous changes, vesiculobullous lesions, and epidermal necrosis
- Lesions often well-demarcated (confined to areas of contact with offending agent and sparing genitocrural folds)

Prognosis and Treatment
- Excellent prognosis if removal of, or protection from, offending agent
- Emollients reestablish cutaneous barrier function
- Topical steroids and immune modulators not helpful

IRRITANT CONTACT DERMATITIS—PATHOLOGIC FEATURES

Microscopic Findings
- Ballooning degeneration and necrosis of surface keratinocytes
- Neutrophil exocytosis in areas of epidermal necrosis
- Interstitial edema and vasodilatation
- Chronic cases can form pseudoverrucous papules, nodules, and dermal fibrosis

Differential Diagnosis
- Allergic contact dermatitis (ACD)
- Eczematous hypersensitivity reaction
- Pemphigus vegetans or bullous pemphigoid

SEBORRHEIC DERMATITIS

Clinical Features

Seborrheic dermatitis is a common eczematous dermatitis occurring in areas of the skin that have the greatest number of sebaceous glands (scalp, face, chest, upper back, axillae, and anogenital skin). Not surprisingly, men are more commonly affected than women. Most patients present during the fourth to fifth decade; however, an infantile form (in babies during first three months) has been described. The affected vulvar skin, more commonly the genitocrural folds, is erythematous with scaling "bran-like" papules and plaques with a "greasy yellow" appearance. Immunosuppressed patients, especially those with human immunodeficiency virus (HIV) infection, have a higher prevalence of this disease. The pathogenesis is unknown; however, *Malassezia* species *(Pityrosporum)* has been implicated as an etiologic factor; in many patients, flares of the disease correlate with proliferation of *Malassezia* spp. and respond to antifungal agents. It is thought that the yeast triggers an immunologic response affecting the hair-bearing epidermis.

Microscopic Features

In its acute form, seborrheic dermatitis features mild spongiosis with a parakeratotic scale crust containing scattered neutrophils (Fig. 1.5). The papillary dermis is mildly edematous with a mixed perivascular inflammatory infiltrate (composed of lymphocytes, histiocytes and, rarely, neutrophils) involving the superficial plexus. As lesions progress, psoriasiform hyperplasia appears and becomes extensive with parafollicular accentuation of the parakeratotic scale ("shoulder parakeratosis") (Fig. 1.6). Neutrophils are commonly observed within the scale crust and within spongiotic foci. In chronic lesions, the psoriasiform hyperplasia is prominent and the parakeratotic scale crust may extend into the interfollicular epidermis.

Differential Diagnosis

The presence of neutrophilic parakeratosis and psoriasiform epidermal hyperplasia raises consideration of *psoriasis*. Features in favor of seborrheic dermatitis are irregular elongation of the epidermal rete, accentuation of parakeratosis and scale crusts about the follicular ostia, and predilection of the follicular and epidermal spongiosis toward the upper layers of the epidermis. However, distinction can be difficult. Neutrophil-rich parakeratosis is also a feature observed in many impetiginized *eczematous dermatitis*. A tissue Gram stain is a helpful adjunct in excluding this possibility.

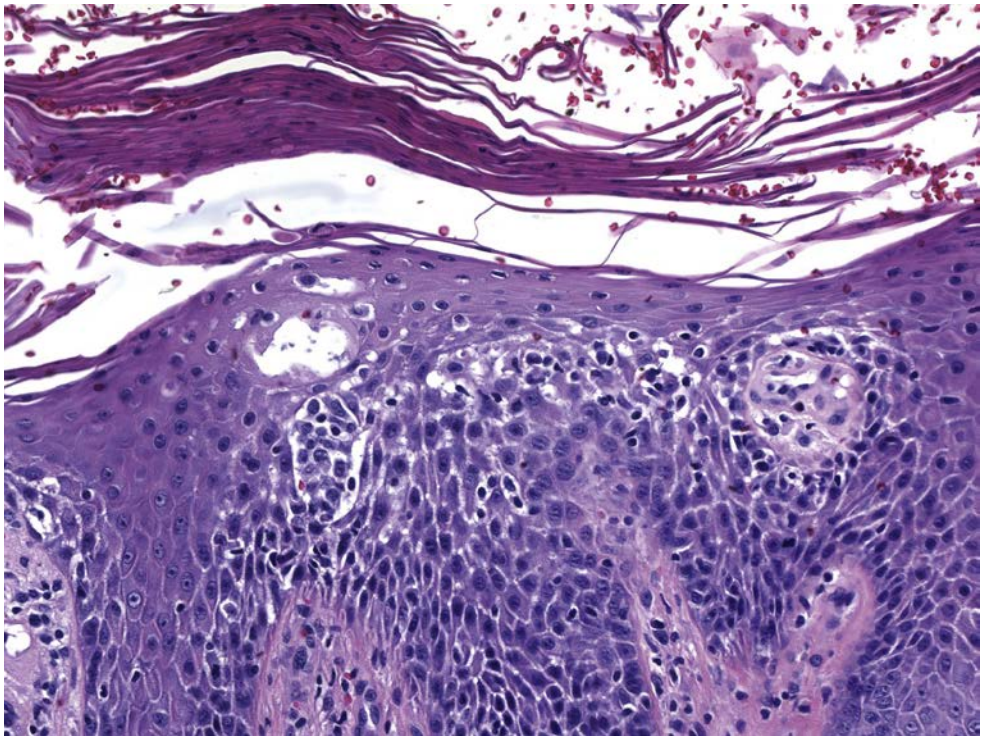

FIG. 1.5

Seborrheic dermatitis. As in other spongiotic dermatoses, there is psoriasiform epidermal hyperplasia with spongiosis and a parakeratotic scale crust. A lymphohistiocytic infiltrate can be seen in the papillary dermis.

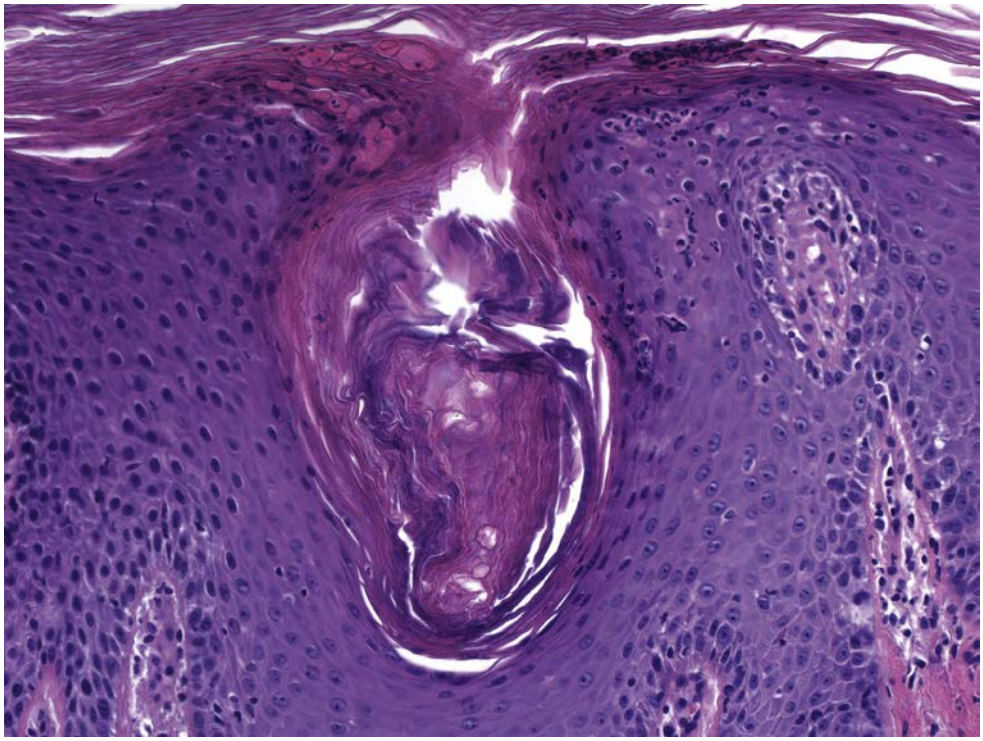

FIG. 1.6

Seborrheic dermatitis. Parakeratosis is characteristically accentuated around the opening of the hair follicles ("shoulder parakeratosis"). Also note the presence of neutrophils in the scale crust and areas of spongiosis.

Prognosis and Treatment

Seborrheic dermatitis generally exhibits a mild chronic clinical course with little discomfort. Treatment is directed towards removal of the scales with keratolytics, followed by sparing use of topical corticosteroids. Topical antifungal agents (i.e., ketoconazole, ciclopirox) constitute an important adjunct in therapy and tend to reduce or eliminate the need for steroid therapy over time when used consistently. Resistance to therapy may be a sign of immunodeficiency, particularly HIV infection.

SEBORRHEIC DERMATITIS—FACT SHEET

Definition
- Common eczematous dermatitis occurring on skin with greatest number of sebaceous glands

Incidence
- Common; approximately 5% prevalence

Morbidity
- Cosmetic

Gender, Race, and Age Distribution
- More common in men than women
- No racial predisposition
- Common in fourth to fifth decade
- Self-limited infantile form in first 3 months of life

Clinical Features
- Erythematous skin, with papules and plaques with fissures causing "bran-like" scale and "greasy yellow" appearance
- Most affect the genitocrural folds
- Extensive therapy-resistant seborrheic dermatitis may indicate underlying HIV infection

Prognosis and Treatment
- Mild clinical course with little discomfort other than cosmetic concerns
- Removal of scale with keratolytics followed by sparing use of corticosteroids and antifungal agents

SEBORRHEIC DERMATITIS—PATHOLOGIC FEATURES

Microscopic Findings

Acute Lesion
- Mild spongiosis with neutrophilic parakeratosis
- Papillary dermal edema and lymphohistiocytic perivascular infiltrate

Advanced Lesion
- Substantial psoriasiform hyperplasia and "shoulder parakeratosis" (perifollicular accentuation of parakeratosis)

Differential Diagnosis
- Psoriasis
- Impetiginized eczema

ACANTHOTIC EPIDERMAL REACTION PATTERN

The acanthotic reaction pattern is defined by an increase in the number of keratinocytes in the epidermis, leading to overall thickening of the epidermis. "Psoriasiform hyperplasia" and historically "squamous cell hyperplasia," are terms that have also been used to describe this reaction pattern.

PSORIASIS

Psoriasis is the prototype of a group of dermatoses characterized by epidermal hyperplasia.

Clinical Features

Psoriasis is a chronic dermatitis characterized by a hyperproliferative epidermis. It is a common disorder, affecting 2 %–4 % of whites (less frequently other ethnicities). The disease usually manifests during early adulthood. Vulvar involvement can be a manifestation of the classic, generalized form or of the so-called *inverse psoriasis* which affects intertriginous areas. The most common clinical vulvar presentation is a pruritic, bilaterally symmetrical, erythematous, well-demarcated, nonscaly, macular eruption or plaque, as opposed to patches and plaques with a "silvery" scale typical of other anatomic regions. The anatomic distribution is wide, and most patients that present with a vulvar psoriasiform lesion will have evidence of lesions elsewhere on the body. These lesions tend to concentrate in areas of persistent trauma or friction (elbows, knees, sacrum, scalp, and intertriginous areas). Other triggers include drugs and infections. Superinfection by yeast, fungi, and bacteria is possible.

Microscopic Features

Psoriasis, like many other dermatoses, has a range of microscopic changes that evolve over time. Early lesions have a nonspecific spongiotic epidermal reaction pattern that includes superficial dermal vascular congestion, edema, and lymphocyte-rich perivascular inflammation. As lesions progress, a characteristic ("psoriasiform") pattern of epithelial hyperplasia appears, characterized by regular acanthosis, elongation of the rete ridges, thinning of the suprapapillary plates, and loss of the granular cell layer (hypogranulosis) (Fig. 1.7). Other typical findings

include mounds of neutrophil-rich parakeratosis and increased basal mitotic activity. Confluence of neutrophilic aggregates within the parakeratosis is seen in mature lesions. Intraepidermal neutrophil collections located in the stratus corneum are termed *"Munroe microabscesses,"* whereas those in the spinous layer are called *"spongiform pustules of Kogoj"* (Fig. 1.8). The accompanying epidermal hyperplasia has a regular appearance, characteristically with intervening thinned suprapapillary plates and subjacent dilated capillaries, frequently in immediate apposition to the overlying epidermis (Fig. 1.9).

Differential Diagnosis

Late-stage *lichen simplex chronicus* can be distinguished from psoriasis by the presence of thicker suprapapillary

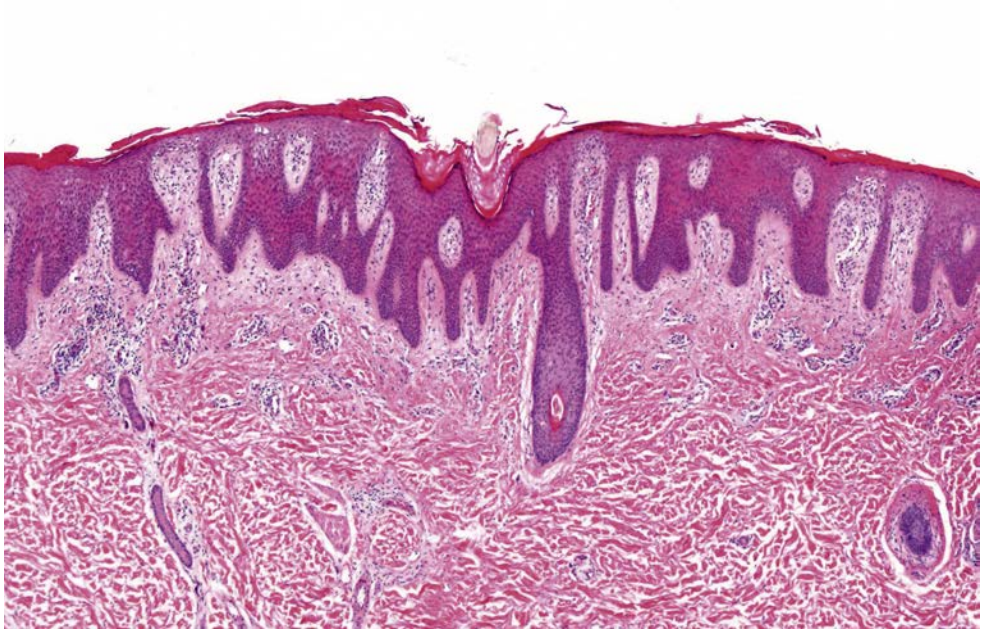

FIG. 1.7

Psoriasis. This lesion exhibits evenly distributed (regular) acanthosis, patchy loss of the granular layer (hypogranulosis), and thinning of the suprapapillary plates.

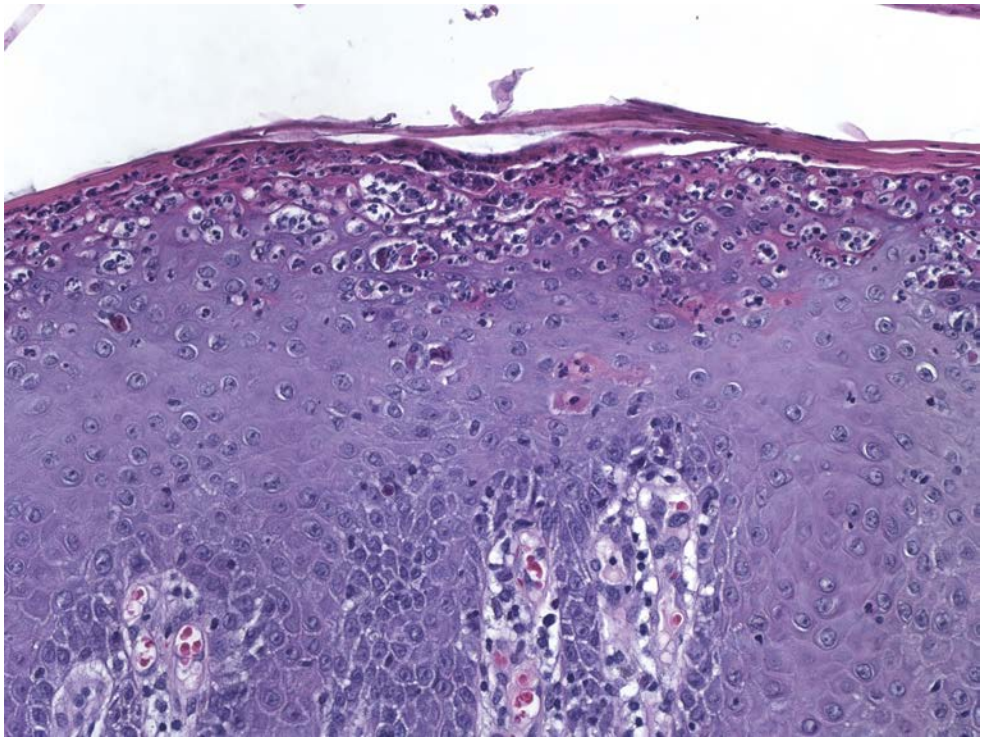

FIG. 1.8

Psoriasis. This mature lesion shows confluent neutrophil-rich parakeratosis and hypogranulosis. Neutrophil collections are seen within the stratum corneum ("Munroe microabscesses") and the stratus spinosum ("spongiform pustules of Kogoj").

plates, hypergranulosis, and thickened vertically oriented collagen bundles within the papillary dermis. Distinction of psoriasis from *seborrheic dermatitis* can be very difficult, particularly at early stages; the presence of spongiosis involving the rete ridges is not typical of psoriasis, and favors seborrheic dermatitis instead. *Chronic candidiasis* and *dermatophytoses* may feature neutrophil exocytosis and psoriasiform epidermal hyperplasia. Therefore, special stains should be routinely considered to exclude the presence of fungal elements.

Prognosis and Treatment

Psoriasis is a chronic condition characterized by frequent relapses. Complications include psoriatic arthritis (seen in up to 30% of patients) and infections. Thus, long-term management is required, focusing on balancing the extent of disease involvement with the potential side-effects of therapy. Topical treatment, in the form of emollients, corticosteroids, tars, vitamin D analogs, and tacrolimus, is utilized for localized plaques. Systemic therapies for severe disease include methotrexate, retinoids, and cyclosporine. Phototherapy and photochemotherapy (psoralen with ultraviolet A) are also used.

PSORIASIS—FACT SHEET

Definition
- Chronic dermatitis characterized by hyperproliferative epidermis and regular epidermal hyperplasia

Incidence
- 2%–4% prevalence rate in whites

Morbidity
- Significant cosmetic impact on quality of life
- Psoriatic arthritis (5%–30%)

Gender, Race, and Age Distribution
- No gender predisposition
- Low prevalence in Asians, Native Americans, and Africans
- Earlier onset in females than males
- Onset before age 40 in ~75% of patients

Clinical Features
- Circumscribed, well-demarcated erythematous patches and plaques
- Wide anatomic distribution, but mostly in areas of persistent trauma or friction

Prognosis and Treatment
- Long-term management due to chronic course of disease
- Topical therapies for localized disease
- Systemic therapies for severe disease, including methotrexate, retinoids, cyclosporine, phototherapy, and photochemotherapy (psoralen with ultraviolet A)

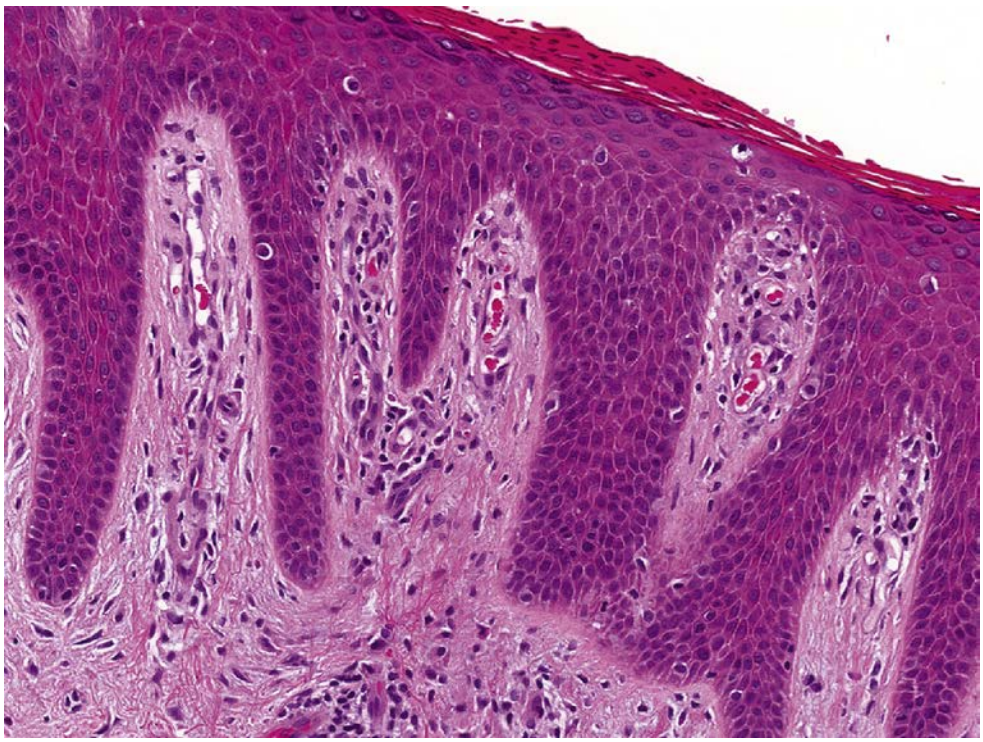

FIG. 1.9

Psoriasis. There is vascular ectasia within the dermal papillae, often seen in immediate apposition to the thinned overlying epidermal plates.

PSORIASIS—PATHOLOGIC FEATURES

Microscopic Findings

Early Lesion
- Epidermal spongiosis
- Papillary dermal vascular congestion and edema
- Sparse perivascular dermatitis

Advanced Lesion
- Regular acanthosis with increased basal mitotic activity
- Mounds of neutrophil-rich parakeratosis
- Hypogranulosis

Mature Lesion
- Marked regular psoriasiform epidermal hyperplasia with thinned suprapapillary plates
- Confluent neutrophil-rich parakeratosis, "Munroe microabscesses," and "spongiform pustules of Kogoj"
- Papillary dermal vascular ectasia
- Lymphocytic-rich perivascular dermatitis

Differential Diagnosis
- Lichen simplex chronicus
- Seborrheic dermatitis
- Dermatophytosis and candidiasis

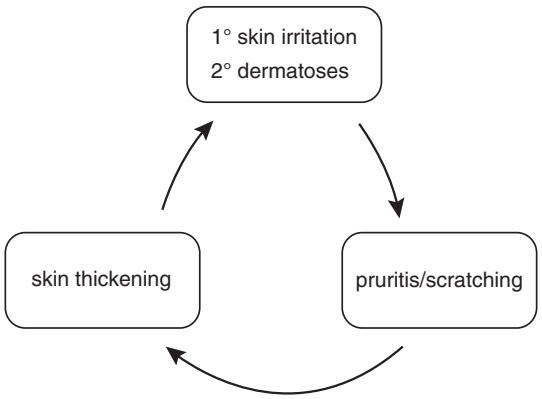

FIG. 1.10
The itch/scratch cycle in lichen simplex chronicus.

LICHEN SIMPLEX CHRONICUS

Clinical Features

LSC is a condition in which scaly plaques are formed in response to repetitive irritation of affected sites by rubbing or scratching. Women are more commonly affected, usually between the third and fifth decades of life. Anatomic sites of predilection include the perianal and genital regions, and the posterior neck, forearms, and pretibial areas. Within the vulvar region, LSC can present as a primary or secondary condition. Heat, sweat, and friction can be a primary cause of skin irritation that can ignite the itch/scratch cycle leading to the features of LSC (Fig. 1.10). Secondary causes can be numerous and are important for the pathologist to identify as the underlying cause of LSC, especially when premalignant or malignant in nature.

Microscopic Features

LSC is characterized by epidermal acanthosis (hyperplasia) with psoriasiform appearance. The epithelium shows broad compact orthokeratosis with hypergranulosis; parakeratosis is present, often with a patchy distribution (Fig. 1.11). Focal erosion or ulceration is common. The rete ridges are thick without suprapapillary plate thinning. A characteristic feature is the presence of thickened eosinophilic bundles of collagen arranged in vertical streaks within the papillary dermis (Fig. 1.12), although compared to the skin this feature is less developed in the mucocutaneous surfaces of the vulva and perineum.

Differential Diagnosis

Superimposed changes of LSC can be observed in virtually all dermatoses, therefore careful evaluation to exclude a primary dermatosis is essential before rendering a diagnosis of idiopathic LSC; this particularly applies to instances in which primary treatment is unsuccessful. Superimposed LSC on *high grade squamous intraepithelial lesion/vulvar intraepithelial neoplasia of usual type (HSIL/u-VIN)*, a human papillomavirus (HPV) associated premalignant skin lesion, is an important differential. Close examination of the lower epithelial layers is key: nuclear enlargement, hyperchromasia, loss of polarity, overlapping, and loss of maturation with mitoses above the basal membrane are features indicative of HSIL. Importantly, HSIL with superimposed LSC will show rather abrupt maturation of the dysplastic epithelium, which may lead to not only misinterpretation as idiopathic LSC but also as a low-grade squamous intraepithelial lesion (LSIL/VIN1) or differentiated VIN. A VIN3 lesion with superimposed LSC can also resemble a VIN2 lesion, but this distinction may not carry clinical consequences. In equivocal cases, strong, nuclear, and cytoplasmic block staining of p16 immunohistochemistry will help point to a diagnosis of HSIL. *Atypical verruciform lesions* of the vulva also present with hyperkeratotic lesions that show irregular epidermal hyperplasia. Verruciform proliferations of the vulva, including the so-called verruciform LSC, are rare and still poorly understood. Importantly, some are regarded as neoplastic in nature. The most important is *verrucous carcinoma*, which is locally aggressive. Unlike LSC, verrucous carcinoma presents clinically as a large

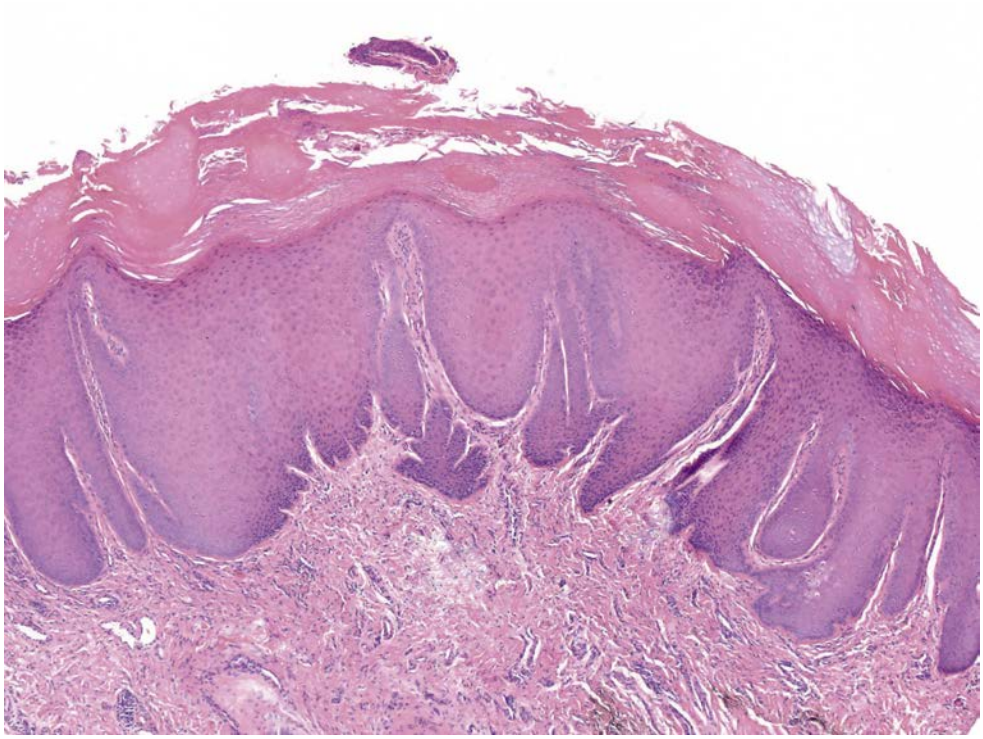

FIG. 1.11

Lichen simplex chronicus. There is marked irregular acanthosis with thick rete ridges of variable sizes, compact orthokeratosis, areas of hypergranulosis, and focal parakeratosis.

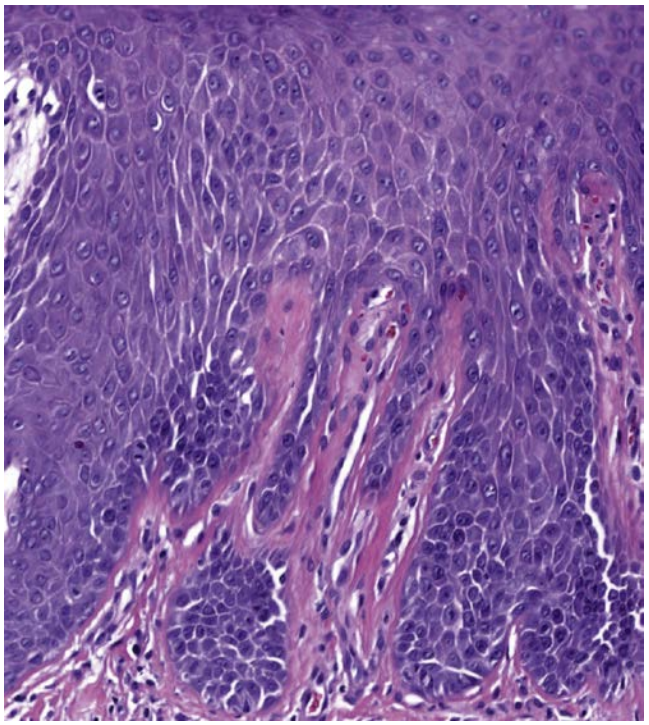

FIG. 1.12

Lichen simplex chronicus. Thick eosinophilic bundles of collagen are arranged in vertical streaks within the papillary dermis.

exophytic mass. Histologically, they show expansile invasion into the vulvar stroma in the form of bulbous nests with broad-fronts and smooth edges. While LSC, if tangentially sectioned, may give this appearance, the depth and complexity of the growth of verrucous carcinoma are usually obvious and exceed that of tangential cutting. Other verruciform lesions that deserve distinction from LSC include entities historically known as *vulvar acanthosis with altered differentiation (VAAD)* and *atypical verruciform hyperplasia*, recently grouped into the term *differentiated vulvar intraepithelial lesion (DEVIL)*. DEVIL presents clinically as plaques or areas of exophytic cauliflower-like growth, corresponding histologically to epithelial acanthosis with verruciform growth lacking cytologic atypia (see Chapter 2). The finding of frequent *PIK3CA* mutations and absence of *TP53* mutations, added to the observation of DEVIL-type lesions preceding or accompanying verrucous carcinoma, has led to consideration of this constellation of atypical verruciform proliferations as a third category of squamous preinvasive neoplasia. It is important to note that verrucous carcinoma and DEVIL have bland cytomorphology throughout, and their distinction from LSC must be based on the severity and distribution of the epithelial proliferation. The distinction between DEVIL-type lesions and LSC can be quite difficult. In fact, the term "verruciform LSC" has been used to describe LSC lesions with prominent exophytic growth, and these lesions have been found to harbor *PIK3CA* mutations linking them to DEVIL. From the diagnostic perspective, it is important to suspect DEVIL if the lesion is exophytic and produces verruciform growth, and if it persists despite treatment or recurs over time. Complete excision and close monitoring may be prudent in this scenario.

Prognosis and Treatment

Identification and treatment of any underlying process, and cessation of the traumatic stimulus, are imperative in the treatment of this condition, something that may be quite difficult in the long-term. Emollients, topical steroids, and simple barrier occlusion may help break the itch–scratch cycle. Behavioral modification and psychological/psychiatric intervention can be beneficial, particularly if no underlying etiologic factor is identified and medical management is not effective.

LICHEN SIMPLEX CHRONICUS—FACT SHEET

Definition
- Condition in which skin becomes thickened with scaly plaques in response to repetitive rubbing and/or scratching of affected sites
- Can be primary (idiopathic) or secondary to an underlying dermatosis that causes itching

Incidence
- Common

Morbidity
- Cosmetic
- Superinfection if abraded and ulcerated lesions

Gender, Race, and Age Distribution
- More common in women than men
- No racial predilection
- Peak incidence between 30 and 50 years

Clinical Features
- Hyperpigmented scaly plaques at sites of repetitive rubbing
- Perianal and genital regions, posterior neck, forearms, and pretibial areas most common

Prognosis and Treatment
- Cessation of the itch–scratch cycle
- Emollients, topical steroids, and barrier occlusion
- Behavior modification and psychopharmacologic agents in select patients

LICHEN SIMPLEX CHRONICUS—PATHOLOGIC FEATURES

Microscopic Findings
- Compact orthokeratosis and focal parakeratosis
- Hypergranulosis with subjacent irregular psoriasiform epidermal hyperplasia
- Thick eosinophilic bundles of collagen in *"vertical streaks"* in papillary dermis
- Variable perivascular inflammation
- Signs of dermatitis, lichen sclerosus, or other dermatoses may be present

Differential Diagnosis
- High-grade squamous intraepithelial lesion
- Verrucous carcinoma
- Atypical verruciform lesions (DEVIL)

LICHENOID REACTION PATTERN

This tissue reaction pattern is characterized by basal keratinocyte damage via T-cell-mediated cytotoxic damage or induction of apoptosis. By convention, the damaged keratinocytes are termed *dyskeratotic cells*, "*Civatte bodies"* if they are confined to the epidermis, and "*colloid bodies"* when they descend into the papillary dermis. In addition to basal keratinocyte damage, vacuolar change may also be present, sometimes more prominent than cell death in certain dermatoses. *Vacuolar change* consists of intercellular keratinocyte vacuole formation and edema with separation from the basement membrane zone. The *distribution of the inflammatory infiltrate* is an important characteristic. The infiltrate may appose the basal layer or obscure the dermoepidermal junction (DEJ). The density and composition of the infiltrate also vary according to the specific disorder. The presence and quantity of displacement of melanin into the dermis ("pigment incontinence") should also be noted. Lastly, the phase of the lichenoid epidermal reaction pattern is important, as it can point towards a specific histopathologic diagnosis. For instance, in acute cytotoxic reactions the epidermis is minimally affected, as in the early lesions of erythema multiforme (EM) (erythema multiforme-like epidermal reaction pattern). In more chronic lesions, such as those found in lichen planus (LP), the epidermis shows signs of reaction such as premature terminal differentiation (lichen planus-like epidermal reaction pattern). Over time, there may be supervening epidermal hyperplasia, which may be regular (psoriasiform epidermal reaction pattern) as in secondary syphilis, or irregular, as observed in discoid lupus erythematosus. The final or end-stage epidermal reaction pattern is found in those dermatoses featuring epidermal atrophy (lichen sclerosus [LS]). Integration of all these findings with the clinical picture will allow the pathologist to make a specific histopathologic diagnosis in most cases.

LICHEN PLANUS

Clinical Features

Lichen planus (LP) is a T-cell mediated inflammatory dermatosis that affects keratinized and nonkeratinized epithelium. While idiopathic in nature, LP is sometimes associated with other disorders such as ulcerative colitis, hepatitis B/C, immunodeficiency, cirrhosis, and peptic ulcer disease. Several clinical variants exist, but there are three most important to the vulva: classic (papulosquamous), hypertrophic, and erosive, each with its own unique clinical and histologic features (Table 1.4). Erosive lesions are a more common presentation at anogenital sites; they appear clinically as ulcerated and

TABLE 1.4
Clinicopathologic Characteristics of Lichen Planus Patterns in the Vulva.

Pattern	Classic (Papulosquamous)	Hypertrophic	Erosive
Location	Keratinized skin	Keratinized skin	Nonkeratinized skin Can include vaginal involvement
Clinical Features	Violaceous-pink flat-topped papule	Raised hyperkeratotic red papules and plaques	Well-demarcated Glazed erythema Hyperkeratotic border Reticulate lacy lesions
Histopathology	Lichenoid infiltrate at epidermal–dermal junction "Wedge-shaped" hypergranulosis Dyskeratotic and vacuolar changes at basilar layer	Lichenoid infiltrate Acanthosis Parakeratosis Hypergranulosis Hyperkeratosis Pseudoepitheliomatous hyperplasia	Lichenoid infiltrate Superimposed erosive ulcer
Differential Diagnosis	Lichenoid drug eruption Early lichen sclerosus Lichen simplex chronicus	Squamous cell carcinoma	Bullous disorders Differentiated vulvar intraepithelial neoplasia (dVIN)
Treatment/ Prognosis	Self-limiting	Self-limiting	Ultra-potent steroids Chronic, poor response to therapy

dVIN, Differentiated vulvar intraepithelial neoplasia

friable patches in the mucosa. Other types of LP clinically appear as reticulate lacy lesions. When chronic, erosive lesions may evolve to scarring.

Microscopic Features

Evolved lesions of *classic (papulosquamous) LP* feature a band-like infiltrate composed of lymphocytes with an admixture of macrophages, which adhere to the basal aspect of the epidermis (Fig. 1.13). The associated basal cell damage is seen as abrupt maturation ("squamatization") of basal keratinocytes, dyskeratotic cells throughout the epidermis (Fig.1.14), and eosinophilic *colloid bodies* in the papillary dermis. The infiltrate does not obscure the interface and does not extend into the suprabasilar epidermis. Plasma cells may be prominent in mucosal epithelium or at mucocutaneous interfaces. Other hallmarks of LP include irregular acanthosis, hyperkeratosis, "*wedge-shaped*" hypergranulosis (adjacent to acrosyringia or acrotrichia), and clefts which appear at the dermoepidermal junction ("*Max–Joseph*" spaces). Importantly, parakeratosis is not a feature of LP and its presence should suggest other disorders. As chronicity ensues, dermal fibrosis becomes apparent and the epidermis becomes progressively flattened and thinned. *Hypertrophic LP* features the same lichenoid infiltrate with accompanying hypergranulosis and acanthosis. The latter can sometimes be quite exuberant, producing the so-called "pseudoepitheliomatous hyperplasia," which can be mistaken for a premalignant or malignant process. *Erosive LP*, as the term implies, exhibits a superficial ulcerative surface with a lichenoid stromal infiltrate. If present, the edge of the lesion will show changes of classic LP (Fig. 1.15).

Ancillary Studies

Immunofluorescence shows irregular fibrin deposits in the DEJ. IgM deposits around necrotic keratinocytes are common and, when prominent, are helpful to confirm the diagnosis of LP. IgG, C3, and IgA deposits can also be present.

Differential Diagnosis

The differential diagnosis of LP in the vulva depends on the variant of LP . Classic/papulosquamous LP features a band-like infiltrate and attention should be drawn to the epidermal reaction pattern and composition of the infiltrate because, although uncommon in flexural or mucosal sites, *lichenoid drug eruptions* may be histologically indistinguishable from LP. Helpful clues in favor of lichenoid drug eruption are: presence of eosinophils within the infiltrate, involvement of the deep vascular plexus, and the presence of parakeratosis. Early lesions of LS are virtually indistinguishable from LP, and a descriptive diagnosis of "lichenoid dermatosis" followed by a differential may be prudent. The diagnosis of LS can, nonetheless, be raised if signs of chronicity are identified (effacement and flattening of the rete pegs,

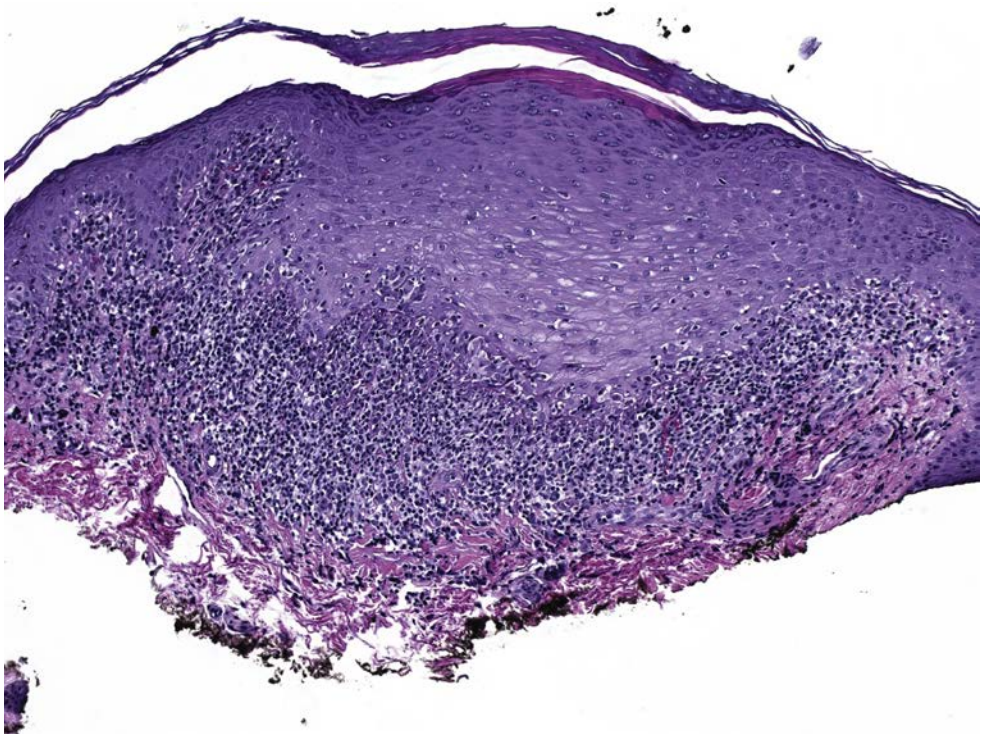

FIG. 1.13

Lichen planus. A band-like ("lichenoid") infiltrate is present at the dermoepidermal interface. The overlying epidermis is acanthotic with hyperkeratosis and hypergranulosis.

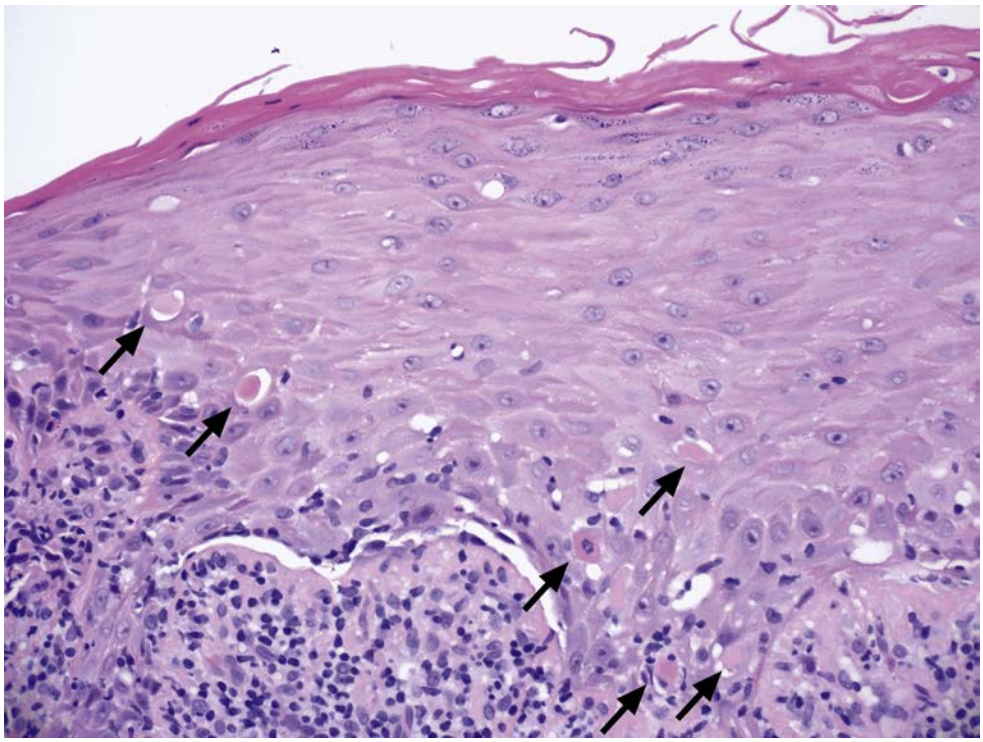

FIG. 1.14

Lichen planus. The lichenoid inflammation results in basal cell damage seen as squamatization of basal keratinocytes and dyskeratotic cells. Necrotic keratinocytes appear as eosinophilic hyaline ovoid bodies in the epidermis adjacent to the dermoepidermal junction ("Civatte bodies", *arrows*) or within the dermis ("colloid bodies"). Sharply angulated ("saw-tooth") rete ridges are also appreciated.

homogenization of the papillary dermis). If the infiltrate is rich in plasma cells, *plasma cell (zoon) vulvitis* may be considered; however, in this disorder the epithelium displays atrophy and hypogranulosis, unlike LP.

Hypertrophic LP may raise the differential diagnosis of a *neoplastic proliferation* such as a *squamous cell carcinoma* due to their overlying pseudoepitheliomatous hyperplasia and lichenoid-type host response. The presence of epithelial atypia and irregular inward growth should raise the possibility of malignancy. Long-standing lesions may overlap morphologically with LSC; the presence of basal cell damage, particularly at the base of the rete ridges, is indicative of LP. *Lichenoid keratosis or* LP-*like keratosis* is a solitary lesion that is essentially a T-cell-mediated regression of a variety of benign "keratoses" including *warts*, *seborrheic keratosis*, and *lentigines*.

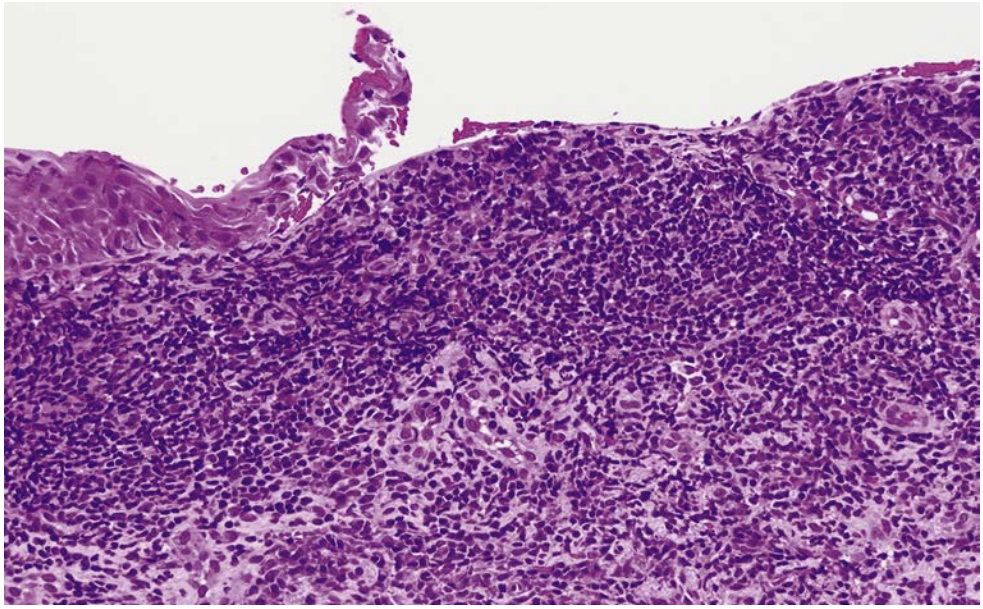

FIG. 1.15

Erosive lichen planus. This pattern, quite common in the vulva, is characterized by denudation of the epithelium and dense lichenoid lymphocyte-predominant dermal inflammation. Adjacent intact epithelium shows dyskeratotic cells.

These may be present alongside the inflammatory infiltrate and be a helpful histologic clue to the diagnosis. As a pitfall, the inflammation associated with regression of pigmented lesions (including *melanoma*) and atypical keratinocytic proliferations (including *squamous cell carcinoma in situ* and *basal cell carcinoma*) may have a striking lichenoid appearance. Any lichenoid infiltrate containing numerous melanophages should be treated with caution, and additional level sections and immunohistochemical stains for melanocytic markers may be useful in evaluating a clinically ambiguous lesion. Likewise, the presence of large epithelioid cells or keratin plugs should prompt consideration for epithelial markers to exclude epithelial neoplasia.

Erosive LP requires distinction from other ulcerative lesions, particularly *aphthous ulcers* and *infections* (fungi, syphilis, herpes). In addition to correlating with the clinical history, it is very important to examine the edge of the eroded area to identify classic LP changes, or microorganisms or viral cytopathic changes in the epithelium. A dense plasma cell infiltrate should raise the possibility of syphilis. A neutrophilic perivascular infiltrate is more in keeping with aphthous ulcers.

Prognosis and Treatment

Most cases of LP have a self-limiting course; indeed, over two-thirds of patients experience spontaneous remission in the 12–18 months following diagnosis. Treatment is largely symptomatic and consists of immunosuppressive agents, either topical or intralesional steroids (for local to regionally confined lesions), or systemic corticosteroids, retinoids, and cyclosporine (for cases with widespread involvement).

LICHEN PLANUS—FACT SHEET

Definition
- Idiopathic T-cell mediated skin disorder
- Prototype of the lichenoid-type reaction

Incidence
- 1% worldwide
- In vulva: erosive subtype>papulosquamous>hypertrophic

Morbidity
- Occasional vulvar scarring as consequence of erosive subtype

Gender, Race, and Age Distribution
- Female predominance
- No racial predisposition
- Rare in childhood; typically 30–60-year range
- No difference in age distribution between variants

Clinical Features
- Predilection for wrists, ankles, and genitalia, but may be widespread, including mucous membranes, nails, and hair
- Erosive
  Well-demarcated glazed erythema
  Hyperkeratotic border
  Reticular lacy lesions
- Hypertrophic:
  Raised hyperkeratotic plaque
- Classic (papulosquamous):
  Violaceous papules
- Pruritic or asymptomatic
- Associated with ulcerative colitis, hepatitis B/C, immunodeficiency disorders, cirrhosis, and peptic ulcer disease

Prognosis and Treatment
- Generally self-limited disorder (12–18 months)
- Topical or intralesional steroids for regionally confined lesions
- Systemic steroids, retinoids, or cyclosporine for widespread involvement

LICHEN PLANUS– PATHOLOGIC FEATURES

Microscopic Findings

- Prototypical lichenoid tissue reaction pattern
- Band-like lymphohistiocytic infiltrate at dermoepidermal junction accompanied by basal keratinocyte damage
- Infiltrate does not obscure dermoepidermal junction or extend into epidermis
- Other epidermal changes include hyperkeratosis, *"wedge-shaped"* hypergranulosis, and clefting at dermoepidermal junction (*"Max-Joseph"* spaces)
- Erosive LP: ulcer surrounded by mucosa with classic LP changes

Ancillary Studies

- Immunofluorescence: clumps of fibrinogen at epithelial base and IgM deposits around necrotic keratinocytes

Differential Diagnosis

- Lichenoid drug eruption
- Lichen sclerosus
- Fixed drug eruption
- Plasma cell vulvitis
- Aphthous ulcer
- Infectious ulcer

ERYTHEMA MULTIFORME

Erythema Multiforme (EM) consists of a clinical spectrum of disorders which affect the skin and may at times involve the mucous membranes. It is secondary to exposure to drugs (nonsteroidal anti-inflammatory drugs [NSAIDs], antibiotics, oral contraceptives) and infections (particularly herpes simplex virus [HSV] and mycoplasma).

Clinical Features

EM typically presents as urticarial papules or papulovesicles often assuming a classical *"targetoid"* morphology, favoring acral rather than axial locations (EM minor). In some cases, there is additional involvement of one or more mucous membranes with epidermal detachment affecting < 10 % of the total body surface area (EM major). Mucosal involvement, usually following ingestion of a drug, is common in Stevens–Johnson syndrome and in toxic epidermal necrolysis, now separated by most experts from the EM spectrum.

Microscopic Features

EM is the prototype of acute cytotoxic vacuolar interface dermatitis. Early lesions are characterized by perivascular and interface lymphocytic inflammation, associated with vacuole formation above and below the basement membrane (Fig. 1.16). As the lesions progress, keratinocyte necrosis ensues, eventuating in whorls of necrotic keratinocytes (Fig. 1.17). When fully evolved, subepidermal vacuoles coalesce forming broad clefts detaching the epidermis. Given the acute nature of the process, the epidermis retains a normal maturation pattern (with a normal "basket-weave" cornified layer) even in the detached portions of the epithelium.

Differential Diagnosis

The epidermal changes of EM are similar to that of a *fixed drug eruption (FDE)*; however, FDE features eosinophils, neutrophils, and deep extension of the infiltrate should allow separation in most cases.

Evolving lesions of herpes simplex virus (HSV) and reactivation of HSV infection may produce histologic features identical to EM. For this reason, level sections are important in evaluating EM if clinical suspicion for HSV infection is high, as viral cytopathic changes may be focal, or confined to hair follicles. Immunohistochemistry for HSV proteins may be helpful. While rare in the vulva, *Staphylococcal Scalded Skin Syndrome* may simulate the progression of EM clinically. This complication of Staphylococcal infection (usually conjunctivitis, rhinitis, or pharyngitis) is more common in children and is accompanied by fever. Histologically, the blistering is due to detachment at the level of the stratus corneum. Thus, histologic preparations of the detached epidermis show only the stratus corneum and sometimes the stratus granulosum. In contrast, the detached epidermis of EM shows all epithelial layers including the basalis. This distinction can be made on frozen section preparations, which are sometimes requested to expedite the treatment.

Prognosis and Treatment

Most cases of EM are self-limited and resolve spontaneously in 2–4 weeks. Treatment is directed at the identification and elimination of the etiologic factor. Active lesions require protective measurements.

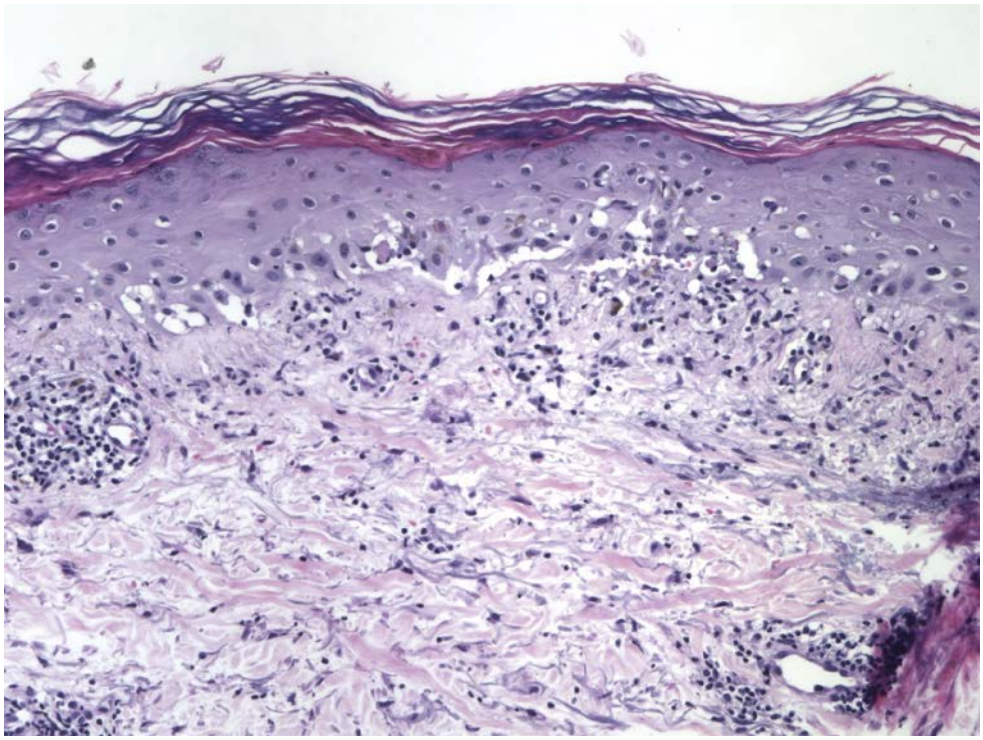

FIG. 1.16

Erythema multiforme. A perivascular lymphohistiocytic infiltrate extends to the dermoepidermal junction causing vacuole formation both above and below the basement membrane.

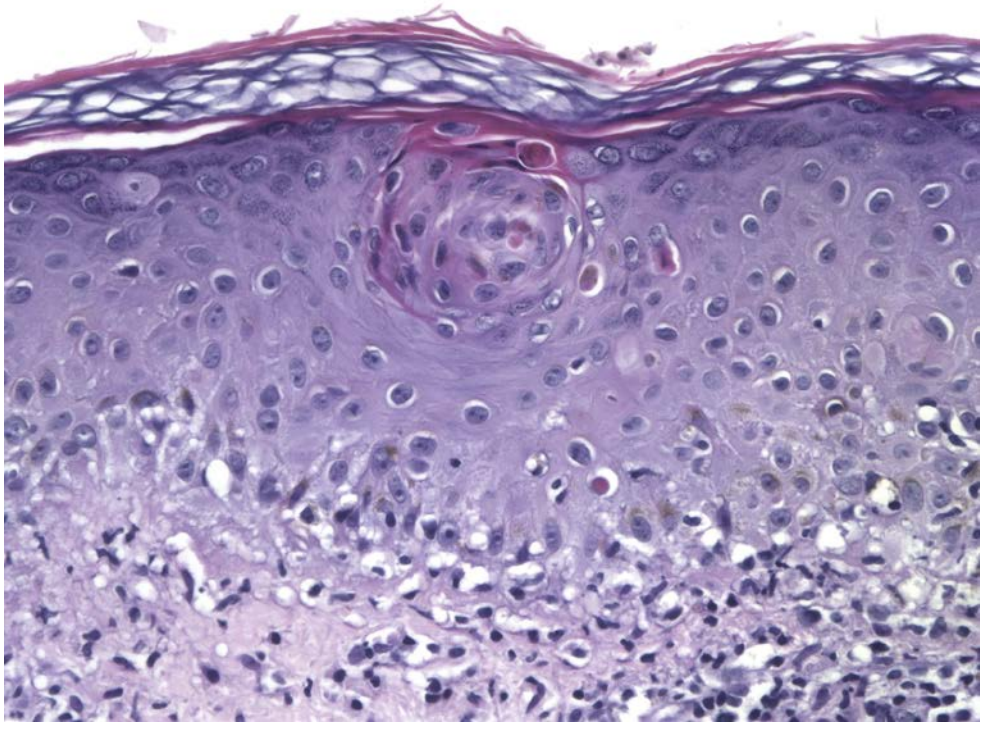

FIG. 1.17

Erythema multiforme, late phase. The spinous layer contains whorls of necrotic keratinocytes. Note the preserved maturation at the level of the stratus corneum, which has a normal "basket-weave" appearance.

ERYTHEMA MULTIFORME—FACT SHEET

Definition
- Prototype disorder of acute cytotoxic vacuolar interface dermatitis

Incidence
- Uncommon

Morbidity
- Typically self-limited, resolving in 2–4 weeks

Gender, Race, and Age Distribution
- Slight male preponderance
- No racial predilection
- Predominantly young adults

Clinical Features
- Urticarial papules/papulovesicles with *"targetoid"* morphology, most commonly acral locations (erythema multiforme minor)
- Erythema multiforme major if involvement of one or more mucous membranes

Prognosis and Treatment
- Excellent prognosis, particularly if etiologic trigger identified
- Supportive skin care for active cutaneous and mucocutaneous lesions

ERYTHEMA MULTIFORME—PATHOLOGIC FEATURES

Microscopic Findings
- Vacuoles both above and below basement membrane
- Lymphocytes present at dermoepidermal junction
- Necrotic keratinocytes in epidermis, as clusters or whorls
- Secondary subepidermal vesicles

Differential Diagnosis
- Fixed drug eruption
- Evolving or recurrent herpesvirus infection (atypical presentations in genital sites may herald herpes simplex virus reactivation)
- Stevens–Johnson syndrome

FIXED DRUG ERUPTION

Clinical Features

Following exposure to an eliciting agent, fixed drug eruption (FDE) occurs repetitively in the same area after each subsequent exposure. Commonly implicated agents include nonsteroidal anti-inflammatories (ibuprofen), salicylates (aspirin), oral contraceptives, barbiturates, and some antibiotics such as tetracycline and trimethoprim-sulfamethoxazole. Genital involvement is common. Acute lesions appear as erythematous ovoid patches and edematous violaceous to brown plaques with blister formation. Areas affected by several episodes develop gray or brown hyperpigmentation.

Microscopic Features

In fixed drug reaction there is usually vacuolar change at the dermalepidermal junction (DEJ) with the formation of single to clustered necrotic keratinocytes both at the DEJ and within the spinous layer (Figs. 1.18 and 1.19). Blistering occurs due to confluence of interface vacuolar change. The perivascular and interstitial dermal infiltrate is mixed (including eosinophils and neutrophil) and extends to the deep dermis. In chronically affected areas, dermal pigment incontinence is conspicuous.

Differential Diagnosis

The principal diagnostic consideration is *erythema multiforme*, which may be histologically indistinguishable from FDE. However, a localized anatomic distribution, history of recurrence limited to the same sites, presence of a mixed inflammatory infiltrate, and dermal melanophages are all features in support of FDE over EM. *Lichen planus* may also be in the differential as they both exhibit lichenoid dermatitis; however, *LP* will only show vacuolar damage at the DEJ, whereas dyskeratotic keratinocytes will be present in all epithelial layers of FDE. In addition, *LP* often shows parakeratosis, which is absent in FDE. If dense, the eosinophilic infiltration may resemble *Well's Syndrome* (eosinophilic cellulitis). This idiopathic disorder is often associated with hematologic malignancies, and is characterized by acute spongiosis and massive eosinophilic inflammation with "flame figures" (aggregates of eosinophilic granules and collapsing eosinophils around collagen fibers) and admixed histiocytes.

Prognosis and Treatment

Withdrawal of the offending agent and symptomatic treatment are generally sufficient. Discontinuation of triggering drug use is imperative. Residual hyperpigmentation is a common sequelae.

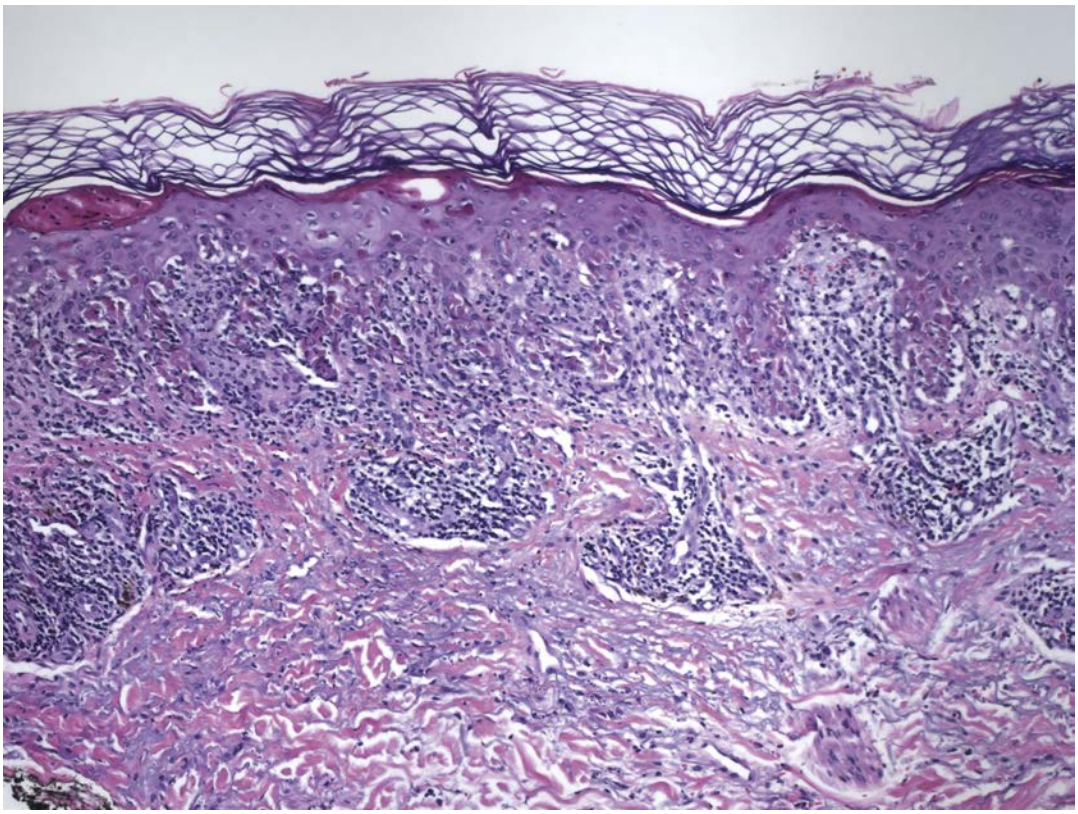

FIG. 1.18

Fixed drug eruption. Lichenoid inflammation involves the dermoepidermal interface, and vessels in the papillary and reticular dermis. Secondary interface changes include basal vacuolization and numerous necrotic keratinocytes, some in clusters and extending upwards beyond the basal layer.

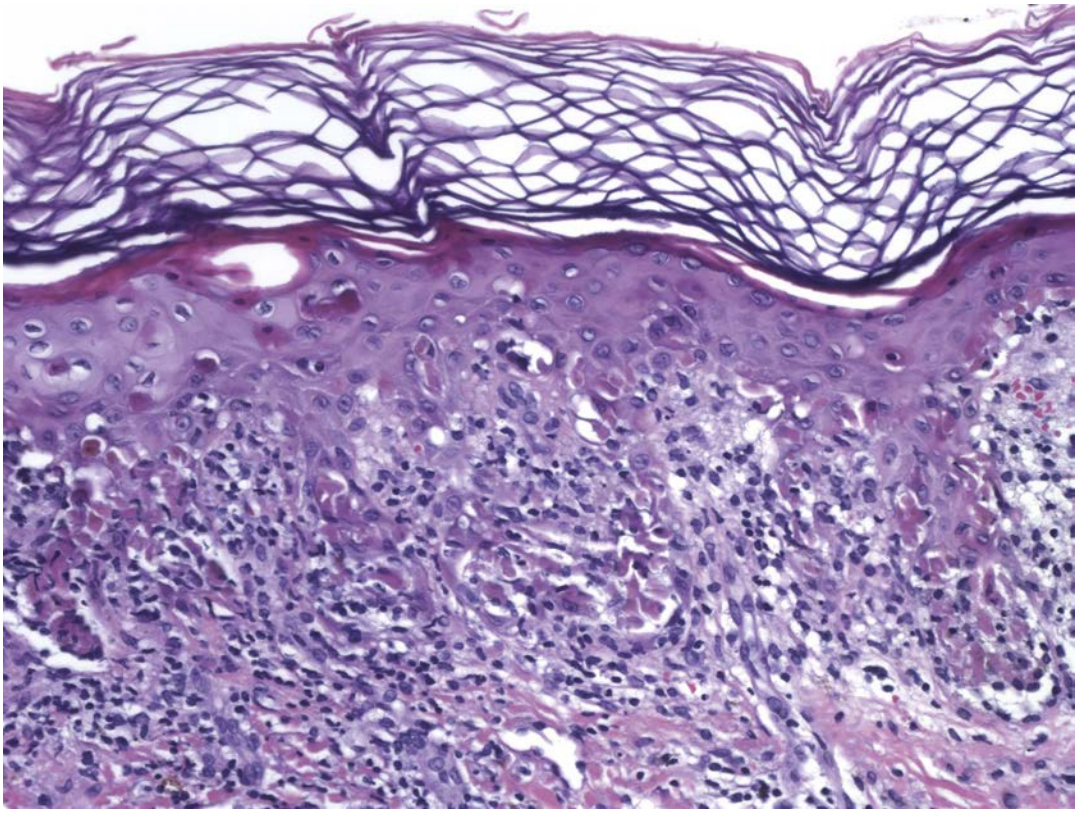

FIG. 1.19

Fixed drug eruption. On higher power view, dyskeratotic cells are present at the stratus spinosum. However, the stratus corneum retains its "basket-weave" appearance.

FIXED DRUG ERUPTION—FACT SHEET

Definition
- Characteristic eruption occurring in the same anatomic area each time the patient is exposed to an inciting agent (usually ingested)

Incidence
- Uncommon

Morbidity
- Mild or absent local and constitutional symptoms
- Persistent hyperpigmentation in some cases

Gender, Race, and Age Distribution
- No specific predilection

Clinical Features
- Erythematous ovoid patches or edematous plaques which may blister in acute lesions
- Persistent areas of gray or brown hyperpigmentation in late-stage lesions

Prognosis and Treatment
- Withdrawal of offending agent and patient education regarding avoidance of the drug to prevent recurrence

FIXED DRUG ERUPTION—PATHOLOGIC FEATURES

Microscopic Findings
- Lichenoid dermatitis
- Dyskeratotic keratinocytes at the dermoepidermal junction and within the spinous layer
- Secondary subepidermal blisters if there is extensive vacuolar change
- Conspicuous melanophages, particularly following repeat exposure to the inciting agent
- Notable pigment incontinence in later lesions, or during resolution

Differential Diagnosis
- Erythema multiforme
- Lichen planus
- Eosinophilic cellulitis

LICHEN SCLEROSUS

Although lichen sclerosus (LS) is listed under the Dermal Homogenization/Sclerosis Pattern in the ISSVD, we have included it here under the lichenoid reaction pattern, as it is this pattern that typifies early lesions of LS. LS is a lichenoid inflammatory condition with a fibrosing dermatitis with a predilection for the anogenital skin of women. It is most likely immune-mediated and characteristically shows an evolution of changes depending on the stage of the disease. The most commonly affected site is the anogenital region (85 %–95 %). Of these, 15 %–20 % also present with extragenital involvement.

Clinical Features

Early lesions present as erythematous plaques and patches in anogenital skin that spares the mucosa. As lesions evolve, they progress to pale "porcelain-white" plaques that coalesce in a "*figure-of-eight*" distribution with a wrinkled surface and follicular plugs. Long-standing lesions result in effacement of the labia majora and urethral stenosis. Symptoms range from absent to intense pruritus, dyspareunia, dysuria, and pain.

Microscopic Features

Early lesions are relatively nonspecific, as they show band-like lymphocytic infiltration of the dermis, psoriasiform epidermal acanthosis and hyperkeratosis, and focal dermal fibrosis; at this stage, morphology is virtually indistinguishable from LP (Fig. 1.20). As the lesions progress over time, the characteristic dermal changes start to appear: the papillary dermis acquires a pale and homogeneous appearance and the superficial vasculature decreases in quantity. As the homogenization of the papillary dermis continues, the inflammatory infiltrate decreases in the surface and becomes more prominent in deeper aspects of the dermis. In turn, the epidermis becomes atrophic with effacement of the rete pegs and epithelial thinning (Fig. 1.21A,B). At this stage, skin injury may result in hemorrhage and bullae formation.

Ancillary Studies

Much of the immunophenotype of LS is known from investigations on its most important differential diagnostic consideration, differentiated vulvar intraepithelial neoplasia (dVIN). It has been shown that LS and dVIN overlap significantly, both showing frequent expression of CK17 (> 90 % in dVIN and 63 % in LS) and p53. Regarding the latter, strong basal p53 staining with positive cells in upper epithelial layers counts as abnormal; up to 80 % of LS cases show this pattern of expression, particularly long-standing cases. Ki-67 is also frequently increased.

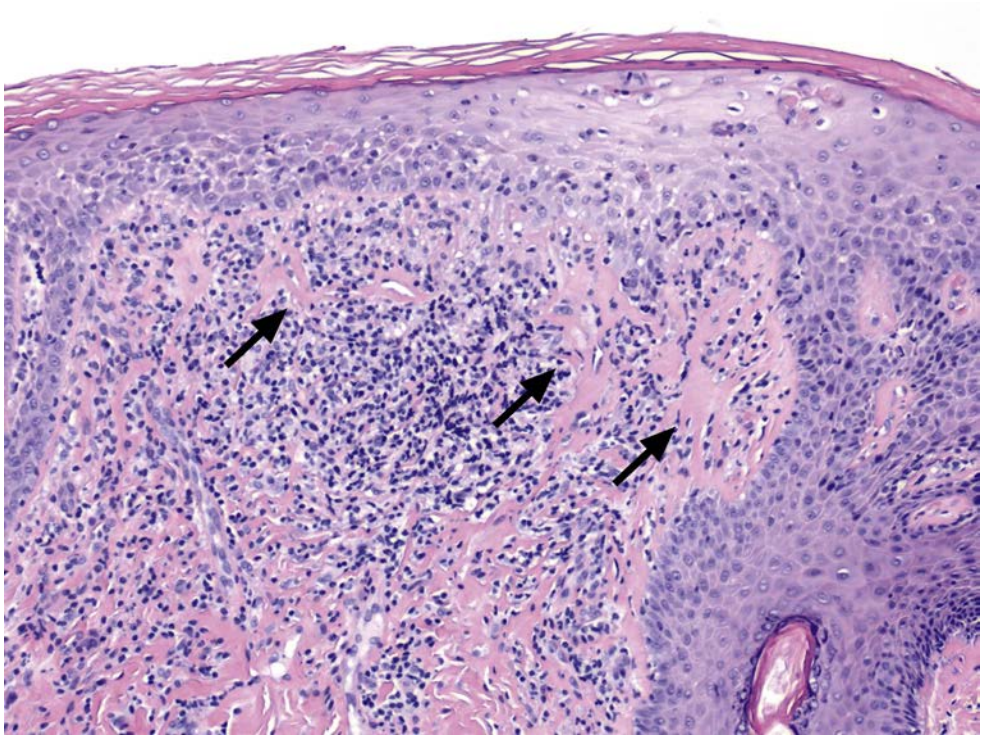

FIG. 1.20

Early lichen sclerosus. There is a dense band-like lymphocytic infiltrate and focal papillary dermal fibrosis *(arrows).* In this example, epidermal acanthosis is not prominent.

Differential Diagnosis

In its early phases, LS is highly similar to *lichen planus* morphologically. Indeed, in many cases the distinction is not possible, and a descriptive diagnosis (e.g., lichenoid dermatosis) followed by a list of differential is prudent. Nonetheless, the presence of pointed rete pegs, basal layer squamatization, wedge-shaped hypergranulosis, and preservation of the superficial elastic tissue are all in keeping with LP over LS. Acute-phase LS can also resemble *lichen simplex chronicus* (LSC); moreover, LSC changes are often superimposed to LS if leading to persistent rubbing. Identification of LS in this context is possible only if signs of chronicity are present. In some cases of *morphea*, there is homogenization of the papillary dermis similar to that observed in late-stage LS. However, morphea is also characterized by preservation of the superficial elastic tissue and formation of thick collagen bundles in the reticular dermis, unlike LS. *Late-stage radiation dermatitis* often exhibits great overlap with late-stage LS; thus, the clinical history is important in this differential. The presence of atypical endothelial cells and fibroblasts, perivascular fibrin deposition, and an admixture of elastotic and sclerotic collagenized stromal changes are more in keeping with late-stage radiation dermatitis. *Differentiated vulvar intraepithelial neoplasia (dVIN)* is a preinvasive squamous lesion with a high risk of progression to invasive squamous cell carcinoma. It arises in a background of a chronic inflammatory dermatosis, typically LS and/or LSC. Indeed, the chronic inflammatory nature of these conditions predisposes the epithelium to DNA damage (frequently via *TP53* abnormalities) and progression to malignancy. Initial and follow-up biopsies in a patient with LS should be carefully examined for the presence of architectural and cytologic features of dVIN (basal and parabasal nuclear enlargement and atypia, individual dyskeratotic cells, acantholysis, elongation and fusion of rete pegs). Immunohistochemistry has a limited value in this differential, as LS usually overlaps with dVIN (see previously in the text). However, a normal (wild type) staining at the base will favor LS, whereas complete absence of p53 staining (null phenotype) should strongly suggest the diagnosis of dVIN.

Prognosis and Treatment

The course of LS is chronic with frequent relapses and only partial regression with treatment. Control of symptomatic lesions with conservative use of topical corticosteroids may be useful. Calcineurin inhibitors are an alternative for maintenance therapy. LS is a recognized risk factor for non-HPV related dysplasia, namely dVIN and vulvar squamous cell carcinoma, occurring approximately in 4% of patients as a long-term complication. If dVIN or carcinoma are highly suspected or confirmed, surgery is the mainstay of primary treatment. Surgery may also be required to prevent or treat stricture.

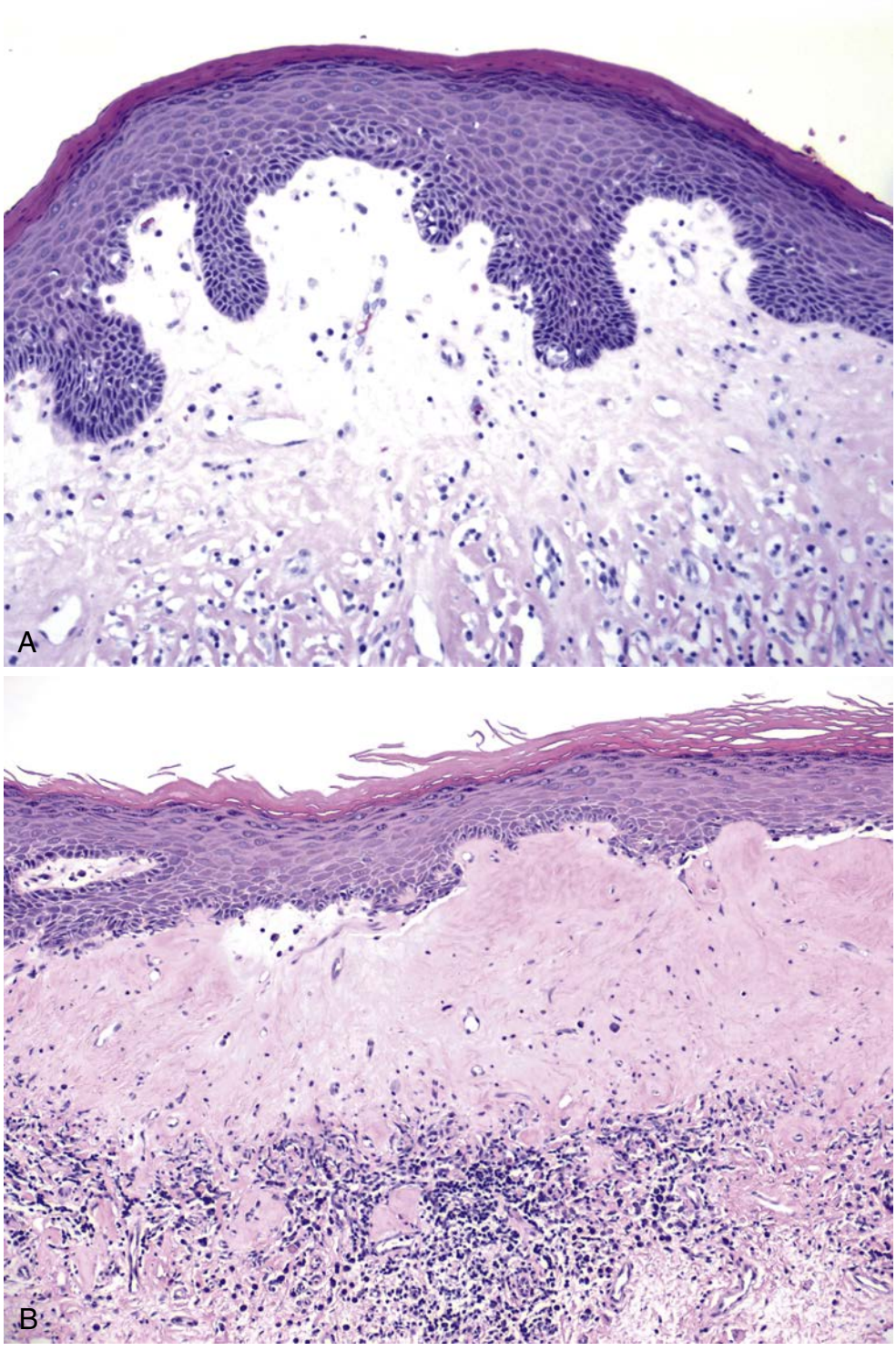

FIG. 1.21

Advanced lichen sclerosus. Marked papillary dermal sclerosis with homogenization and vascular "drop-out" are present. The homogenized dermis may show pallor (A) or a more uniform eosinophilic "hyaline-like" appearance (B). Notice the flattening of the dermoepidermal interface due to loss of rete ridges. There is some residual lichenoid inflammation, which usually subsides as the lesion ages.

LICHEN SCLEROSUS—FACT SHEET

Definition
- Fibrosing dermatitis with predilection for anogenital skin in women

Incidence
- 14.6 per 100,000 woman-years
- More common in gynecologic than dermatologic practices

Morbidity
- Vanishing of labia majora and urethral stenosis may occur in long-standing lesions
- Secondary differentiated vulvar intraepithelial neoplasia (dVIN) and squamous cell carcinoma (~4%)

Gender, Race, and Age Distribution
- Female predominance (10:1)
- More common in whites
- Bimodal distribution: prepubescent and perimenopausal (fifth decade)

Clinical Features
- *"Figure-of-eight"* distribution and *"porcelain-white"* plaques with wrinkled surface and follicular plugging

Prognosis and Treatment
- Chronic waxing and waning clinical course
- Topical steroids and calcineurin inhibitors for local control, but uncommon complete resolution
- Regular observation for development of dysplasia
- Surgery if severe introital stenosis or complicated by dVIN or squamous cell carcinoma

LICHEN SCLEROSUS—PATHOLOGIC FEATURES

Microscopic Findings
- Early lesion
  Psoriasiform epidermal hyperplasia with band-like lymphohistiocytic infiltrate, papillary dermal fibrosis, and hyperkeratosis
- Mature lesion
  Papillary dermal homogenization, pallor, and vascular drop-out with epidermal atrophy

Ancillary Studies
- Frequent expression of CK17, p53 overexpression, and high Ki-67

Differential Diagnosis
- Early lesions
  Lichen planus
  Lichen simplex chronicus
- Mature lesions
  Chronic radiation dermatitis
  Localized scleroderma (Morphea)
  Differentiated vulvar intraepithelial neoplasia

GRAFT VERSUS HOST DISEASE

Graft versus host disease (GVHD) is a systemic complication due to allo-hematopoietic stem cell transplant (allo-HSCT), characterized by a T-cell mediated immune response of the donor cells to mismatch of minor histocompatibility antigens in the host. GVHD is relatively common: it complicates ~3 % of bone marrow transplantations, thus clinical history of a prior stem cell transplant should prompt consideration for the diagnosis of GVHD. It has also been documented in 15 % of peripheral blood transfusions. Genital involvement of GVHD usually presents within the chronic phase (> 100 days from transplantation). Extragenital involvement of skin, oral cavity, liver, gastrointestinal tract, and eyes is common but sometimes vulvar involvement is the only manifestation of chronic GVHD. Of importance, primary ovarian failure is another manifestation of GVHD and a subtle one, sometimes interpreted as a consequence of chemotherapy (as many patients with GVHD have a previous hematologic malignancy).

Clinical Features

In early forms, GVHD manifests with vaginal dryness, pain or burning sensation, and dyspareunia. Long-standing lesions progress to introital stenosis or complete vaginal closure. The severity of symptoms can range from mild discomfort and erythema, moderate desquamation and erosions, to severe fibrosis, vaginal stenosis, and occlusion.

Microscopic Features

The microscopic features depend on the clinical lesion biopsied. An earlier lesion will show the prototypical histopathologic features of a lichenoid infiltrate with hypergranulosis and irregular acanthosis. Dyskeratotic cells in the epidermis adjacent to lymphocytes are features unique to GVHD (Fig. 1.22). Lesions with a protracted course may still show a lichenoid infiltrate but may also have more fibrosis in the dermis. The inflammatory infiltrate is composed of CD4 and CD8 T-cells, with a predominance of cytotoxic (CD8-positive) cells.

Differential Diagnosis

The histomorphology of early lesions of GVHD can be identical to *lichen planus*. Both dermatoses demonstrate a lichenoid infiltrate with hypergranulosis and irregular acanthosis. Moreover, hypergranulosis in GVHD can have a "wedge-shaped" distribution further mimicking LP. Lesions of GVHD that have a prolonged presentation can appear similar to *lichen sclerosus*, exhibiting dermal fibrosis. A lichenoid infiltrate may still persist.

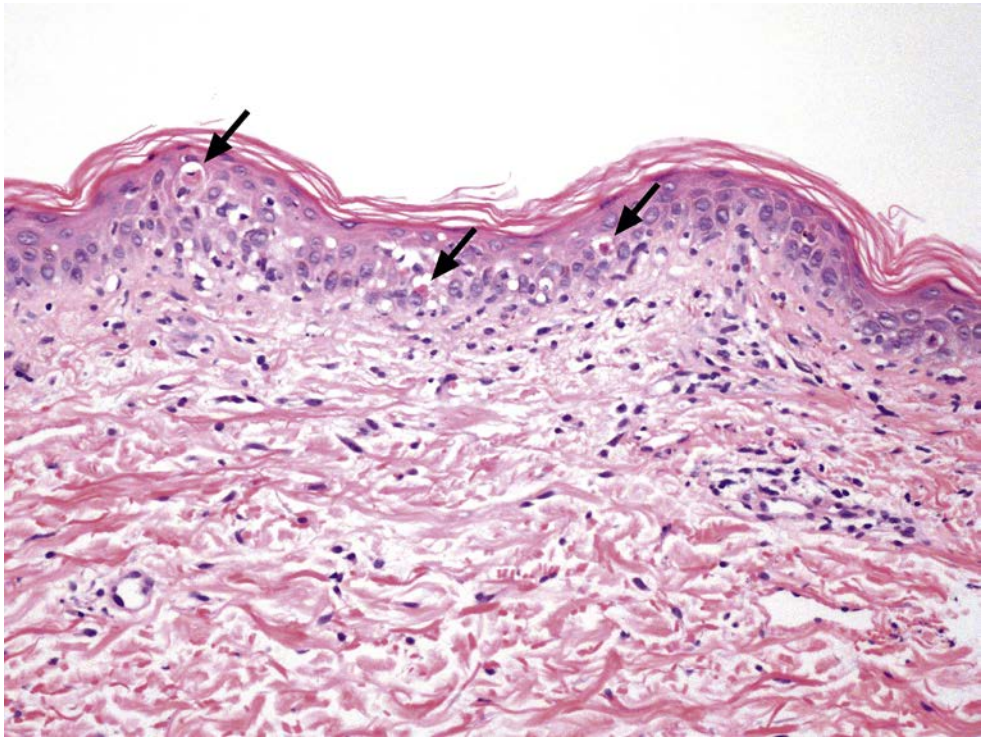

FIG. 1.22

Graft versus host disease. There is liquefaction degeneration (vacuolar alteration) of the basal keratinocyte layer and dyskeratotic keratinocytes *(arrows),* which sometimes are found adjacent to lymphocytes ("satellite cell necrosis").

Prognosis and Treatment

The prompt recognition of the disorder and treatment with potent glucocorticosteroids can help ameliorate the severity of the disease and prevent complications such as ovarian failure. Long-term surveillance is recommended to monitor ovarian function and detect recurrences early.

GRAFT VERSUS HOST DISEASE—FACT SHEET

Definition
- Systemic T-cell mediated immune disorder following allo-hematopoietic stem cell transplant

Incidence
- 3% of bone marrow recipients
- 15% of peripheral blood recipients
- Increasing as allo-HSCT rate increases

Morbidity
- Dependent on severity and time to treatment
- Introital stenosis or complete vaginal closure

Gender, Race, and Age Distribution
- No age or race predilection

Clinical Features
- Dryness, burning, pain, dyspareunia
- Lichen planus-like features, lichen sclerosus-like features

Prognosis and Treatment
- Rapid treatment with high-dose steroids
- Long-term gynecologic follow up required

GRAFT VERSUS HOST DISEASE—PATHOLOGIC FEATURES

Microscopic Findings
- Lichenoid inflammation
- Hypergranulosis
- Irregular acanthosis
- Dyskeratotic cells surrounded by lymphocytes

Immunohistochemical Features
- Mix of CD4+ and CD8+ cells with predominately CD8+ cells in the dermis

Differential Diagnosis
- Lichen planus
- Lichen sclerosus

ACANTHOLYTIC REACTION PATTERN

Acantholytic disorders are due to disruptions in the intercellular adhesions tethering keratinocytes together which results in clefting between keratinocytes and rounding of keratinocytes *("acantholytic cells")* within the epidermis.

PAPULAR GENITOCRURAL ACANTHOLYSIS

Papular genitocrural acantholysis is also known as *papular acantholytic dyskeratosis of the vulvocrural area* and *acantholytic dermatosis of the genitocrural/perineal region*.