Noninfectious Inflammatory Disorders of the Vulva

2

Sara C. Shalin

Abstract

A myriad of diseases that affect the skin can involve the perigenital regions, including the vulvar skin and mucosa. Some of these processes may mimic neoplastic lesions, while others may increase the risk of developing neoplasia or may indicate a risk for subsequent disease/malignancy. Many processes carry substantial morbidity and will affect the patient's quality of life. Familiarity with the histologic spectrum of inflammatory processes involving the vulva will allow for appropriate treatment and further triage/screening of patients. This chapter provides a framework by which to recognize many of these inflammatory dermatoses, discusses the clinical presentations, associated conditions, histopathologic findings and differential diagnoses, and suggests practical ways in which to handle biopsies provided with minimal clinical information.

Keywords

Inflammatory · Contact dermatitis · Lichen simplex chronicus · Psoriasis · Lichen planus · Lichen sclerosus · Plasma cell vulvitis · Pemphigus · Pemphigoid · Hidradenitis · Pyoderma

2.1 Introduction

Many of the same diseases that affect skin can also involve vulvar skin and mucosa. Some of these processes may mimic neoplastic lesions, while others may increase the risk of developing neoplasia or may indicate a risk for subsequent disease/malignancy. Many processes carry substantial morbidity and will affect the patient's quality of life. Familiarity with the histologic spectrum of inflammatory processes involving the vulva will allow for appropriate treatment and further triage/screening of patients.

Dermatopathologists generally search for inflammatory reaction patterns to help classify cutaneous rashes (Table 2.1). The same inflammatory reaction patterns will be seen in the vulvar region, with some occasional but important differences. This chapter provides a framework by which to recognize many (although not all!) of the inflammatory dermatoses which may affect vulvar skin and mucosa.

Inflammatory reaction patterns encompass entities which affect predominantly the epidermis (spongiotic and psoriasiform patterns and some blistering diseases), the junction of the epidermis and dermis (lichenoid and interface dermatoses as well as some blistering diseases), or the dermis (granulomatous, vasculopathic, and perivascular). A number of diseases may manifest in the vulnerable vulvar region clinically as ulceration (Tables 2.2 and 2.3); such entities are given consideration in the ensuing chapter so that specific diagnoses may be suggested to the treating clinician rather than the nonspecific diagnosis of ulcer. Still other dermatologic conditions affecting the vulva may be due to inflammation of the hair follicle or sweat gland apparatus. Recognition of the inflammatory reaction pattern is generally the first clue to establishing a diagnosis. This chapter will give the reader the tools to recognize the reaction patterns in vulvar biopsies, discover salient histologic features of particular disease entities, and practical advice for the handling of both straightforward and complex vulvar biopsies of inflammatory disease.

S. C. Shalin (✉)
Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Department of Dermatology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
e-mail: SCShalin@uams.edu

W. Zheng et al. (eds.), *Gynecologic and Obstetric Pathology, Volume 1*, https://doi.org/10.1007/978-981-13-3016-2_2

Table 2.1 Inflammatory reaction patterns and disease examples that may involve the vulva

Spongiotic	Psoriasiform (acanthotic)	Lichenoid and interface	Blistering and acantholytic	Granulomatous	Vasculopathic	Folliculocentric/ follicular occlusion
Allergic contact dermatitis	Psoriasis	Lichen planus	Pemphigus vulgaris	Crohn disease	Behcet disease	Hidradenitis suppurativa
Irritant contact dermatitis	Lichen simplex chronicus	Lichen sclerosus (et atrophicus)	Pemphigus vegetans	Sarcoidosis	Zoon vulvitis	Fox–Fordyce disease
Atopic dermatitis	Reiter syndrome	Fixed drug eruption	Linear IgA bullous dermatosis		Pyoderma gangrenosum	
Tinea (see chapter on infectious diseases)		Erythema multiforme/ Stevens Johnson syndrome/toxic epidermal necrolysis	Cicatricial pemphigoid			
Candida (see chapter on infectious diseases)		Graft-versus-host disease	Papular acantholysis of the vulvocrural folds			
Amicrobial pustulosis of the folds		Lupus erythematosus	Hailey–Hailey disease			
Inverse psoriasis		Plasma cell (Zoon) vulvitis	Darier disease			
			Herpes simplex virus infection (see chapter on infectious diseases)			
			Acute spongiotic dermatitis			
			Bullous fixed drug eruption			
			Stevens Johnson Syndrome/ Toxic Epidermal Necrolysis			

Entities in red font are diseases that are typically classified with a different reaction pattern but based on location or acuity may present with a less classic reaction pattern. See text for full details

Table 2.2 Diseases to consider that present with vulvar ulceration

Common disease involving vulva, ulceration is common presentation	Common disease involving vulva, ulceration is a rare presentation	Rare disease involving vulva, ulceration is a common presentation	Rare disease involving vulva, ulceration is a rare presentation
Lichen planus	Allergic or irritant contact dermatitis	Crohn disease	Reiter syndrome
	Lichen sclerosus	Behcet disease	Graft-versus-host disease
	Psoriasis	Pyoderma gangrenosum	
		Pemphigus vulgaris	
		Plasma cell (Zoon) vulvitis	
		Fixed drug eruption	

Table 2.3 Seeing past vulvar ulceration: clues to a more precise diagnosis

Disease presenting with ulceration	Clues to diagnosis (not always present)
Lichen planus (erosive variant)	Most commonly involves inner aspects of labia minora Presence of lichenoid band of inflammation in adjacent intact epithelium Oral and cutaneous involvement
Lichen sclerosus	Eosinophilic homogenization of collagen in areas without ulcer Focal basal vacuolar change Lymphocyte predominant infiltrate, infiltrating between thickened collagen bundles
Allergic or irritant contact dermatitis	Clinical history of contact with offending agent
Pemphigus vulgaris	Suprabasilar acantholysis in areas of intact epithelium Often oral and possibly cutaneous involvement Positive direct and/or indirect immunofluorescence studies

(continued)

Table 2.3 (continued)

Disease presenting with ulceration	Clues to diagnosis (not always present)
Crohn disease	Presence of gastrointestinal disease Dermal granulomas Eosinophils may favor Crohn disease over sarcoidosis
Behcet disease	Oral ulcers present Evidence of vasculitis (predominantly lymphocytic) Absence of lichenoid inflammation in adjacent intact epithelium
Pyoderma Gangrenosum	Neutrophilic dermatosis Negative special stains for organisms Pathergy present Healing with cribriform scarring Association with rheumatologic disease, inflammatory bowel disease, or lymphoproliferative disease
Psoriasis	Ulcerations and fissures limited to skin folds Presence of more conventional and classic psoriatic plaques on other body surfaces Typically bilateral and symmetric
Plasma cell (Zoon) vulvitis	Involves mucosa (labia minora, introitus) Plasma-cell-rich infiltrate Diamond-shaped keratinocytes in attenuated epithelium
Graft-versus-host disease	Involves mucosa May mimic lichen sclerosus or lichen planus History of transplant

2.2 Spongiotic Reaction Pattern

2.2.1 Eczematous Dermatitis: Contact (Allergic and Irritant) and Atopic Dermatitis

The term "eczematous dermatitis" encompasses a spectrum of inflammatory diseases linked by a spongiotic reaction pattern. Eczematous dermatitis can include irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), and atopic dermatitis (AD), among others. Eczematous dermatitis is not unique to the vulva as it commonly affects cutaneous skin, but it represents some of the most commonly encountered vulvar dermatoses. The exact prevalence is unknown, with some sources citing 15–30% of women being affected [1]. However, as these conditions may be established relatively confidently through clinical history and physical exam, biopsies of these entities may be less common than other vulvar dermatoses such as lichen sclerosus, lichen simplex chronicus, and lichen planus [2–4].

Allergic contact dermatitis (ACD) is a type IV hypersensitivity reaction. As such, it requires sensitization to an allergen through penetration of the stratum corneum. The sensitizing agent, generally a low molecular weight, lipid-soluble molecule, interacts with endogenous proteins to release a cascade of cytokines and chemokines that activate dendritic cells which drain to regional lymph nodes to stimulate and expand T cell populations [5, 6]. Reexposure to the allergen elicits the cutaneous reaction clinicians appreciate as an allergic contact dermatitis. The delay between exposure and presentation (often at least several days) may preclude the determination of the precise allergen. ACD generally occurs in predisposed individuals, which means that reactions to various substances may be idiosyncratic and unpredictable between women. This is in contrast to irritant contact dermatitis, in which an irritant generally produces the same reaction in women with sufficient exposure. ACD may be particularly common in the vulva due to constant moisture and friction at these sites. Estrogen deficiency may further disrupt the epidermal barrier and allow for easier penetration of allergens into the skin [7].

Irritant contact dermatitis (ICD) is an immediate reaction to an irritating agent and does not require prior sensitization. ICD can be directly cytotoxic to keratinocytes or can disrupt the normal lipid barrier of the skin [6]. Given the moist environment of the vulva, vulvar skin and mucosa is particularly susceptible to ICD.

Atopic dermatitis (AD) of the vulva is seen in genetically predisposed individuals with a history of atopic dermatitis on other body sites. The presence of this chronic inflammatory skin condition should not exclude a practitioner from considering a superimposed ACD or ICD, as these can exist together.

Careful history and physical exam is often sufficient to suggest the diagnosis. Common irritants include body fluids (urine, feces, semen, and some vaginal discharges), soaps and detergents, sanitary pads, feminine hygiene products, and topical medications. Vigorous scrubbing of the vulvar skin can also damage the epithelial barrier and be an irritant in itself. Common allergens implicated in ACD include topical antibiotics (neomycin), topical anesthetics (benzocaine), fragrance, and nickel [6]. In one study of vulvar ACD specifically, 39% of women with vulvar pruritus symptoms had a relevant positive patch test, with fragrances, topical medications, and preservatives representing the most frequently encountered allergens [8]; another similar study most frequently implicated topical pharmaceutical agents as relevant allergens [9].

2.2.1.1 Clinical Features

Eczematous dermatoses present clinically in a similar manner, although presentation will depend on the degree and duration of exposure to the irritant or allergen. Irritant der-

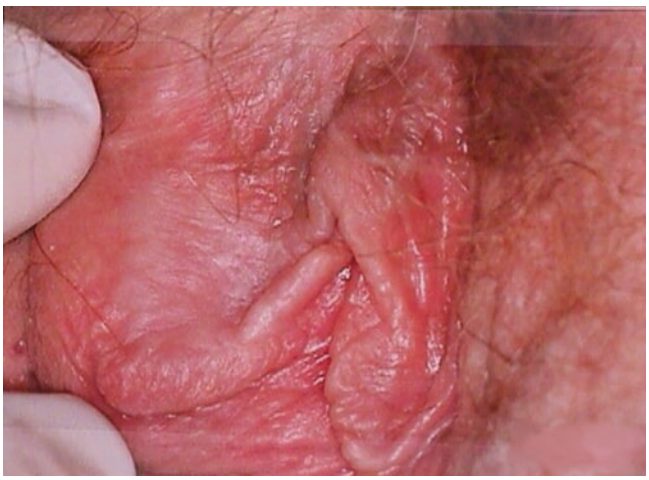

Fig. 2.1 Chronic spongiotic dermatitis. The vulvar skin shows thickened plaques and erythema. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

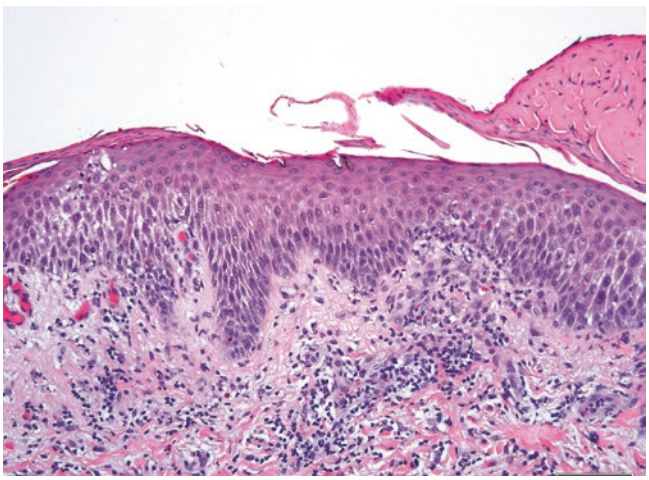

Fig. 2.2 Spongiotic dermatitis. There is increased intraepidermal edema, parakeratosis, and serum crust. There is exocytosis of a few lymphocytes into the epidermis, and a dermal infiltrate consisting of lymphocytes and eosinophils

matitis more commonly elicits complaints of burning, stinging, and pain, whereas patients with allergic contact and atopic dermatitis more often complain of pruritus [10]; however, there may be considerable overlap. Patients with seborrheic dermatitis and atopic dermatitis typically have skin lesions not limited to the vulvar area.

Allergic or irritant dermatitis will present as erythematous to edematous patches and plaques with maceration, erosion, and vesiculation in severe and/or acute cases. Contact dermatitis may be suspected by sparing of the skin folds, which may be protected from exposure to the allergen or irritant. Generally, early lesions are well demarcated, while subacute and chronic contact dermatitis becomes more poorly demarcated and scaly. With increasing chronicity, the skin becomes lichenified, with thickened, edematous plaques that display increased skin markings (Fig. 2.1). Hyperpigmentation is not infrequent, particularly in skin of color, and excoriations may attest to the clinical complaints of itching [6].

Identification of the offending contact allergens is paramount, as treatment relies on removal of the irritant or allergen. In general, recommendations begin with gentle vulvar hygiene, cessation of all fragrance-containing products, and cessation of all topical anesthetics and antibiotics. Bland petroleum jelly as a topical emollient is frequently recommended [6].

2.2.1.2 Histopathologic Features

Similar to the clinical presentation of eczematous dermatoses, the microscopic features are similar regardless of the precise etiology but depend greatly on the duration and severity of the symptoms. In general, distinction between ICD, ACD, AD, and other entities with the spongiotic reaction pattern is not possible on histologic grounds alone. All eczematous dermatoses are manifest by spongiotic dermatitis. The term "spongiosis" refers to the presence of epidermal edema, leading to increased apparent space between adjacent keratinocytes (Fig. 2.2).

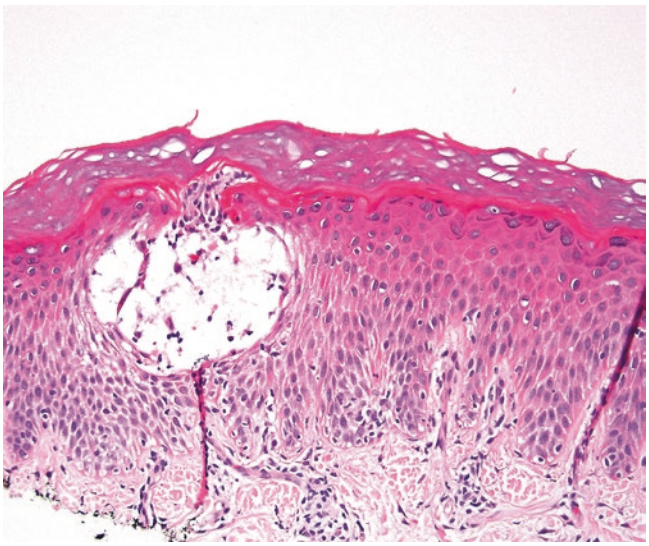

Fig. 2.3 Spongiotic dermatitis. A Langerhans cell microabscess in the epidermis is characteristic, with surrounding epidermal edema. Langerhans cell microabscesses are associated with, but not entirely specific for, allergic contact dermatitis

Early or acute eczematous dermatitis shows abundant intracellular edema; in some instances, this marked spongiosis can lead to mechanical failure of keratinocyte adhesion complexes (desmosomes) and the appearance of an intraepidermal vesicle or blister. Exocytosis, or the movement of lymphocytes into the epidermis, frequently accompanies spongiosis. Similarly, the presence of clusters of intraepidermal Langerhans cells (normal residents of the epidermis in single numbers) is a frequent finding and reflects the antigen processing inherent in these conditions. Langerhans cell microabscesses have been described as a common feature (Fig. 2.3) with a positive predictive value of 78% for ACD in one study

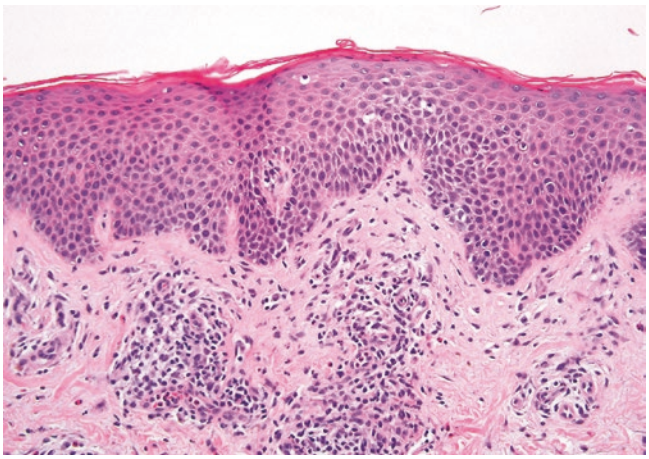

Fig. 2.4 Mild spongiotic dermatitis. There is slight acanthosis, mild epidermal edema, and parakeratosis. The dermal infiltrate shows a mix of lymphocytes and eosinophils

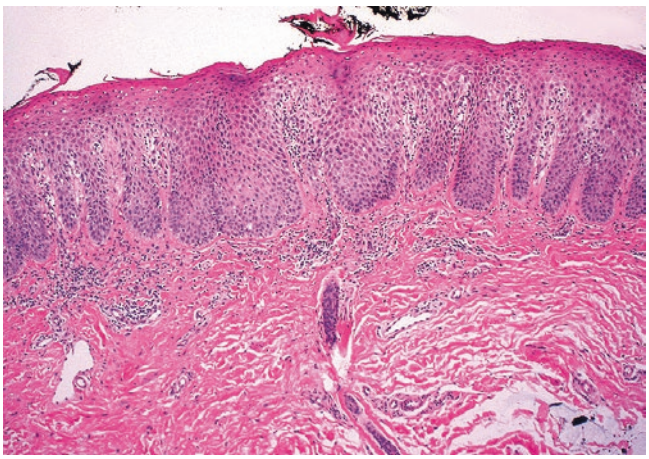

Fig. 2.5 Chronic spongiotic dermatitis. With time and continued stimulation, spongiotic dermatitis becomes chronic, characterized by more acanthosis and less spongiosis. Parakeratosis is still often seen. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

[11], but they are not unique to ACD and may be seen in other spongiotic dermatoses, albeit somewhat less commonly [12]. Some authors suggest that the presence of keratinocyte necrosis may suggest specifically an irritant contact dermatitis [6, 13], while other studies have not found this to be a specific differentiating feature [11, 12]. In addition to marked spongiosis, early and acute eczematous processes will show minimal acanthosis and focal parakeratosis (Fig. 2.4). Parakeratosis, or the retention of keratinocyte nuclei beyond the granular layer, reflects an impaired keratinocyte maturation sequence and is seen in a wide variety of inflammatory, premalignant, and malignant processes. In early or acute spongiotic dermatitis, parakeratosis may be accompanied by a serum-rich and neutrophilic crust on the epithelial surface. Within the dermis, there is generally edema and a perivascular inflammatory infiltrate comprised of lymphocytes, histiocytes, and a variable number of eosinophils. While eosinophils have traditionally been associated with allergic contact dermatitis, their presence was not more common in patients with a positive patch test compared to those with a negative patch test [11]. The presence of eosinophils, while not particularly useful in differentiating between causes of spongiotic dermatitis, may be useful in excluding other inflammatory dermatoses as they are notably absent to very rare in entities such as psoriasis, lichen planus, and connective tissue disease [14, 15]. Neutrophils may be seen, particularly if there is epidermal erosion or ulceration nearby. Plasma cells are not typically part of the inflammatory infiltrate in spongiotic dermatitis. However, it should be remembered that plasma cells are a normal component of perigenital sites and therefore a few plasma cells within the infiltrate may be permissible on vulvar skin and mucosa [1]. The presence of spongiosis centered on the hair follicle with parakeratosis specifically concentrated on the lip of the follicle (so-called "shoulder parakeratosis") can suggest the possibility of seborrheic dermatitis.

With time and continued exposure to the inciting agent, the histopathologic features of spongiotic dermatitis change. In response to continued stimulus, the skin attempts to strengthen its barrier function by thickening. Acanthosis and parakeratosis become prominent, and spongiosis becomes less prominent (Fig. 2.5). Frequently there may be superimposed changes of lichenification (lichen simplex chronicus) due to rubbing and scratching by the patient in response to pruritus. Lichenification may be recognized by an increased granular layer (or formation of a thin granular layer on what should be normal mucosal epithelium), dermal or subepithelial fibrosis, and pigment (melanin) drop out into the superficial dermis.

In summary, spongiotic dermatitis represents a commonly encountered inflammatory reaction pattern. The exact etiology may not be determined on histology alone and always require correlation with the clinical presentation. It is this author's practice to sign out reports as "Spongiotic Dermatitis" with a comment that the features would be compatible with allergic or irritant contact dermatitis, atopic dermatitis, or other spongiotic processes.

2.2.1.3 Immunohistochemical Features

Immunohistochemical stains are not required to diagnose the spongiotic reaction pattern. As a superficial fungal infection (both dermatophyte and *Candida* sp.) may elicit a spongiotic reaction pattern, periodic acid-Schiff (PAS) or Grocott's methenamine silver (GMS) special stain is recommended as an ancillary test in the diagnosis of a spongiotic dermatitis.

2.2.1.4 Differential Diagnosis

The histologic differential diagnosis of spongiotic dermatitis can include blistering disorders, infection, and a drug eruption.

Spongiosis should be distinguished from acantholysis (see subsequent section on pemphigus) which may indicate

an autoimmune-mediated blistering disease. In acantholysis, the desmosome complex failure is a primary process, leading to intraepidermal blistering, and the keratinocyte cytoplasm often retracts or collapses around the nucleus resulting in a rounded cell appearance. In contrast, vesiculation due to spongiosis results from keratinocytes being stretched to their limits until the edema overwhelms the desmosome complex. As a result, spongiosis can be suspected by angulated cytoplasmic fragments and a stellate, rather than rounded, cell shape. However, in cases in which a primary blistering disease is a consideration and definitive distinction between spongiosis and acantholysis is not possible, direct immunofluorescence studies will be necessary to exclude or confirm the possibility. Hailey–Hailey disease, an inherited genodermatosis characterized by defective desmosomal complexes resulting in extensive acantholysis of the epidermis, may be suspected when extensive acantholysis is seen in the absence of serum crusting, spongiosis, or significant dermal inflammation.

Infections may also mimic ACD, ICD, AD, and other spongiotic processes. Dermatophyte and Candida infections should be excluded through the use of GMS and/or PAS special stains. Herpetic infections may elicit a robust intraepidermal vesiculation and thereby mimic an acute spongiotic process; identification of the characteristic viral cytopathic effect will confirm this diagnosis.

Drug eruptions may sometimes result in identical histopathologic features as eczematous dermatoses. Careful correlation with clinical medication history is required.

Lastly, eczematous dermatitis may sometimes mimic other inflammatory dermatoses, namely early lichen sclerosus, a fixed drug eruption, or psoriasis. Moreover, superimposed ACD or ICD on one of these other inflammatory processes is always a possibility, particularly as patients try topical medications or home remedies either as directed by their physician or as an attempt to self-treat their skin disease. The most accurate diagnosis is made through a careful consideration of both clinical and histopathologic features.

2.3 Psoriasiform (Acanthotic) Reaction Pattern

2.3.1 Lichen Simplex Chronicus

Lichen simplex chronicus (LSC) is a histologic manifestation of excessive rubbing and scratching and is not a diagnosis in and of itself. LSC may be the end result of any inflammatory process that causes pruritus but it may also result from primary scratching without an identifiable underlying inflammatory process (i.e., idiopathic and/or neurodermatitis). LSC is a relatively frequent diagnosis in vulvar biopsies in general [3, 4], and was the most common diagnosis (26% of cases) in patients biopsied due to vulvar itching [16]. Pruritus is therefore the most common clinical symptom reported by patients with LSC. LSC indicates the presence of an itch-scratch cycle, in which itching precipitates scratching, and the scratching precipitates epidermal disruption that releases mediators that induce additional itching. The scratching and rubbing may be done consciously, unconsciously, or subconsciously, and will frequently occur during sleep [1, 17]. Histologic features of LSC may therefore be seen in isolation (for idiopathic or primary processes) or superimposed on other reaction patterns. In one study of vulvar biopsies, slightly more than 10% of vulvar biopsies showed two or more diagnosable processes; LSC was the second diagnosis in nearly all of these cases [3].

2.3.1.1 Clinical Features

LSC on the vulva may be recognized by thickened, erythematous plaques and papules, often with surface scaling. Lichenification refers to the presence of increased skin markings on the skin surface. Pigmentary changes (hyper- or hypopigmentation) are not infrequent. LSC most typically affects the vulvar regions surfaced by keratinizing squamous epithelium (as opposed to mucosal surfaces), namely the labia majora, peri-anal areas, and mons pubis [1]. Excoriations adjacent to the areas of lichenification will often be present.

The clinical differential diagnosis of LSC includes other inflammatory, infectious, and neoplastic vulvar skin conditions, and therefore skin biopsy is a common technique to establish the diagnosis and rule out other, more serious underlying conditions.

Treatment of LSC involves addressing any underlying inflammatory process, but ultimately requires breaking of the itch-scratch cycle. Topical steroids or steroid sparing agents may be helpful [18], but recurrences are not uncommon.

2.3.1.2 Histopathologic Features

LSC is classified by the International Society for the Study of Vulvovaginal Diseases (ISSVD) as having an "acanthotic" pattern [19]; dermatopathologists also often refer to this pattern as "psoriasiform." As may be inferred by this classification, LSC is characterized by thickening of the entire epidermis (acanthosis), generally in an irregular way. Irregular acanthosis means that the normal rete ridge pattern is expanded, but not in a uniform fashion (in contrast to psoriasis, which tends to demonstrate regular epidermal hyperplasia). Hyperkeratosis and hypergranulosis are seen at the surface, with parakeratosis a more variable finding (Fig. 2.6). Zones of pale keratinocytes have been reported in about three-quarters of vulvar LSC biopsies and were noted to be statistically more common in LSC than in other vulvar dermatoses examined [3]. Within the dermis, LSC generally shows papillary dermal fibrosis, with collagen fibers often

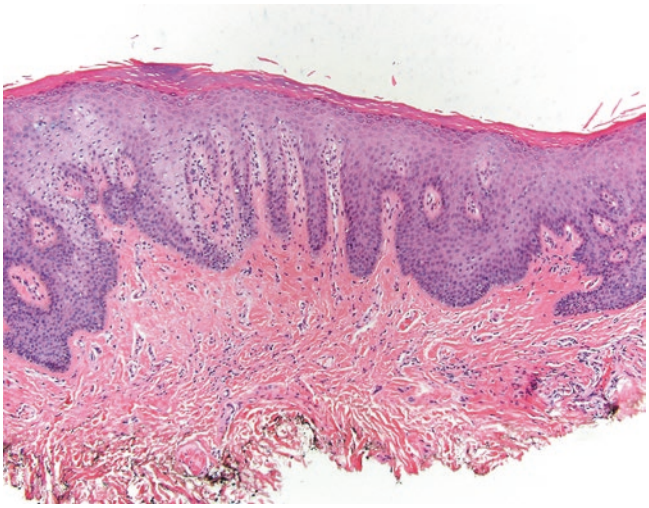

Fig. 2.6 Lichen simplex chronicus. The biopsy shows irregular acanthosis, hypergranulosis, and hyperkeratosis. There is minimal inflammation in the dermis

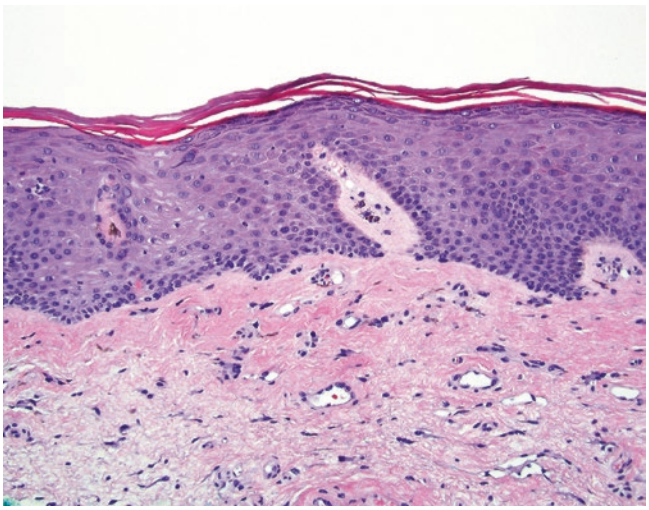

Fig. 2.7 Lichen simplex chronicus. On vulvar skin and mucosa in particular, the findings of lichen simplex chronicus may be subtle. Here there is slight acanthosis and a hint of an increased granular layer. There is slight melanin drop out in the subepithelium and a few multinucleate stromal cells

arranged in a characteristic vertical orientation in between dermal papillae; however, this feature has been suggested as less reproducible in biopsies from the vulvar region [3]. Instead of vertically oriented fibrosis, prominent stromal fibroblasts, including multinucleate forms (Fig. 2.7), have been suggested as a helpful clue to the diagnosis and were seen in more than half of biopsies in one histopathologic study of vulvar LSC [3]. There may be scant perivascular lymphocytes and a prominent vascularity in the superficial dermis. Of note, just because the name says "lichen" does not imply the necessity of a lichenoid pattern of inflammation. In fact, LSC as a primary process generally lacks a robust inflammatory infiltrate and the inflammation is not usually "band-like" in the superficial dermis. Melanin drop-out (pigment incontinence) may also be seen as a result of chronic rubbing.

2.3.1.3 Immunohistochemical Features

As with eczematous dermatoses, immunohistochemical stains are generally not required in the diagnosis of LSC. Similar to eczematous dermatoses, performance of PAS or GMS special stains to exclude a fungal infection is recommended routinely. If pale intraepidermal keratinocytes are prominent, the pathologist may toy with the possibility of extramammary Paget disease. This diagnosis can be excluded with a small panel of immunohistochemical stains: generally Paget disease is cytokeratin 7, CAM 5.2, and mucicarmine positive, while LSC should be negative for these markers.

2.3.1.4 Differential Diagnosis

As previously mentioned, LSC may be an end result or a superimposed pattern on many inflammatory or preneoplastic conditions. Detection of even slight amounts of spongiosis, parakeratosis, or dermal eosinophils may suggest the possibility of a spongiotic dermatitis as the underlying process, and a diagnosis of "spongiotic dermatitis with secondary changes of lichenification" may be a more helpful diagnosis to treating clinicians than simply "lichen simplex chronicus." Detection of prominent dyskeratosis may suggest one of the diagnoses with a lichenoid pattern of inflammation. If the epidermal hyperplasia appears more regular in nature, with areas of granular layer loss and intraepidermal neutrophils, then psoriasis should be a preferred consideration. The presence of keratinocyte atypia is unusual in LSC. The presence of keratinocyte atypia should warrant careful examination to exclude a subtle high grade squamous intraepithelial neoplasia (VIN usual type) or differentiated vulvar intraepithelial neoplasia (d-VIN) with superimposed LSC. Overall, in the author's experience, the diagnosis of LSC is reserved for biopsies in which histologic features are limited to acanthosis, hyperkeratosis, hypergranulosis, papillary dermal fibrosis, and nonspecific chronic inflammation. The presence of any other histologic feature generally prompts a comment about the likelihood of secondary changes of lichen simplex chronicus complicating the diagnosis of another primary process.

2.3.2 Psoriasis

Psoriasis is a common skin condition which relatively uncommonly affects the vulvar skin and mucosa. The prevalence of psoriasis differs among demographic groups (being more common in adults than in children) and among

geographic regions (being more common in countries more distant from the equator) [20]. Estimations of the prevalence range from approximately 0.5 to 8%, depending on the population sampled [20–22]. Most patients present in early adulthood, and women may present at a slightly earlier age than men [22]. Genital involvement is estimated to occur in about 30–40% of patients with psoriasis [23], and 2–5% of patients with psoriasis are estimated to have exclusive involvement of the genital skin [24]. Vulvar psoriasis seems to present in a similar age group of patients [21]. Children may also present with psoriasis and are more likely than adults to report a family history of the disease [21]. Classic psoriasis presents with a symmetric eruption of dry scaly plaques on the extensor surfaces. Inverse psoriasis refers to a distribution of lesions that affects the body folds (axillae, groin, umbilicus, inframammary creases, and antecubital and popliteal fossae). Inverse psoriasis does not always (but may) indicate the presence of genital psoriasis [25].

The pathogenesis of psoriasis is complex and multifactorial, and thorough discussion is beyond the scope of this chapter. Genetic and epigenetic events result in an autoinflammatory disorder skewed toward the Th-1 and Th-17 immune responses. The resultant altered immunity results in a hyperproliferative state of the epidermis, corresponding with the histologic elements of acanthosis and parakeratosis, and the clinical perception of scaly plaques.

Genetic susceptibility definitely plays a role in development of psoriasis. About 30% of patients with the disease have an affected first-degree relative [22]. Several genetic loci linked to familial cases of psoriasis have been documented, the most strongly linked being PSORS1, located on chromosome 6p. The various psoriasis susceptibility loci that have been found in genetic linkage studies encompass genes important for Th1 cell differentiation, Th17 cell differentiation, interferon signaling, keratinocyte growth, and antigen presentation [26]. Expression of the major histocompatibility complex (MHC) class I allele HLA-Cw6 is strongly linked to psoriasis and is encoded near the PSORS1 locus [22, 26]. Epigenetic alterations also seem to play a role in development of psoriasis, with research focusing on the role of posttranslational histone modifications, DNA methylation, and microRNAs [26].

Regardless of genetic influences, patients with psoriasis demonstrate altered immune responses. Induction of a Th-17 immune response is mediated by interleukin (IL)-23 and TNF-α release. IL-23 release stimulates differentiation of naïve T-cells to Th-17 type helper T-cells [27]. Th-17 cells then elicit a cascade of cytokines (notably including IL-17) that act on keratinocytes of the epidermis to become hyperproliferative [26] as well as feeding back to reactivate and amplify the cytokine cascade. IL-17 is also important in the recruitment of neutrophils and the upregulation of antimicrobial peptides that play a role in pathogenesis [27]. Psoriasis also shows features of a Th-1 immune response, with interferon-γ, IL-2, and IL-12 notably increased in the serum of patients with psoriasis and correlating with disease severity [22, 26].

Patients with psoriasis have a higher incidence of Crohn disease, type 2 diabetes and the metabolic syndrome, and depression [22, 25]. Patients also have a slightly increased risk of developing lymphoproliferative diseases (which may in part be related to risks imparted by systemic treatment for the disease) [25, 28].

Treatment of psoriasis depends on disease severity. Gentle skin care regimens are advised, and skin lesions may be treated with topical corticosteroids and steroid sparing agents such as calcineurin inhibitors or topical vitamin D analogues. Skin atrophy and fragility due to prolonged corticosteroid use is a particular problem in the treatment of genital skin [24], and many of the topical preparations used elsewhere on the body may be irritating to vulvar skin [21]. Systemic therapies are utilized for psoriasis refractory to topical treatments or when there is considerable body surface involvement. Systemic therapies target the cytokines known to be elevated in patients with psoriasis and broadly include TNF-α inhibitors, IL-12 and IL-23 inhibitors, and IL-17 inhibitors [26].

2.3.2.1 Clinical Features

The clinical appearance of lesions of genital psoriasis depends on the precise anatomic area involved, corresponding with the transition in this region from stratified squamous to mucosal type epithelium. Familiarity with the variation in presentation can aid diagnosis (Fig. 2.8). One study noted that of a cohort

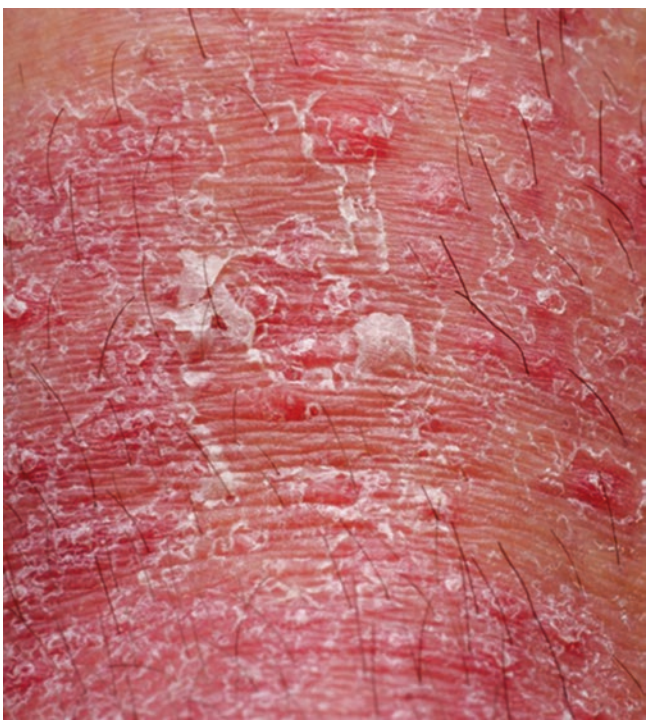

Fig. 2.8 Psoriasis. The lesion shows salmon colored, erythema, thin plaques and multiple scaly lesions in the vulvar region (Courtesy of Dr. Kenneth Hatch, University of Arizona)

of patients ultimately diagnosed with vulvar psoriasis at a vulvar specialty clinic, only 12% of the patients had been referred with a provisional diagnosis of psoriasis [21]. The mons pubis will show lesions resembling classic psoriasis vulgaris, with scaly salmon-colored, raised plaques that typically lack ulceration [21]. Involvement of the labia majora shows a more variable presence of scale, increased erythema, and occasionally erosions and ulceration [1, 21]. Vulvar regions of the inner labia majora, labia minora, and clitoris will lack scale and typically consist of well-demarcated erythematous to shiny plaques [21–23]. The inguinal folds often show symmetric, bright erythema without any scaling and a higher propensity for erosive and ulcerative lesions [1]. The vagina is generally not involved by psoriasis, so vaginal lesions should prompt consideration of other inflammatory disorders [21–23]. Of note, vulvar discomfort, including burning sensation and pruritus, is common in patients with psoriasis, even if there are no discernable skin/mucosal lesions [29]. In one study specifically of vulvar psoriasis, nearly 95% of women reported itching as a significant symptom [21].

Psoriasis is generally diagnosed on clinical exam. Examination of other body sites may reveal the classic silvery, dry scaly plaques distributed symmetrically on the extensor surfaces (knees, elbows, scalp). Examination of the gluteal cleft may reveal well-demarcated erythema. Nail involvement is a frequent finding in psoriasis, characterized by oil spots, pitting, and distal onycholysis (lifting of the nail plate from the nail bed) [22, 24]. Pustular lesions may be seen, particularly on the palms and soles, but pustules in the vulvar regions are distinctly uncommon [22]. Vulvar psoriasis is rarely unilateral in distribution [21].

The clinical differential diagnosis includes infectious etiologies (superficial fungal infections to include *Candida* sp., and dermatophyte/tinea), chronic spongiotic dermatoses (irritant and allergic contact dermatitis), lichen simplex chronicus, fixed drug eruptions, and even malignancies such as extramammary Paget disease [21]. Nonresponsiveness to antifungals and negative cultures can help exclude infectious etiologies. Biopsy is strongly recommended for patients who are not responsive to usual treatments to exclude extramammary Paget disease. Distinguishing psoriasis from irritant or allergic contact dermatitis may best be accomplished through clinical exam and history.

2.3.2.2 Histopathologic Features

The histologic features of vulvar psoriasis vary depending on the precise anatomic site involved and biopsied. The classically described histopathologic features of psoriasis as seen on other cutaneous sites may be seen on the hair-bearing sites of the mons pubis and labia majora; however, the features may be less specific and more variable on mucosal sites and the intertriginous folds of the female genitalia. One study suggested that biopsy should be performed predominantly to rule out other pathologies such as Paget disease and lichen sclerosus rather than as a means to confirm the diagnosis, noting that none of the five biopsies from patients with clinically diagnosed psoriasis demonstrated the "typical" features associated with the disease [21].

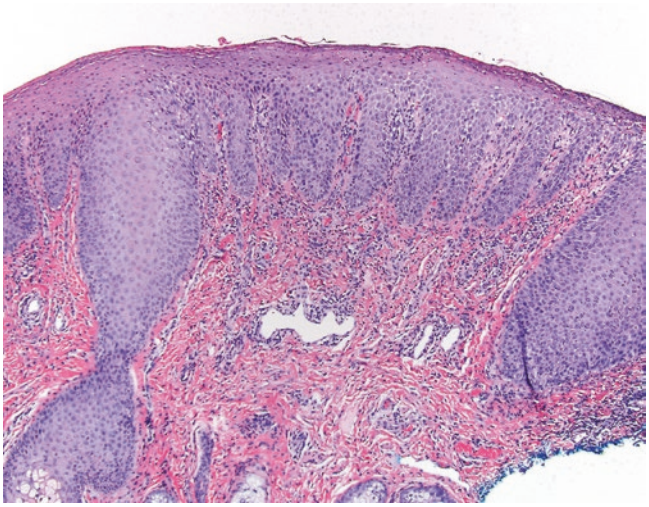

Fig. 2.9 Psoriasis. Low-power magnification shows regular epidermal hyperplasia with parakeratosis and intraepidermal neutrophils. Spongiosis is not prominent

Classic psoriasis, and thus its histologic appearance in biopsies of the external vulva and mons pubis, is characterized by regular epidermal hyperplasia, loss of the granular layer, and confluent parakeratosis (Fig. 2.9). Regular epidermal hyperplasia (or acanthosis) means that all rete ridges are elongated to a similar degree (as opposed to the irregular acanthosis that typifies lichen simplex chronicus). Neutrophils migrate into the epidermis, forming small aggregates known as spongiform pustules in the stratum spinosum and stratum corneum. Blood vessels in the superficial dermis are dilated and prominent within the dermal papillae. There is typically a scant perivascular lymphocytic infiltrate in the dermis. Eosinophils are typically absent, although they may be more common in biopsies from children [1] and a recent study suggests they may be more common in inverse psoriasis specifically [30]. Biopsies from mucosal sites or the intertriginous folds are more likely to show spongiosis, generally have less pronounced acanthosis, and the acanthosis may more often be irregular rather than regular [30]. Spongiosis may also be more prominent in early lesions of psoriasis (Fig. 2.10). In the author's experience, biopsies from the vulvar region are often not specific for psoriasis, but the possibility may be included in the differential diagnosis of a vulvar biopsy with slight acanthosis, spongiosis, and parakeratosis. In the absence of detailed clinical information and images, these biopsies are often reported as "Psoriasiform and spongiotic dermatitis," with a differential diagnosis including chronic spongiotic processes and psoriasis.

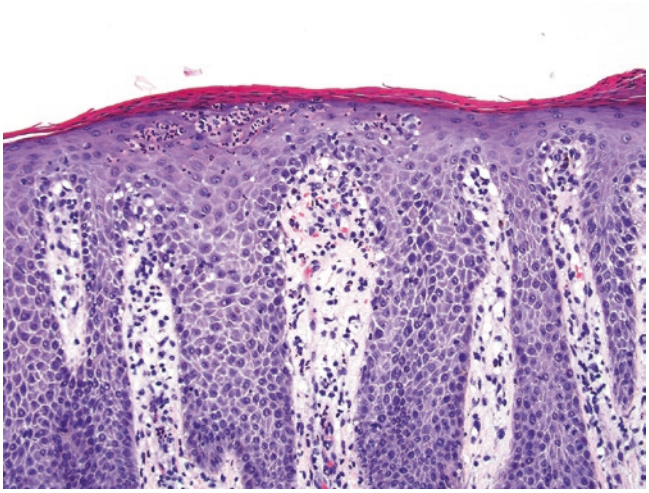

Fig. 2.10 Psoriasis. High-power magnification shows spongiform pustules, confluent parakeratosis, and suprapapillary thinning. This biopsy also shows a degree of spongiosis, which is more commonly seen in vulvar biopsies of psoriasis

The epidermis in psoriasis is hyperproliferative, and the normal sequence of keratinocyte maturation is sped up in psoriasis. Both cell cycle time and time for keratinocytes to transit from the basal layer to the top of the spinous layer is markedly accelerated [27]. As such, the presence of basilar mitotic figures (and occasionally suprabasally) is not an uncommon feature in psoriasis. The presence of basal mitoses should not be mistaken as a marker of a premalignancy/vulvar intraepithelial neoplasia.

2.3.2.3 Immunohistochemical Features

Particularly when the features of psoriasis are not classic, special stains to exclude a superficial fungal infection are recommended. These special stains would be reasonable even in the setting of otherwise classic psoriasis to exclude a secondary superimposed infection. Other ancillary testing is typically not indicated. Immunohistochemical evaluation of the proteins expressed in psoriatic plaques [31] or in the immune infiltrate [32] of psoriasis biopsies has indicated some differences compared to normal or other inflammatory skin diseases; however, to the author's knowledge, no assay is universally useful or routinely used in clinical practice to differentiate psoriasis from other cutaneous inflammatory conditions.

2.3.2.4 Differential Diagnosis

The histologic differential diagnosis includes fungal infection, chronic spongiotic dermatoses, lichen simplex chronicus, and Reiter syndrome. Fungal infection is easily excluded through the use of special stains PAS and/or GMS. Chronic spongiotic dermatoses (including atopic dermatitis, allergic or irritant contact dermatitis) may have considerable histologic overlap with psoriasis. The presence of abundant dermal eosinophils may somewhat favor contact or other spongiotic dermatitis, as large numbers of eosinophils are not typically induced in the Th1 and Th17 immune response that typifies psoriasis. Seborrheic dermatitis can involve the vulva and has considerable histologic overlap with psoriasis, but spongiosis preferentially involving hair follicle epithelium and parakeratosis adjacent to the follicle openings have been suggested as differentiating clues in seborrheic dermatitis. Lichen simplex chronicus classically shows irregular rather than regular epidermal hyperplasia. Reiter syndrome is rare but may be histologically identical to psoriasis and requires specific knowledge of the clinical presentation.

2.3.3 Reiter Syndrome

Another consideration when encountering a psoriasiform reaction pattern would be Reiter syndrome (reactive arthritis). This rare syndrome is characterized by the classic triad of urethritis, conjunctivitis, and arthritis. Pustular psoriasis-like lesions are also a commonly reported sign, historically referred to as keratoderma blennorrhagica. The syndrome is uncommon in females, and the presence of all of the classic signs is not required for diagnosis, thus leading to an atypical presentation. This atypical presentation may be more common in female patients [33], and vulvar involvement is exceptionally reported.

Reiter syndrome has been linked to genetic predisposition in patients possessing the antigen HLA B27 as well as infectious etiologies. The incidence of detection of the HLA B27 antigen is reported in as high as 90% of cases of Reiter syndrome, although the antigen may be less commonly detected in female patients [33]. This genetic disposition, when coupled with a urogenital or enteric infection, is thought to result in disease manifestation, with development of cross-reacting immune complexes [1]. Infections caused by *Chlamydia*, *Neisseria*, *Ureaplasma*, *Yersinia*, *Campylobacter*, *Shigella*, and *Salmonella* sp. have all been implicated as preceding infections in Reiter syndrome.

2.3.3.1 Clinical Features

The classic description of Reiter syndrome is the triad of urethritis, conjunctivitis, and arthritis, arising in young adult male patients. Females are less commonly affected but may have cervicitis. Arthritis typically involves the heels, knees, and back joints [34]. This differs from the arthritis associated with psoriasis, which more commonly involves the small joints of the hands. Mucocutaneous ulcerations may be present, and may precede the development of the other salient features of the disease.

Cutaneous lesions present as psoriatic, hyperkeratotic plaques in a similar distribution as psoriasis. Perigenital

lesions and mucosal lesions are often ulcerative with exudative surface. Vulvar ulcerations have been described as shallow, sometimes rimmed by small papules arranged in a circular (annular) configuration [34]. Linear, rather than annular, ulcerations have also been described [33]. Verrucous lesions and pustules have also been described [1].

The clinical differential diagnosis of the mucocutaneous lesions typically includes pustular psoriasis or sexually transmitted diseases presenting with genital ulceration. Psoriasis typically does not involve the cervix, so cervical involvement would support Reiter syndrome over psoriasis, as would the previously mentioned distribution of joints affected by arthritic symptoms [34]. Sexually transmitted diseases such as lymphogranuloma venereum could be considered in the setting of vulvar ulceration and recent genital infection; this entity typically presents with lymphadenitis and the absence of extragenital manifestations, which is uncommon in Reiter syndrome [33].

Treatment regimens vary, and topical steroids, methotrexate, and retinoids all have been reported as being therapeutic.

2.3.3.2 Histopathologic Features

Biopsies from vulvar lesions show features similar to psoriasis. Epidermal acanthosis, hypogranulosis with diffuse parakeratosis, suprapapillary thinning, and intraepidermal neutrophilic microabscesses are typically seen. Pustules may be present. One author noted pseudoepitheliomatous hyperplasia with deep dermal pustules/microabscesses [33].

2.3.3.3 Immunohistochemical Features

Ancillary tests suggested in the workup of possible Reiter syndrome include a PAS stain to exclude a superficial fungal infection. Urethral or genital cultures or polymerase chain reaction may detect the presence of an infectious disease, which may be supportive of the disease as well [33].

2.3.3.4 Differential Diagnosis

The histopathologic differential diagnosis with the classically described features would include psoriasis, and distinction of the two entities may be impossible on histologic grounds alone. The presence of pseudoepitheliomatous hyperplasia in one reported case led to consideration of pemphigus vegetans; direct immunofluorescence studies were negative to help exclude this possibility [33].

There are no histopathologic features that are pathognomonic or specific for Reiter syndrome. Pathology reports should emphasize that the features may be supportive of the diagnosis assuming the clinical impression supports the diagnosis of Reiter syndrome. Ultimately, however, the diagnosis is a clinical one, although it may be suggested by the astute pathologist if he/she is provided with sufficient clinical information.

2.4 Lichenoid and Interface Reaction Pattern

2.4.1 Lichen Planus

Lichen planus (LP) is a relatively common condition that may affect both skin and mucosa of adults. It is estimated to be the cause of approximately 1% of dermatology visits. A subset of patients with LP will have mucosal disease, with oral cavity (tongue, buccal mucosa, gingiva) being the most commonly affected mucosal site, and mucosal LP may exist in the absence of cutaneous LP. At least half and up to three-quarters of patients with oral LP will also have genital disease [23, 35], and patients with vulvar LP are more likely to have oral involvement than cutaneous involvement [36]. The true incidence of vulvar involvement by LP is unknown; this is due to delays in diagnosis, occasional absence of symptomatology, and nonspecific clinical and histologic presentations. LP may present on the vulva in one of three forms: classic, hypertrophic, and erosive. Classic LP is similar to cutaneous disease and is generally more straightforward to diagnose. Hypertrophic LP is unusual but documented on vulvar skin [37]. Erosive LP is unique to mucosal sites (including vulva and vagina) and carries particular morbidity, including impairment in sexual relations, dyspareunia, scarring with stenosis, and a small but real increased risk of developing cancer.

LP affects perimenopausal or postmenopausal adults, generally presenting in the fifth or sixth decade of life. In one large series, the mean age of presentation of vulvar LP was 57 years (range 23–87) [36] and 55 years (range 12–87) in another [38]. Presentation during childhood is rare. LP is generally believed to be an autoimmune chronic disease mediated by cytotoxic T lymphocytes to a yet undiscovered antigen [35, 39]. Cytotoxic damage to keratinocytes is the basis of the histologic features seen in LP. The cytokine profile in LP is generally a Th-1 phenotype [40].

Patients with cutaneous LP have an increased incidence of hepatitis types B and C; this association has not been detected in patients with vulvar LP, at least in a few European-based studies [36, 41]. In contrast, patients with vulvar (specifically erosive) LP have been shown to have a higher incidence of associated autoimmune disorders than in a control population. In a large case-controlled series, nearly one-third of patients with erosive LP (29%) had at least one autoimmune-associated disease, including thyroid disease, vitiligo, alopecia areata, celiac disease, and rheumatoid arthritis [42].

Patients with LP are at an increased risk to develop squamous cell carcinoma (SCC) at some sites of involvement, particularly of the lip, tongue, oral cavity, esophagus, larynx, and vulva, but notably not in cutaneous skin [43]. Cancer risk in the vulva is generally an increased likelihood of

developing SCC, which is unrelated to human papillomavirus infection [44, 45]. Although overall a rare phenomenon, vulvar SCC arises in older women, on mucosal (non-hair-bearing) surfaces of the vulva, and may be solitary or multifocal. In the largest series of vulvar SCC arising in LP (38 patients), SCC arose in the setting of erosive LP in one-third of patients and nonerosive LP in the remaining two-thirds of patients. Differentiated vulvar intraepithelial neoplasia (d-VIN) was present in the excision specimen in 22 of 38 patients, likely representing a precursor lesion [45]. SCC arising in the setting of vulvar LP is aggressive, with a large subset of patients demonstrating lymph node metastasis at presentation, high rates of recurrence, and 30% disease-related mortality [45].

Treatment of LP involving the vulva includes strategies designed to decrease symptoms and prevent scarring sequelae. Full resolution of lesions is difficult, and the disease generally runs a chronic course. Management generally involves high potency topical steroids and topical steroid-sparing agents such as tacrolimus, with progression to systemic immunosuppressive agents for refractory disease. Surgical management may be required if adhesions, stenosis, or significant scarring develop. Regular interval follow-up visits are important for surveillance given the increased risk of SCC, and biopsy is recommended for any nonhealing vulvar lesions [35, 36, 38, 46, 47].

2.4.1.1 Clinical Features

The majority of patients with vulvar LP present with complaints of soreness, burning, and pain; about half of patients may also report pruritus [47]. The symptoms reported may reflect the types of lesions the patients have, as classic LP lesions may be asymptomatic or pruritic, hypertrophic lesions tend to be itchy, and erosive lesions are painful [35]. Physical examination should not be limited to the genital skin; patients with LP usually have oral disease and may have cutaneous lesions. Hair involvement (scarring alopecia as lichen planopilaris or frontal fibrosing alopecia) and nail involvement may also be seen.

Classic LP presents as a papulosquamous disorder. Lesions consist of flat topped erythematous to violaceous papules and plaques surfaced by fine white lines called "Wickham's striae." Cutaneous lesions of LP usually involve the flexor surfaces of the extremities. When the vulva is involved, the labia majora and the interlabial sulci may show papules of LP, whereas the labia minora and clitoral hood will show flatter lesions with a white reticular network on the surface [35] (Fig. 2.11). Classic LP may clinically mimic lichen simplex chronicus, lichen sclerosus, and allergic or irritant contact dermatoses.

Erosive LP occurs on the mucosal aspect of the vulva and is usually painful. Erosive LP presents as glazed/shiny erythema that easily bleeds with any kind of manipulation. This

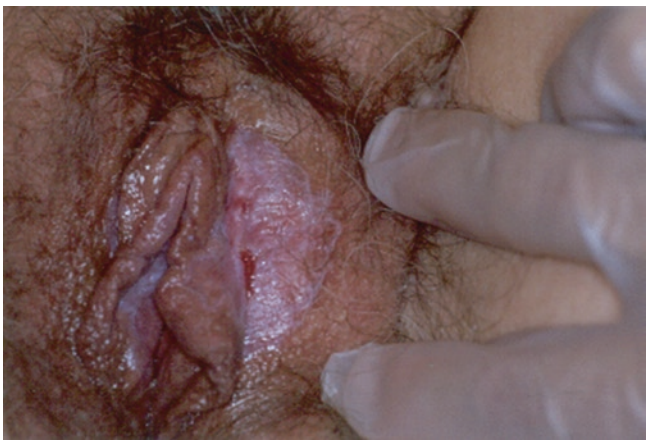

Fig. 2.11 Lichen planus. The labia are surfaced by a flat-topped lavender to white plaque with a white reticular network on the surface. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

erythema may be surrounded by a lace-like, white reticular and slightly hyperkeratotic border. Identification of this characteristic border is helpful in clinically suspecting the diagnosis, although it is not always present. Erosions are generally well demarcated and involve the inner aspect of the labia minora, the introitus, and vestibule [23, 36, 47, 48]. Over time, scarring can lead to obliteration of normal vulvar and vaginal architecture; the clitoral hood and labia may appear resorbed, there may be fusion of labia, and there may be stenosis of the vaginal opening [47]. Vaginal involvement is common in patients with erosive vulvar LP [49]. Patients with vaginal LP may present with a desquamative inflammatory vaginitis, complaining of symptoms such as irritation, painful sexual intercourse, and pain with increased vaginal secretions [50]. Nine diagnostic criteria for vulvar erosive LP have been proposed by a series of experts and include clinical signs, symptomatology, and histologic features (Table 2.4); fulfillment of three criteria is required for diagnosis [51].

Hypertrophic LP rarely presents in the vulva, but when seen, lesions will be verrucous and hyperkeratotic. Clinically, hypertrophic LP lesions will mimic condyloma or other squamous intraepithelial neoplasia, so biopsy is warranted to confirm the diagnosis.

The clinical differential of LP, particularly the erosive variant, includes lichen sclerosus (LS), graft-versus-host disease, immunobullous diseases (mucous membrane pemphigoid or pemphigus vulgaris), acute irritant or allergic contact dermatitis, infections (particularly candidiasis or herpes virus), and vulvar intraepithelial neoplasia [35, 36]. LS has significant clinical and histologic overlap, and some important distinguishing features are included in Table 2.5. Clinically, mucosal LP is more likely to involve the inner aspect of the labia and patients often have nongenital involvement (most often oral erosions and ulcerations) than LS. It should be noted that LP and LS can coexist [52].

Table 2.4 Diagnostic criteria in the diagnosis of vulvar erosive lichen planus

1. Clinical signs: Well-demarcated erosions or glazed erythema present at vaginal introitus
2. Clinical signs: Hyperkeratotic white border around erythematous areas/erosions ± identifiable Wickham's striae on skin
3. Symptoms: Pain or burning
4. Clinical signs: Scarring and/or loss of normal vulvar architecture
5. Clinical signs: Vaginal inflammation
6. Clinical signs: Involvement of other mucosal sites
7. Histologic features: Well-defined inflammatory band involving the dermal–epidermal junction
8. Histologic features: Inflammatory band predominantly composed of lymphocytes
9. Histologic features: Basal layer degeneration (Civatte bodies, basal layer keratinocyte death, abnormal keratinization)

Adapted from *Simpson RC, Thomas KS, Leighton P, and Murphy R. Diagnostic criteria for erosive lichen planus affecting the vulva: an international electronic-Delphi consensus exercise. Br J Dermatol. 2013 Aug;169(2):337–43*

Table 2.5 Clinical and histologic features to distinguish lichen planus from early lichen sclerosus

	Lichen planus	Lichen sclerosus
Age at presentation	Adults (peri- and postmenopausal)	Children and adults
Site of vulvar involvement	Inner aspects of labia minora Can involve vagina (erosive variant)	Outer aspects of labia minora, perianal skin Does not involve vagina
Associated symptoms	Burning, ulcerations, and pain > pruritus	Pruritus
Helpful clinical clues	White, reticular border around erosions Sometimes hyperkeratotic	Atrophic or hyperkeratotic, figure of eight/hourglass appearance, purpuric
Associated disease	Oral or cutaneous LP, autoimmune disease	Autoimmune disease Extragenital involvement unusual
Epidermal changes	Squamatization of basal epithelium Angulated, "saw-tooth" rete ridge pattern Hypergranulosis (wedge shaped) Less common exocytosis	No squamatization of basal epithelium Attenuated rete ridge pattern ± hypergranulosis Exocytosis of lymphocytes
Basement membrane zone changes	Obscuring inflammation No basement membrane thickening	± obscuring inflammation Thickened basement membrane
Superficial dermal changes	No homogenization of dermal collagen Preservation of elastic fibers (usually) Cytoid bodies and melanophages	Homogenization of dermal collagen (papillary dermal tips) Loss of elastic fibers Subepithelial edema Hemorrhage and hemosiderin occasionally

Graft-versus-host disease may be clinically indistinguishable from LP, but will arise in the unique setting of prior hematopoietic stem cell transplantation. Immunobullous diseases, infection, and neoplastic processes can be readily distinguished from LP through biopsy.

Given the importance (for management and prognosis) in distinguishing between LP and LS, and given the clinical overlap of LP with preneoplastic and neoplastic entities, biopsies are frequently useful and necessary in the workup of a patient with presumed vulvar LP. Ideally, the biopsy should encompass non-eroded/ulcerated skin to decrease the chances of detecting nonspecific features of inflamed ulceration [50]. The best location to take a biopsy to confirm the diagnosis is the lacy border showing Wickham striae; however, this border may not be clinically evident [36]. If autoimmune blistering diseases are being considered in the clinical differential diagnosis, additional samples for direct immunofluorescence (submitted in Michel's or Zeus medium) should be included.

2.4.1.2 Histologic Features

LP is the prototypic example of a lichenoid inflammatory reaction pattern. The histologic features of cutaneous LP are reproducible and recognizable. Erosive LP may have less specific histologic features, particularly when the epidermis is ulcerated. Familiarity with the spectrum of patterns seen may increase the diagnostic yield. In one study of 38 women with clinically confirmed vulvar LP and biopsies available, biopsy results were supportive of the diagnosis in 25 (biopsies were classified as "diagnostic" in 18 and "consistent with" in 7). The remainder of patients had nonspecific features on biopsy [36]. This further underscores this difficulty in correctly diagnosing mucosal LP.

The classic histologic features of LP include wedge-shaped hypergranulosis, angulated or serrated rete ridges (often referred to as "saw-tooth"), and a lichenoid band of inflammation in the superficial dermis which obscures the normal dermal–epidermal interface (Fig. 2.12a, b). Lymphocytes may be seen moving into the epidermis (exocytosis), and cytotoxicity to keratinocytes is evidenced by apoptotic, brightly eosinophilic keratinocytes (Civatte bodies) interspersed within the epidermis, but favoring the basal epithelial layer. Cytoid bodies are clumps of brightly eosinophilic material (degenerated keratin fragments from dying keratinocytes) that deposit in the superficial dermis. The dermal infiltrate is composed predominantly of lymphocytes, although a minor plasma cell cohort is permissible. On mucosal sites, the abovementioned features may be subtle or absent. Mucosa normally lacks a granular layer, so presence of a slight acquired granular layer on mucosa may be a histologic clue to the diagnosis. Epithelium may be attenuated and parakeratosis alternating with slight hyperkeratosis may be seen [39] (Fig. 2.13). The presence of ero-

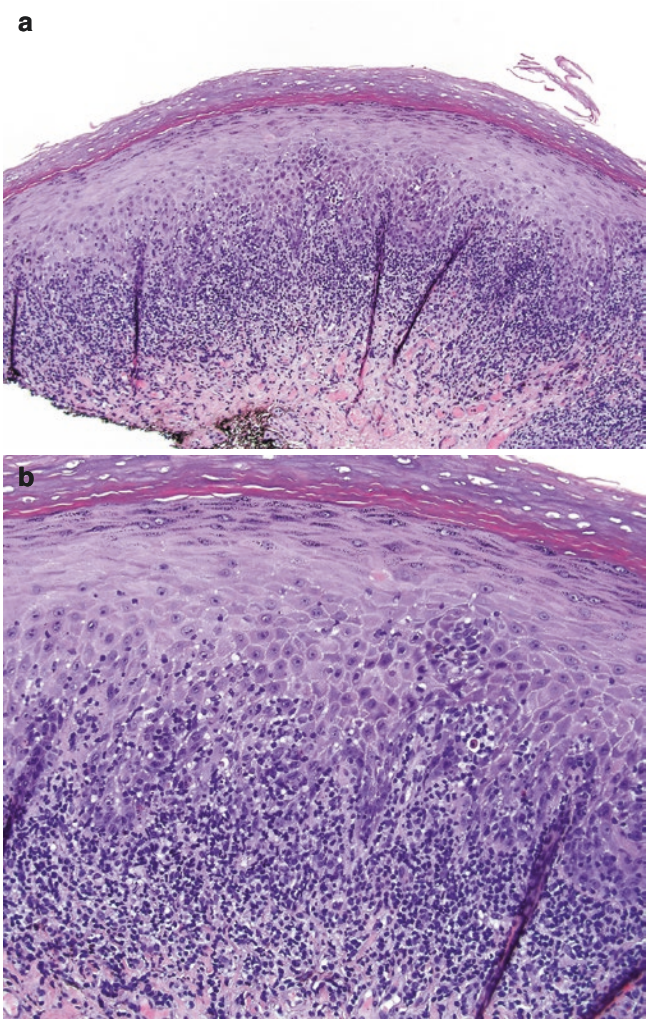

Fig. 2.12 Lichen planus. (**a**) Low-power magnification shows hyperkeratosis, hypergranulosis, and a band of inflammation that obscures the dermal–epidermal junction. (**b**) Higher power magnification demonstrates the saw tooth like rete ridge pattern, scattered dying keratinocytes approximated along the basal epidermis, and a vague "wedge-shape" can be appreciated in the hypergranulosis

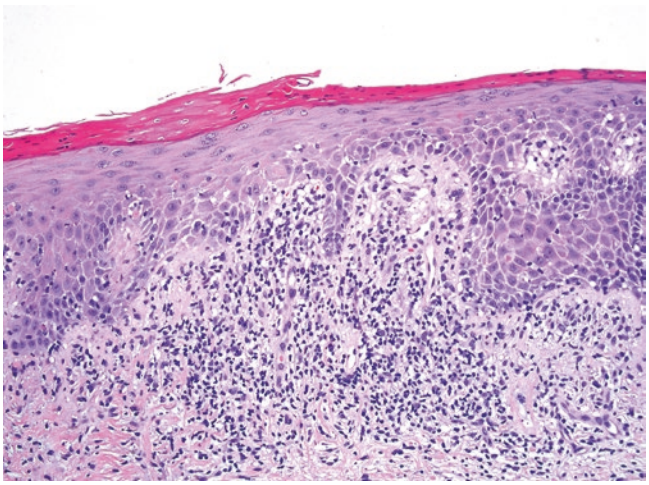

Fig. 2.13 Lichenoid dermatitis suggestive of lichen planus. There is parakeratosis with a hint of a granular layer. There is slight angulation of rete ridges with dying keratinocytes along the basilar epithelium

sion or ulceration with reepithelialization may result in reactive epithelial atypia, evidenced by nuclear enlargement, pleomorphism, and hyperchromasia. Basilar mitotic figures should not be increased and should not be atypical (if noted) [53].

2.4.1.3 Immunohistochemical Features

Ancillary testing is generally not required in the workup of LP. Direct immunofluorescence studies will be negative for any basement membrane zone or intercellular staining with immunoglobulin. However, fibrin may be apparent along the dermal–epidermal junction, and cytoid bodies may react with IgM and be visualized as small immunoreactive clumps in the superficial dermis. Ancillary stains may be useful to exclude infectious etiologies. Immunophenotyping of the inflammatory infiltrate within LP and LS has not shown any significant and distinguishing features and is therefore not useful in differentiating these two entities [54].

2.4.1.4 Differential Diagnosis

Histologic distinction between LP and early LS is known to be difficult (Table 2.5). Basal keratinocyte squamatization, hypergranulosis, pointed (rather than effaced) rete ridges, and cytoid bodies are all seen much more frequently in LP than in early LS [54]. Another study examining histologic features specifically of vulvar LP noted the relative rarity of these features [2]. One study has also suggested that wiry fibrosis and eosinophils within the infiltrate may favor LS over LP [3], and another study noted that the presence of basement membrane thickening, ectatic superficial dermal blood vessels, and early subtle sclerosis were helpful in discriminating between LS (where the features were seen) and LP (where the features were absent) [2]. Elastic fiber loss in the subepithelial space has been suggested as a helpful and differentiating feature in the diagnosis of LS [54], but other authors have reported similar elastic fiber loss in LP as well [2]. Ultimately, if a confident diagnosis cannot be made, the diagnosis of "lichenoid mucositis" may be made, with a comment detailing that the differential diagnosis includes both LP and the inflammatory phase of early LS (see further discussion in section and images below). It should be noted that LP and LS can coexist [52].

Besides LS, other histologic considerations within the differential diagnosis of LP include infection, other ulcerative diseases such as Behcet or Crohn disease, plasma cell (Zoon) vulvitis, and differentiated vulvar intraepithelial neoplasia (d-VIN). Infections (most commonly Candidiasis, herpes virus, and syphilis) may be excluded through the use of ancillary special or immunohistochemical stains. Other ulcerative conditions may show nonspecific ulceration or epithelial erosion, and both Behcet and Crohn disease may have oral involvement as well. Presence of a portion of intact epidermis to evaluate for the characteristic lichenoid infiltrate or vacuolar changes and cytotoxic damage to the epithelium that would characterize erosive LP is the most helpful

way to differentiate these disorders. While LP and plasma cell vulvitis share a dense band-like infiltrate, LP generally shows a lymphocyte predominant infiltrate, and the presence of Civatte bodies in LP will be a distinguishing feature not seen in plasma cell vulvitis [55]. In one series comparing the two entities, the presence of Civatte bodies, lymphocyte predominance, and an accentuation of the granular layer were all noted in LP but lacking in plasma cell vulvitis [55]. D-VIN is a precursor of vulvar squamous cell carcinoma. D-VIN is unrelated to human papilloma virus infection and is thought to arise through a p53-dependent pathway. D-VIN is recognized by elongated, sometimes anastomosing rete ridges, with keratinocyte atypia (atypical mitotic figures, dyskeratosis, nuclear enlargement, and prominent nucleoli) restricted to the basal layer. Although parakeratosis is present, the squamous epithelium appears overall mature and may be confused with reactive epithelial atypia on low-power evaluation. By immunohistochemistry, d-VIN often shows diffuse confluent staining for p53 (basal and suprabasilar layer only) but rarely exhibits a null pattern of reactivity (no p53 staining) compared to weak patchy (wild type) staining of non-lesional epithelium. However, inflammation and stress can prolong the half-life of the p53 protein and result in a positive staining pattern. Therefore, a positive p53 stain should be interpreted in the proper clinical and histomorphologic context. Not surprisingly, studies are mixed with regard to the utility of p53 staining as an adjunct in distinguishing reactive atypia in erosive LP from d-VIN, with some studies indicating negative patterns of staining [54], while others have reported confluent p53 positivity in a subset of biopsies of erosive LP [53].

2.4.2 Lichen Sclerosus

Lichen sclerosus (LS) is a relatively common disorder that most commonly involves genital skin, including vulvar skin and mucosa. Women are affected much more commonly than men. Estimated to represent less than 1% of patients referred to a dermatologist [56] but at least one-third of cases seen at a vulvar specialty clinic [57], LS commonly presents as genital pruritus, discomfort, and dyspareunia. The disease is chronically progressive, and, if untreated over time, LS leads to significant alteration and scarring of the genital architecture.

In contrast to LP, LS demonstrates a broad age range of presentation. Although overall rarely diagnosed in children, LS represents approximately one-fifth of the vulvar complaints in prepubertal girls [58], and childhood LS is estimated to represent between 9% and 15% of all LS cases [59, 60]. Postmenopausal women make up the second, bimodal peak in incidence of LS, but occurrence during reproductive years may also be seen.

The exact mechanism for the development of LS is not known, although an autoimmune mechanism directed against antigens in the lower epidermis has been proposed [56, 61, 62]. Chronic irritation from exposure to urine has been suggested as a contributing factor [56]. Infectious triggers have been investigated, and *Borrelia burgdorferi* has been isolated from a substantial subset of LS biopsies in Europe but not in the United States [56].

Patients with LS have been shown to have a higher incidence of associated autoimmune disorders than in control populations [56, 60]. In a large case-controlled series, nearly one-third of patients with LS (28%) had at least one autoimmune-associated disease, including thyroid disease, vitiligo, alopecia areata, celiac disease, and rheumatoid arthritis [42].

The diagnosis of LS carries with it an associated risk of developing squamous cell carcinoma. The risk of developing carcinoma is estimated at 2–5%, with differentiated vulvar intraepithelial neoplasia (d-VIN) thought to represent an important precursor lesion (see differential diagnosis section below). The average time between diagnosis of LS and diagnosis of squamous cell carcinoma is 18 years [56]. Importantly, LS and the associated risks of dysplasia and carcinoma are unrelated to infection with human papillomavirus [63].

Management of patients diagnosed with LS is multifactorial. Vulvar self-examination and routine gynecologic examination is important. Management consists of avoidance of irritants, topical emollients, and ultrapotent topical corticosteroids. Steroid-resistant LS has been managed with calcineurin inhibitors, topical retinoids, and photodynamic therapy [56]. Early diagnosis, early treatment, and treatment compliance have all been associated with improved symptomatology, decreased scarring, and prevention of disease progression [56]. Given the risk of progression to squamous cell carcinoma, routine examination and low threshold for biopsy is mandatory.

2.4.2.1 Clinical Features

Characterized clinically by white, parchment paper-like atrophy and obliteration of normal vulvar landmarks (Fig. 2.14), LS imparts considerable morbidity to patients. LS has a fairly classic clinical appearance when well established in the course of the disease; early manifestations may be more difficult to discern as there may be overlap with other entities. LS occurs most commonly on the labia majora and labia minora but also frequently involves the clitoris and perineum. In contrast to lichen planus, the vagina and cervix are not involved by LS. Classic descriptors of the appearance of well-established LS include "figure of eight," which refers to the combined involvement of the labia minora and majora, clitoris and clitoral hood, perineum, and perianal areas [56]. Lesions initially appear as ivory to white (or porcelain), flat-topped lichenoid papules. Lesions may be single and small or can involve the entire vulva and extend to involve the perineal area and inner thighs [60]. With time, the cutaneous appearance becomes more atrophic, hypopigmented, and sclerotic. Secondary fissuring, erosions, ulcerations, and lichenifica-

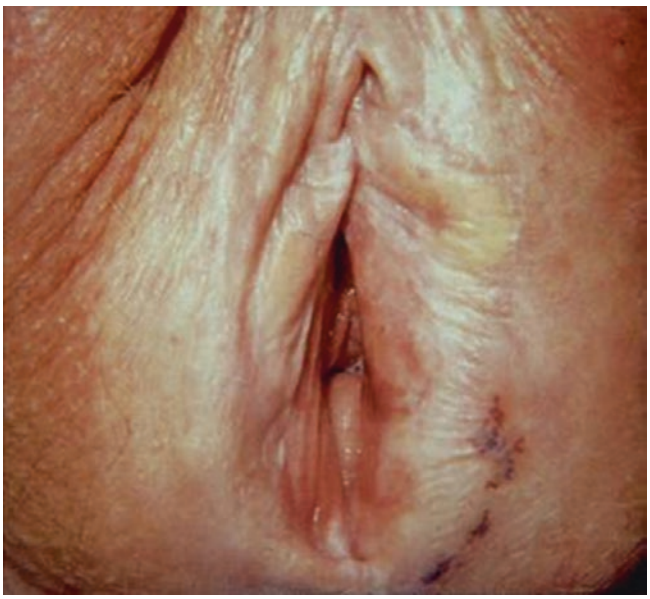

Fig. 2.14 Lichen sclerosus (well developed). White atrophic plaques encircling the vulva and obliterating normal vulvar architecture is present. There is hemorrhage into the plaques (bottom right)

tion are not uncommon. Vascular fragility may give rise to purpura and ecchymoses. Fissures and ulcerations may occur in the interlabial sulci or in the perineum [56]. Pigmentary alterations are not uncommon, and hyperpigmentation from vulvar hypermelanosis may be mistaken for a melanocytic neoplasm [61]. Over time, there may be distortion of regional anatomy, with resorption and fusion of the labia minora, stenosis of the vaginal introitus, and entrapment of the clitoris [56].

Although LS may occur at extragenital sites, extragenital manifestations are not common, and disease is often restricted to the vulva. Examination of nongenital skin may therefore be unrevealing. Oral disease or nail abnormalities are not typically seen, in contrast to lichen planus.

The appearance of thick and irregular white plaques or new ulcers and erosions in a patient with LS may herald the presence of an associated squamous cell carcinoma and should prompt biopsy [60], although the hypertrophic variant of LS may also have this clinical appearance [62].

2.4.2.2 Histologic Features

LS has a range of histologic features depending on the time course in which it is biopsied. Early in the disease, there is a lichenoid band of inflammation aligning along the dermal–epidermal junction. As the disease becomes more established, this band of inflammation is pushed down into the deep papillary/superficial reticular dermis and replaced by increasing amounts of the diagnostic hyalinized eosinophilic collagen. The spectrum of changes that may be encountered in LS is detailed below.

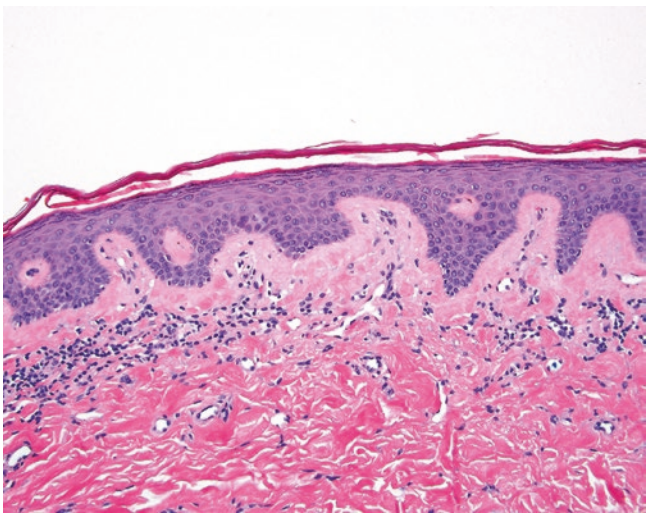

Fig. 2.15 Lichen sclerosus. The epidermal architecture is relatively preserved but there is papillary dermal homogenization with a slight band of lymphocytes in the dermis

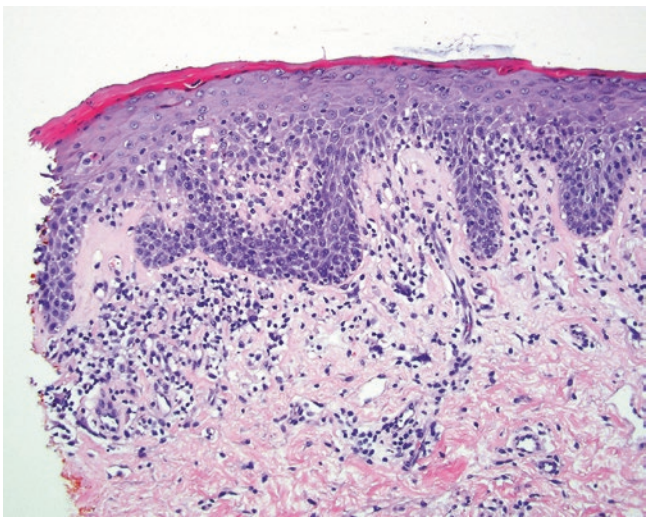

Fig. 2.16 Inflammatory phase of lichen sclerosus. There is vacuolar interface change with occasional dyskeratosis in the epidermis. There is very focal homogenized collagen in the papillary dermal tips (upper right), which suggests early lichen sclerosus

Early LS

Biopsies of early LS show a blend of a lichenoid and vaguely psoriasiform inflammatory reaction pattern. The lichenoid infiltrate is composed predominantly of lymphocytes and may be mild (limited to perivascular inflammation and lymphocyte scatter between collagen bundles) to band-like. There may be vacuolar interface alteration involving basilar keratinocytes, and occasional dyskeratosis may be noted. The epidermis in LS may be atrophic, and there is often overlying hyperkeratosis. Requisite for the diagnosis of LS is the deposition of homogenized eosinophilic papillary dermal collagen (Fig. 2.15). This material may be only very focal (or not at all visible) in very early cases of LS

(Fig. 2.16), and thus diagnosis at this early stage may be difficult. When sclerosis is not prominent or even absent (estimated in one study to occur in about 40% of biopsies of LS), the most helpful clues to arriving at the correct diagnosis include minute foci of homogenized tissue in dermal papillae, marked thickening of individual papillary dermal collagen fibers, and thickening of the papillary dermis as a whole, with lymphocytes aligned linearly between wiry collagen fibers [3, 64]. Basement membrane zone thickening has been suggested as a clue helpful to differentiate LS (present) from LP (absent) [54]. Of note, some authors have suggested that even lesions of long clinical standing may demonstrate this psoriasiform and lichenoid pattern, and thus designation of "early" LS may be misleading [62, 64]. Biopsies demonstrating the features described above may have significant histologic overlap with other entities. It may therefore be necessary (and in the patient's best interest [2]) to avoid assigning a definitive diagnosis if there are insufficient features for an unequivocal diagnosis. Reports may be signed out as "Lichenoid dermatitis," with a comment indicating that the differential includes the early inflammatory phase of LS, as well as other entities such as lichen planus, fixed drug eruption, or even spongiotic dermatitis.

Late LS

Biopsies of established LS have relatively classic and distinctive features. The epidermis may be atrophic or acanthotic, and there may be subtle basal vacuolar change along the dermal–epidermal junction. There is often compact hyperkeratosis and follicular hyperkeratosis. The rete ridges of the epidermis often become effaced, which ultimately can result in detachment of the epidermis from the dermis. In one large series evaluating LS, approximately 60% of cases were found to have the characteristic broad papillary dermal homogenization [64]. This altered dermal collagen lacks cellularity and appears amorphous. Blood vessels may become fixed within the sclerosis, resulting in fragility and easy disruption with subsequent hemorrhage (Fig. 2.17). Evidence of remote hemorrhage may be seen in scattered hemosiderin laden macrophages in the dermis.

Pushed down below the sclerotic papillary dermal collagen is generally a lymphocyte-rich infiltrate. Sparse perivascular and interstitial lymphocytes or a dense band of lymphocytes may be seen. Eosinophils are never a large component of the infiltrate, but may be seen, possibly indicating an associated hypersensitivity component [3]. Together, all of these features impart a zonal appearance to the biopsy that has been termed the red, white, and blue sign (Fig. 2.18): epidermis (pink or red), band of sclerosis (white), and band of inflammation (blue).

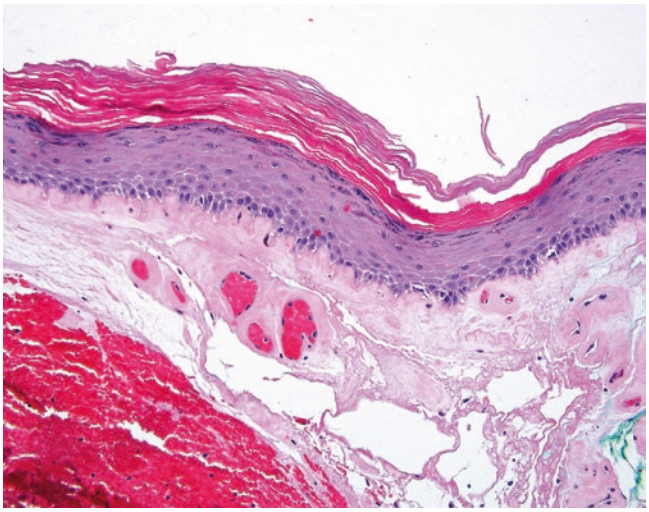

Fig. 2.17 Long-standing lichen sclerosus. There is attenuation of the epidermal rete ridge pattern, hyperkeratosis, and a broad band of homogenized dermal collagen with entrapped dilated vessels. Inflammation is minimal

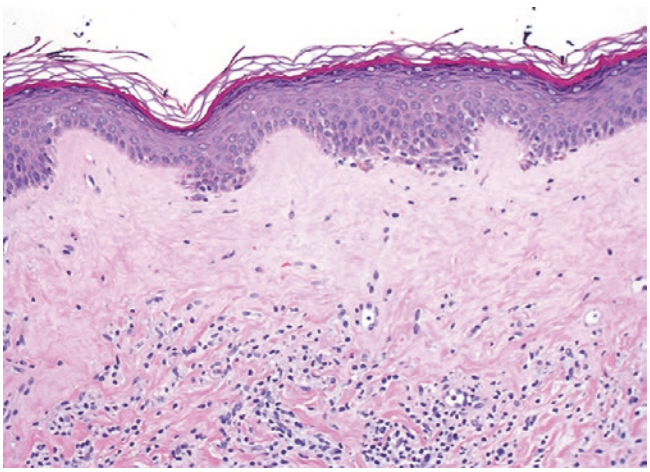

Fig. 2.18 Lichen sclerosus: the red, white, and blue sign. The zonal appearance in classic lichen sclerosus shows epidermis (pink or red) on top of a band of sclerosis (white) with underlying band of inflammation (blue). Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

Hypertropic LS

The hypertrophic variant of LS may have epidermal thickening (acanthosis), hypergranulosis, and orthokeratosis rather than the more usual epidermal atrophy (Fig. 2.19). This may in part arise due to repetitive rubbing and scratching of lesions of LS. While dyskeratosis and parakeratosis in such specimens are permissible and do not seem to pose an increased risk of progression to SCC, hypertrophic LS should not show nuclear atypia, basal cell crowding and disarray, or increased mitotic activity [62]. Parakeratosis, when seen, is often present in vertical columns. Hypertrophic LS is less likely to have obvious, well-defined dermal sclerosis and may appear more fibrotic.

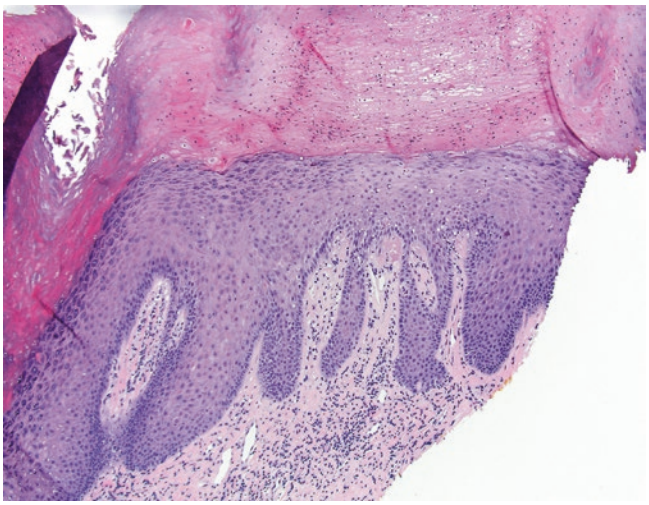

Fig. 2.19 Hypertrophic lichen sclerosus. Marked epithelial hyperplasia, columns of parakeratosis, and focal homogenization of collagen in papillary dermal tips

2.4.2.3 Immunohistochemical Features

Immunohistochemical staining is not required for the diagnosis of LS. Special stains may be utilized if there are features that suggest the possibility of coexistent infection. The use of elastic tissue stains may be helpful to establish loss of papillary dermal elastic fibers. In the author's experience, and as might be expected, the most robust loss of elastic fibers is seen in established lesions, where the diagnosis is less often in question. Immunohistochemical studies have identified a Th1 cytokine profile in the inflammatory milieu of LS (increased staining for IFN-γ, TNF-α, IL-1, CD25, IL-11a), but these stains are not routinely used in establishing the diagnosis and patterns are shared with other inflammatory disorders [65]. Tissue matrix metalloproteinases (MMP) and their inhibitors have been investigated as important to the collagen remodeling and sclerosis that occurs in LS, and MMP 2 and 9 have been shown to be increased by immunohistochemistry in biopsies of LS [66].

2.4.2.4 Differential Diagnosis

The differential diagnosis of LS varies depending on whether one is considering an early or established lesion. Early LS and lichen planus (LP) have considerable overlap both histologically and clinically and comprise one of the most important differentials. Histologic distinction between early LS and LP is known to be difficult (Table 2.5). Basal keratinocyte squamatization, hypergranulosis, pointed (rather than effaced) rete ridges, and cytoid bodies are all seen much more frequently in LP than in early LS [54]. However, another study examining histologic features specifically of vulvar LP noted the relative rarity of these features [2]. It has been suggested that wiry fibrosis and eosinophils within the infiltrate may favor LS over LP [3], and the presence of basement membrane thickening, ectatic superficial dermal blood vessels, and early subtle sclerosis have been described as helpful in discriminating between LS (where the features were seen) and LP (where the features were absent) [2]. Elastic fiber loss in the subepithelial space has been suggested as a helpful and differentiating feature in the diagnosis of LS [54], but other authors have reported similar elastic fiber loss in LP as well [2, 64]. Melanophages may be more common in LP than in LS [64]. Ultimately, if a confident diagnosis cannot be made, the diagnosis of "lichenoid dermatitis/mucositis" may be made, with a comment detailing that the differential diagnosis includes both LP and the inflammatory phase of early LS.

Other entities within the differential diagnosis of early LS include psoriasis, lichen simplex chronicus (LSC), irritant or allergic contact dermatitis, candidiasis, and mycosis fungoides (cutaneous T-cell lymphoma). Psoriasis and LSC in particular have considerable overlap with the hypertrophic variant of LS. Careful examination for the subtle, early papillary dermal homogenization will secure the appropriate diagnosis of LS. LSC generally lacks a lichenoid infiltrate in the dermis and the columns of vertical parakeratosis that can be seen in hypertrophic LS [62]. Psoriasis demonstrates suprapapillary thinning, hypogranulosis, and intraepidermal neutrophils. Irritant or allergic contact dermatitis shows less pronounced and less regular epidermal hyperplasia, more spongiosis and a polymorphous infiltrate in the dermis. Mycosis fungoides generally lacks dyskeratosis within the epidermis and in the best case scenario will show lymphocyte atypia.

The histologic differential diagnosis of established LS includes other sclerosing disorders of the skin, namely morphea, radiation dermatitis, and sclerodermoid graft-versus-host disease. Morphea is a sclerosing disorder of the reticular dermis and subcutis, in contrast to the sclerosis of the papillary dermis that typifies LS. In morphea, swollen collagen bundles replace adnexal structures and infiltrate into the subcutis, without an increase in the number of fibroblasts. Chronic radiation dermatitis has considerable overlap with LS but in general tends to have less inflammation, prominent dilated vessels, and stellate hyperchromatic fibroblasts. Radiation dermatitis can also extend more deeply into the reticular dermis than LS. Sclerodermoid graft-versus-host disease may be virtually indistinguishable although may extend more deeply into the reticular dermis and arises in the specific clinical setting of a prior hematopoietic stem cell transplant.

When evaluating a biopsy for LS, care should be taken to evaluate for the possibility of coexistent or background differentiated vulvar neoplasia (d-VIN). d-VIN is a precursor of vulvar squamous cell carcinoma (SCC). d-VIN is unrelated to human papilloma virus infection and is thought to arise through a p53-dependent pathway. d-VIN is recognized by

elongated, sometimes anastomosing rete ridges, with keratinocyte atypia (atypical mitotic figures, dyskeratosis, nuclear enlargement, and prominent nucleoli) restricted to the basal layer. Although parakeratosis is present, the squamous epithelium appears overall mature and may be confused with reactive epithelial atypia on low-power evaluation. Retrospective review of a cohort of biopsies from patients with LS who ultimately progressed to SCC led to revised diagnoses of d-VIN in 42%, leading authors to speculate that d-VIN is underdiagnosed in biopsies of LS [67]. The authors also noted that in biopsies from patients whose biopsies showed LS without meeting criteria for d-VIN but who ultimately progressed to squamous cell carcinoma, parakeratosis, dyskeratosis, hyperplasia, and basal cell atypia were more often noted [67], although this conclusion has been called into question by another study [62]. Of note, by immunohistochemistry, d-VIN often shows diffuse confluent staining for p53 (basal and suprabasilar layer only) but rarely exhibits a null pattern of reactivity (no p53 staining) compared to weak patchy (wild type) staining of non-lesional epithelium. However, inflammation and stress can prolong the half-life of the p53 protein and result in a positive staining pattern [68]. Therefore, a positive p53 stain should be interpreted in the proper clinical and histomorphologic context.

2.4.3 Plasma Cell (Zoon) Vulvitis

Plasma cell vulvitis (PCV) has also been named Zoon vulvitis or vulvitis plasmacellularis. First described as a disorder affecting mucosal surfaces of the uncircumcised penis (Zoon balanitis), subsequent reports documented similar presentations and corresponding histologic features at other mucosal sites, including the vulva. The term "idiopathic lymphoplasmacellular mucositis-dermatitis" has been proposed as a unifying terminology for similar conditions now reported on virtually all mucosal sites [55]. PCV has been suggested to represent a mucosal reaction pattern to chronic irritation, moisture, and friction [69]. Poor hygiene and perspiration have also been proposed as predisposing factors and at least one author has postulated an autoimmune reaction to a yet unidentified mucosal antigen [70].

The disorder most often presents in middle age females but wide ranges of age presentation have been reported [69, 71]. There is frequently a significant (several year) delay in diagnosis, speculated to be due to a combination of patient factors and unfamiliarity of physicians with the condition [71].

PCV is thought to be idiopathic and patients generally lack associated diseases or syndromes, although rarely PCV has been reported in the setting of autoimmune polyglandular endocrine failure [70], hypothyroidism [72], and lichen sclerosus [73]. PCV does not seem to indicate a risk of transformation to or subsequent development of squamous cell carcinoma.

Treatment of PCV is often difficult. Topical steroids have been suggested as beneficial [72, 74], as has imiquimod [73]. In some patients, lesions persist over years but slow resolution without treatment is possible [1].

2.4.3.1 Clinical Features

Patients present most often complaining of pruritus, burning, and dyspareunia; however, a minority of patients may be asymptomatic [69, 71]. Patient-reported symptoms are frequently severe and may affect quality of life [71].

Clinically, lesions may present singly or as multiple bright red, red-orange to red-brown, well-circumscribed glistening or shiny erythematous macules or patches [69, 71] (Fig. 2.20). Erosions, epithelial friability, and the presence of pinpoint "cayenne pepper" petechial spots may sometimes be seen and are supportive of the diagnosis. Only mucosal-lined vulvar surfaces are involved, with one series reporting sites of common involvement to include (in order of decreasing frequency) the introitus, inner face of the labia minora, the periurethral area, vulvar vestibule, and clitoris [71]. Multifocal involvement of the vulva does not necessarily correlate with increasing severity of symptoms.

The clinical differential diagnosis may include squamous intraepithelial neoplasia, squamous cell carcinoma, extramammary Paget disease, blistering disorders, infectious etiologies, erosive lichen planus, and fixed drug eruption. Given this differential diagnosis, clinicians should have a low

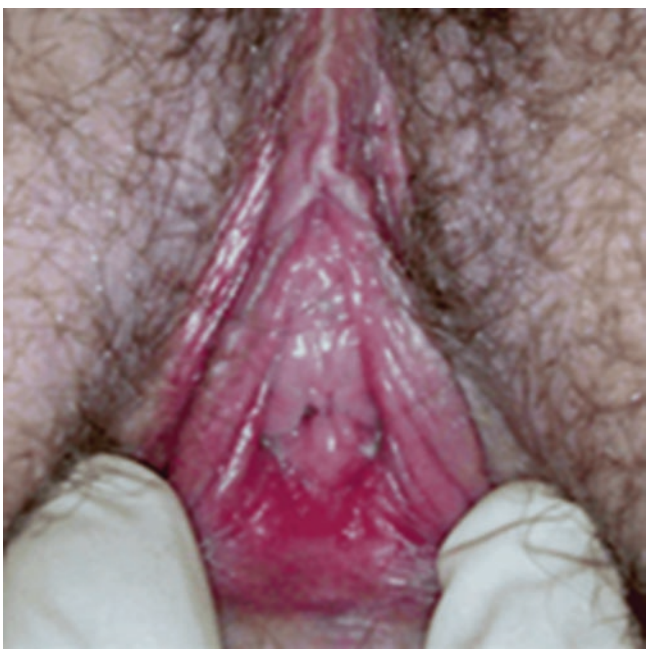

Fig. 2.20 Plasma cell vulvitis. A glistening red patch on vulvar mucosa. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

threshold for biopsy, which will readily be able to ascertain the presence or absence of cancer. Distinction between other entities which have some histologic overlap are discussed further in the section below.

2.4.3.2 Histopathologic Features

Low-power histopathologic examination reveals an attenuated mucosal epithelium with a dense band of inflammation obscuring the mucosal/submucosal junction. Epithelial atrophy is seen commonly (in approximately two-thirds of cases), but occasionally acanthosis can be present [55] (Fig. 2.21). Erosion of the epithelium is more often visualized than frank ulceration (Fig. 2.22). Higher power examination may show focal vacuolar change at the mucosal-submucosal junction, exocytosis of neutrophils into the epithelium, and diamond- or "lozenge"-shaped keratinocytes in the suprabasal layer (Fig. 2.23). The lozenge-shaped keratinocyte was defined as a diamond-shaped suprabasilar keratinocyte that is wider than it is tall [55]. The frequency of identifying these distinctive keratinocytes in PCV ranges from rare to approximately 50% [55, 75]. Within the dermis/submucosa of PCV, there is consistently a dense band-like infiltrate rich in plasma cells. Admixed neutrophils, eosinophils, lymphocytes, and mast cells may be present, but the majority of the cells (greater than or equal to 50%) should be plasma cells. Intermediate numbers of plasma cells (25–50%) with additional supportive histologic features and a congruent clinical impression are permissible, but fewer than 25% plasma cells has generally been found to be nonspecific and site related and thus should draw into question the diagnosis of PCV [75]. Erythrocyte extravasation and hemosiderin deposition is a frequently identified feature, leading some authors to postulate a relationship to pigmented purpura and lichen aureus in particular [69]. Vasculature may be prominent with dilated vessels, and fibrosis may be appreciated [55, 74]. Occasionally, mucinous metaplasia has been reported in the epithelium, which can lead to erroneous diagnosis of extramammary Paget disease if the pathologist is unaware of this phenomenon in PCV [76]. Mucinous metaplasia, when present in PCV, shows a uniform replacement of the normal epithelium, no cytologic atypia, and no pagetoid spread of mucin-containing cells, thus helping to differentiate it from Paget disease [76].

In reality, all of the above-described features may not be identified. The most consistently present features of PCV

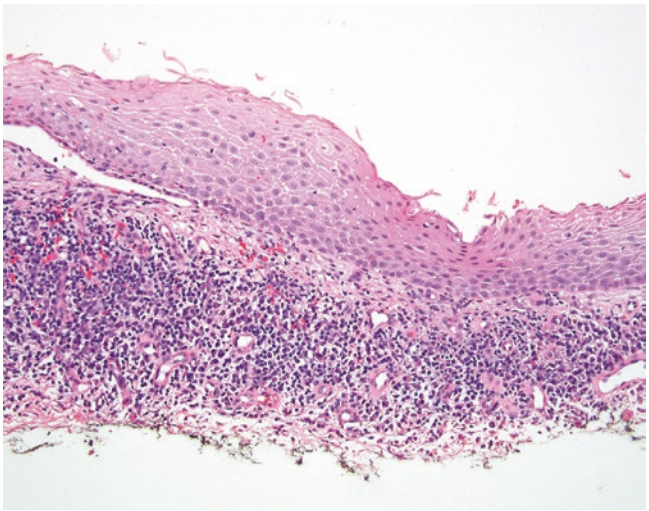

Fig. 2.21 Plasma cell vulvitis. Mucosal epithelium with an underlying band of inflammation rich in plasma cells is present. Dermal hemorrhage can also be appreciated

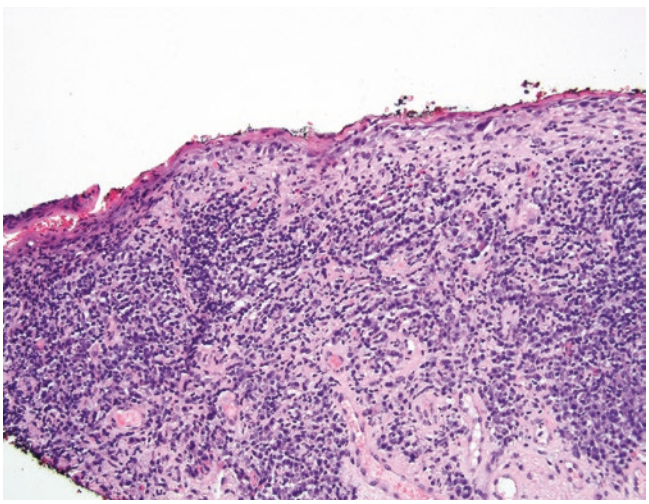

Fig. 2.22 Plasma cell vulvitis. Mucosal erosion or ulceration is commonly present in plasma cell vulvitis. The inflammatory infiltrate in the dermis is almost exclusively plasma cells

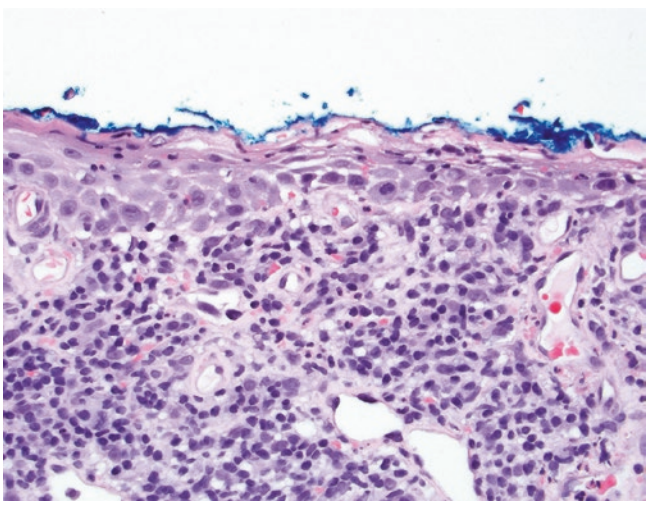

Fig. 2.23 Plasma cell vulvitis. High-power magnification reveals occasional "lozenge-shaped" keratinocytes, suprabasilar keratinocytes wider than they are tall

include the dense band of polyclonal plasma cells admixed with other inflammatory cell types and erythrocyte extravasation with hemosiderin deposition. More variable in their presence, but helpful features when present, include the distinctive lozenge-shaped keratinocytes and epithelial erosion or ulcer [55, 75].

2.4.3.3 Immunohistochemical Features

Ancillary testing in the evaluation of PCV involves exclusion of infectious etiologies. This may be accomplished by immunohistochemical staining for herpes virus and treponemal organisms, and PAS or GMS stains to exclude a fungal infection. An iron stain (Prussian blue or Perl's) may be useful to confirm the impression of hemosiderin deposition but is not requisite. If there is histologic concern for a plasma cell neoplasm, immunohistochemical stains or in situ hybridization should reveal a polytypic mix of kappa- and lambda-expressing light chains.

2.4.3.4 Differential Diagnosis

The histologic differential diagnosis includes lichen planus, other lichenoid dermatoses, infections (syphilis, Lyme, and herpes, among others), and contact dermatitis.

While lichen planus and PCV share a dense band-like infiltrate, lichen planus generally shows a lymphocyte predominant infiltrate, and the presence of Civatte bodies in lichen planus will be a distinguishing feature not seen in PCV [55]. In one series comparing the two entities, the presence of Civatte bodies, lymphocyte predominance, and an accentuation of the granular layer were all noted in lichen planus but lacking in PCV [55].

Syphilis typically demonstrates a plasma-cell-rich infiltrate. This possibility can and should be excluded with immunohistochemistry for *Treponema pallidum* and recommendations to the clinician to correlate with serological and laboratory data.

In cases with intermediate numbers of plasma cells (20–50%) and the absence of readily identifiable hemosiderin deposition, it may be more prudent to offer a descriptive diagnosis of lichenoid mucositis with a differential diagnosis to include PCV, lichen planus, fixed drug eruption, or a lichenoid contact reaction.

2.4.4 Other Diseases with a Lichenoid and Interface Pattern

Other diseases may demonstrate a lichenoid or interface inflammatory reaction pattern. They are mentioned here briefly for completeness. Histologically they may demonstrate identical features ranging from focal interface alteration and rare dyskeratosis to full thickness epidermal necrosis with a variable dermal infiltrate.

2.4.4.1 Erythema Multiforme, Stevens Johnson Syndrome, and Toxic Epidermal Necrolysis

Entities such as erythema multiforme (EM), Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) exist on a clinical spectrum defined by the clinical appearance, the involvement of mucosal surfaces, and the percent of body area affected by blistering or desquamation. EM is a rash with targetoid to blistering appearing clinical lesions and may be precipitated by infection (herpes virus or *Mycoplasma* infections are classic offenders) or by exposure to a drug. SJS and TEN are life-threatening blistering disorders often due to an adverse drug effect, presenting clinically with widespread erythema progressing to desquamation of the skin and mucosa. About 75% of patients with TEN will have genital lesions, with the vulva involved more often than the vagina [77]. Significant loss of full thickness epidermis puts affected patients at risk for water loss, temperature instability, and infection, which comprises the major causes of morbidity and mortality. The vulva may be involved in EM, SJS, or TEN, but as there is usually other skin and mucosal involvement, it would be an unusual choice to biopsy the vulva to establish the diagnosis [23]. EM is generally self-limited, and SJS/TEN are treated supportively after removal of any identifiable inciting drug. Long-term scarring sequelae may result from severe SJS and TEN, but fortunately is seen in only a minority of patients [77]. Adenosis (the presence of glandular epithelium in the surface epithelium) has been reported following SJS and TEN [78, 79].

2.4.4.2 Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) arises in the setting of post hematopoietic stem cell transplant and may be acute (fewer than 100 days after transplant) or chronic (greater than 100 days after transplant). It results when donor lymphocytes recognize the host tissue as foreign and generally affects the skin, gastrointestinal tract, liver, and lung. Genital involvement is estimated to occur in approximately one-quarter to one-half of patients with GVHD [80, 81], although the disease is often under-recognized despite its considerable impact on patients' quality of life [82]. Most gynecologic complications arise between 7 months to 1 year after transplant, presenting with symptoms that include vulvar dryness, irritation and pain, and dyspareunia [1, 80]. Clinically, genital involvement by GVHD presents on a spectrum with erythema in mild cases and labial fusion, scarring and vaginal stenosis in severe cases. The vulva is usually affected before the vagina. Individual lesions can mimic both lichen sclerosus and lichen planus clinically, as pale, hypopigmented atrophic plaques or white reticulated patches, respectively [82]. Ulcerations, fissuring, and erosive plaques are signs of greater severity. While vulvar GVHD usually arises in con-

cert with extragenital manifestations, rarely genital GVHD may occur in isolation [82].

Early detection and treatment with topical immunosuppressants and estrogens decrease the long-term severe sequelae [83]. Routine gynecological exams are of importance as posttransplant patients are at increased risk of human papilloma virus and subsequent cervical cancer. Use of immunosuppressive therapy also predisposes patients to other genital infections, such as herpes virus and *Candida* [82].

2.4.4.3 Fixed Drug Eruption

Fixed drug eruption (FDE) is a peculiar specific drug reaction whereby systemic ingestion of a drug leads to a reproducible mucocutaneous reaction. Clinically, one or several well-demarcated annular plaques appear after ingestion of a triggering drug, most often anti-inflammatory drugs (nonsteroidal anti-inflammatory drugs), antibiotics, and sedatives [23]. Any mucosal or cutaneous site may be involved, with women having a high incidence of FDE on distal extremities, while men have a high rate of FDE on genital skin and mucosa [84]. Genital sites are thought to comprise about 20% of FDEs [23]. Vulvar involvement is not uncommon, with both vulvar keratinized skin and mucosa being affected by FDE. In one series of vulvar FDE, women ranged in age from 15 to 84 at presentation [85]. Classically, FDE presents as round erythematous lesions, but on the vulva lesions may be bilaterally symmetric, erosive and non-pigmenting making it more difficult to recognize [1, 85]. FDE is usually locally symptomatic, with patients complaining of intense itching, stinging, or burning at the site of inflammation [23].

FDE is a Type IV hypersensitivity reaction, so the first presentation of FDE may be several weeks after exposure to an offending drug, but subsequent drug exposures shorten the latency to lesion development. In one study, lesions appeared on average 2 days after exposure to the drug [84]. With removal of the drug, the inflammation dissipates but classically leaves residual hyperpigmentation; however, post-inflammatory hyperpigmentation is less common in the vulva [85]. Reexposure to the drug results in inflammation in the same anatomic location as previously. Overall, a high index of suspicion is required to diagnose FDE as the clinical signs and histology may be relatively nonspecific, post-inflammatory pigmentation may not be present in the vulva, and a link to the offending medication may not be recognized. Once identified as a FDE, treatment involves removal of the triggering drug.

2.4.4.4 Histologic Features

The histopathologic features for EM, SJS, TEN, GVHD, and FDE are remarkably similar and thus considered together. They also show histologic overlap with previously discussed entities such as early lichen sclerosus, lichen planus, and plasma cell vulvitis. There is vacuolar interface dermatitis with orthokeratosis (parakeratosis is generally absent). Dying keratinocytes are peppered throughout the epidermis. The degree of dyskeratosis may range from focal and only apparent upon careful, high power evaluation (as in low-grade, acute GVHD) to moderate (as in classic examples of EM and FDE) (Fig. 2.24) to extensive (as in classic SJS/TEN). In low-grade acute GVHD, dyskeratosis may be very focal; more severe clinical examples are associated with more extensive cytotoxicity to keratinocytes. Satellite cell necrosis (the presence of lymphocytes surrounding a dying keratinocyte in the epidermis) is a buzzword for GVHD, but the finding is not specific nor always identified. With sufficient damage to keratinocytes, there may be formation of a subepidermal blister and full thickness necrosis of the epidermis (Fig. 2.25). Complete loss of the epidermis may lead to an appearance of nonspecific ulceration with or without

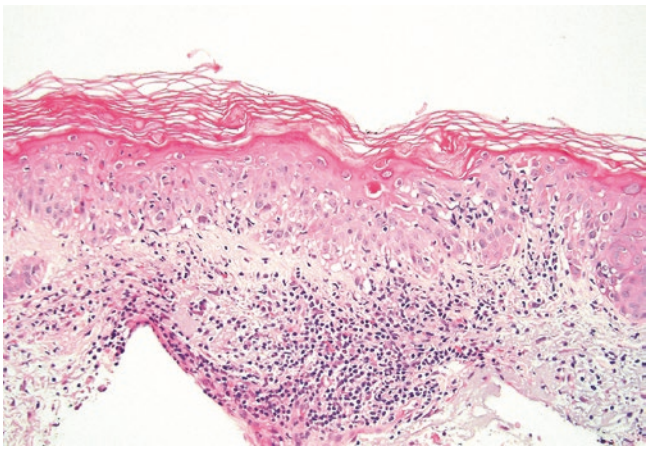

Fig. 2.24 Interface dermatitis. This is an example of erythema multiforme, showing dyskeratosis at all levels of the epidermis, orthokeratosis, and a moderate dermal inflammatory infiltrate

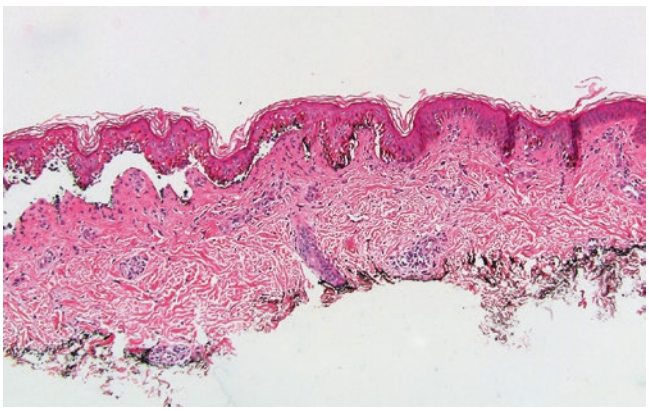

Fig. 2.25 Interface dermatitis. Cytotoxic damage to the epidermis has resulted in a subepidermal blister in this case of Stevens Johnson syndrome/toxic epidermal necrolysis. The dermis is almost devoid of inflammation

dermal inflammation. Nonspecific and nondiagnostic biopsies are common in vulvar FDE [85].

Within the dermis of these entities there may be sparse to robust inflammatory infiltrate. SJS/TEN and GVHD tend to have a sparse inflammatory dermal infiltrate. EM generally has more inflammation and FDE, particularly if active, has a more florid mixed inflammatory infiltrate comprised of lymphocytes, histiocytes, eosinophils, and neutrophils. The infiltrate in FDE can extend more deeply than EM and other lichenoid/interface dermatoses. The paradoxical presence of orthokeratosis (signifying acute onset) at the same time melanophages are prominent in the dermis (suggesting chronicity) is sometimes a clue to FDE, although in the vulva these changes may not be present as post-inflammatory pigmentation is usually minimal or absent at this site (Fig. 2.26).

Of note, in EM/SJS/TEN, the degree of epidermal damage and inflammation does not always correlate with the clinical severity of disease; this author has seen full thickness epidermal necrosis in EM and only moderate dyskeratosis in biopsies clinically compatible with TEN. In the author's opinion, the best way to handle such biopsies is to report "Interface dermatitis, compatible with the clinical spectrum of EM/SJS/TEN." Similarly, a biopsy of GVHD can support the diagnosis but is rarely in and of itself fully diagnostic. Acute GVHD and adverse drug reactions have both clinical and histologic overlap and no histologic features have been determined to definitively distinguish between the two. The diagnosis of FDE can be made fairly confidently if there is a clinical impression of a fixed plaque that becomes inflamed with ingestion of an offending agent coupled with the above-described histology, but as mentioned above, this scenario may be uncommon at genital sites.

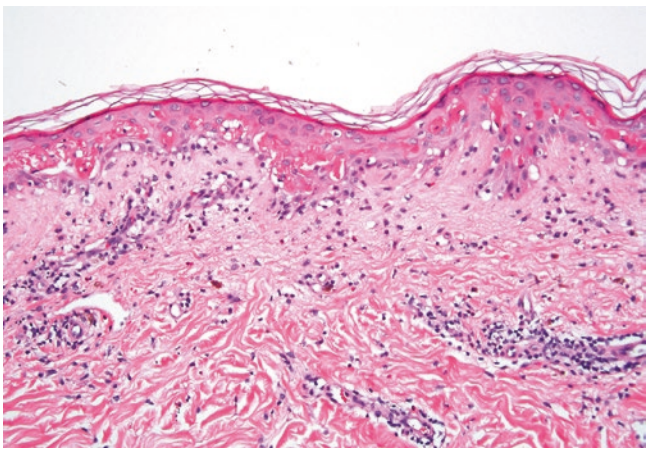

Fig. 2.26 Interface dermatitis. In this example of a fixed drug reaction, you can appreciate numerous dying keratinocytes in the epidermis. There is a sparse dermal infiltrate including neutrophils and eosinophils, and you can also appreciate some sparse melanin pigment in the dermis. Often fixed drug eruptions are more inflammatory than this case

2.4.4.5 Differential Diagnosis

The differential diagnoses for these entities include lichen planus, the inflammatory phase of lichen sclerosus, plasma cell vulvitis, and autoimmune-mediated blistering disorders. In lichen planus, dying keratinocytes are generally confined to the lower levels of the epidermis, and the infiltrate is brisk, with saw-tooth rete ridges and overlying hypergranulosis. The inflammatory phase of lichen sclerosus may have considerable overlap, but if homogenization of dermal collagen can be identified, even focally, the diagnosis can be favored. Lichen sclerosus also less likely presents as erosive or blistering plaques, so clinical impression may be useful if available in parsing out the differential. Plasma cell vulvitis will have a plasma-cell-rich infiltrate without epidermal necrosis or dyskeratosis. Autoimmune blistering diseases will show blister formation (intra- or subepidermal) without interface dermatitis or dyskeratosis. Positive direct immunofluorescence studies are useful to confirm the diagnosis (see Sect. 2.5).

2.5 Blistering Diseases and Acantholytic Disorders Affecting the Vulva

Blistering diseases and acantholytic processes generally result from a defect in normal adhesion between keratinocytes. The adhesion between keratinocytes and the dermis may also be abnormal and result in a blistering process. Most acquired blistering diseases affecting the vulva are in the pemphigus family of diseases (including pemphigus vulgaris and pemphigus vegetans, both discussed more in depth below) and are autoimmune-mediated with targets against cell–cell adhesion molecules. Blistering diseases can also result in subepithelial blisters, as in mucous membrane (cicatricial) pemphigoid or linear IgA bullous dermatosis. Acantholytic disorders are generally inherited due to a genetic defect in similar proteins involved in cellular adhesion. Pertinent details distinguishing diseases with a blistering reaction pattern are detailed in Table 2.6.

2.5.1 Intraepidermal Blistering Diseases: Pemphigus Vulgaris, Pemphigus Foliaceous, and Pemphigus Vegetans

Pemphigus vulgaris (PV) and its related variants pemphigus foliaceous (PF) and pemphigus vegetans (PVeg) are diseases with considerable morbidity which greatly affect patient's quality of life. Vulvar involvement, including the vulvar skin and mucosa, is relatively common in patients with PV and PVeg, whereas PF only rarely involves genital mucosa. The genital tract is thought to be the second most affected site (after oral mucosa) in PV, found in approximately one-third

Table 2.6 Blistering disorders affecting the vulva

Disorder	Clinical presentation	Autoimmune mediated?	Histologic features	Direct immunofluorescence results
Pemphigus Vulgaris	Flaccid blisters and erosions Mucous membrane involvement common	Yes	Suprabasilar acantholysis (intraepidermal blister)	Intercellular staining of keratinocytes by IgG and C3
Pemphigus Foliaceous	Superficial erosions of cutaneous skin; mucous membrane involvement unusual	Yes	Acantholysis in the corneal or granular layer	Intercellular staining of keratinocytes by IgG and C3
Pemphigus Vegetans	Verrucous plaques with maceration in intertriginous areas	Yes	Intraepidermal blister with acanthosis and eosinophilic microabscesses; acantholysis may be only focal	Intercellular staining of keratinocytes by IgG and C3
Mucous Membrane Pemphigoid	Tense blisters on an erythematous base Healing with scarring Vulvar involvement common, along with oral and conjunctiva	Yes	Subepidermal blister with eosinophils Subepithelial scarring possible	Linear IgG and C3 deposited along basement membrane zone
Bullous pemphigoid	Tense blisters on an erythematous base Vulvar involvement unusual	Yes	Subepidermal blister with eosinophils	Linear IgG and C3 deposited along basement membrane zone
Linear IgA bullous dermatosis	Annular lesions clustered with rimming by blisters or crusting	Yes	Subepidermal blister with neutrophils	Linear IgA (±C3) deposited along basement membrane zone
Hailey–Hailey disease	Intertriginous papules and plaques with maceration and erosion	No	Full thickness epidermal acantholysis; dyskeratosis unusual	Negative
Darier disease	Hyperkeratotic papules on face, chest, neck, back, ears, and groin	No	Acantholysis and dyskeratosis; corps ronds and grains; involvement of follicles	Negative
Papular Acantholytic Dykeratosis	Keratotic lesions limited to vulvar folds and upper thighs	No	Can look like Hailey Hailey disease or Darier disease	Negative

to one-half of patients with the disease [86–88]. Rarely, vulvar involvement by PV may be the sole manifestation of the disease [89]. Patients present in adulthood, with mean age of presentation generally in the early 40s to early 50s [86, 88, 90]. In some studies, women are slightly more commonly affected [90], while other studies note similar incidences in men and women [88].

Desmosomes are a multi-protein complex located on cell surface membranes designed to ensure that keratinocytes stay connected to their neighbors. Pemphigus is an acquired, autoimmune-mediated blistering disease due to autoantibodies targeting the desmoglein proteins of the desmosome. Desmoglein 3 is the main target in PV and PVeg, while desmoglein 1 is the main target in PF. IgG autoantibodies against this/these protein(s) are generated, leading to an incompetent connection to adjacent keratinocytes and altered subsequent downstream signaling [91]. This altered downstream signaling may involve further destruction of the desmosomal protein complex [91]. The resultant loss of cell–cell adhesion results in acantholysis and an intraepidermal blister that is visualized histologically. Desmoglein 3 in particular is highly expressed in mucosal epithelium, which is why patients with PV almost always have mucosal involvement. Desmoglein 1 has lower expression in mucosal epithelium, resulting in less frequent mucosal involvement in PF.

Patients with PV (and to a much lesser degree PF) may be susceptible to infection and subsequent mortality given the loss of their protective epidermal layer. Management is complex and usually requires long-term corticosteroid treatment. As chronic steroid use is limited by a high-risk profile and side effects, additional adjuvant therapeutics may also be employed with some degree of benefit. These medications include azathioprine and cyclophosphamide (which have a steroid sparing effect), intravenous immunoglobulin (which helps with rapid, early control of disease), and mycophenolate mofetil (which seems to lengthen the time to disease relapse) [92]. Topical epidermal growth factor has been shown to help with healing of mucosal erosions [92]. Other topical treatments include soaking baths with antiseptic additives and topical corticosteroids [88].

2.5.1.1 Clinical Features

The most commonly affected gynecologic sites in pemphigus are the labia minora, labia majora, the vagina, and less commonly the cervix or clitoris [86, 87]. Lesions present as relatively superficial but painful erosions distributed on the vulvar

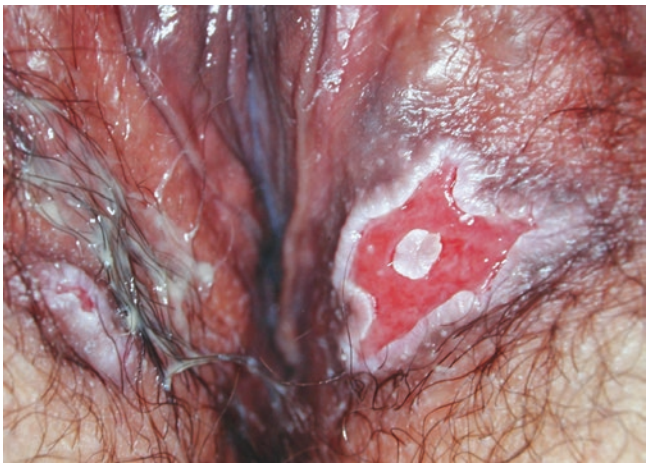

Fig. 2.27 Pemphigus vulgaris. Superficial erosions on the vulvar skin and mucosa. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

skin and mucosa (Fig. 2.27). The presence of flaccid blisters may be a clue to the diagnosis but may be difficult to detect as they are generally easily ruptured leading to the more commonly visualized erosions. If there is vaginal involvement, the patient may present with a desquamative inflammatory vaginitis, complaining of symptoms such as irritation, painful sexual intercourse, and pain with increased vaginal secretions [50].

Lesions of PVeg have a verrucous or vegetative appearance. They are usually multiple in number, and clear evidence of a blister may be lacking. Lesions may appear macerated and become superinfected [89, 93].

Clinical exam should focus on evaluation of other mucosal sites for erosions and blisters. The oral cavity is almost always involved in PV, and about half of patients will have involvement of nasal mucosa. The sites of frequent cutaneous involvement include the face, scalp, and trunk [90]. Patients with PF have superficial erosions of the cutaneous skin and are less likely to involve genital mucosa. Patients with PVeg may have involvement of other intertriginous sites such as the inframammary folds or the axilla, as well as the mucosal involvement as seen in PV [94].

The clinical differential diagnosis of PV includes erosive lichen planus, Behcet disease, infections, and mucous membrane pemphigoid. The clinical differential diagnosis for PVeg includes infectious entities, including sexually transmitted diseases, some of the inherited acantholytic disorders (namely Hailey–Hailey disease and acantholytic dermatosis of the genital-crural region), noncontiguous/"metastatic" Crohn disease, and pyodermatitis vegetans. Clinical history and physical exam will help discern all of the body sites affected by disease and any associated symptoms and signs. Tissue cultures are helpful when the differential diagnosis includes infection. Biopsy is generally helpful in confirming the diagnosis of an autoimmune blistering disorder, particularly if a second sample is submitted in Michel's solution (not formalin!) for direct immunofluorescence studies.

2.5.1.2 Histologic Features

Biopsy should try to encompass non-eroded/ulcerated skin to decrease the chances of detecting nonspecific features of inflamed ulceration [50]. Whenever a blistering disease is suspected, it is recommended that a second biopsy of non-affected or perilesional skin be taken for direct immunofluorescence studies. This second biopsy should be submitted in an isotonic transport media that will stabilize proteins for immunofluorescence, such as Michel's solution or Zeus media. If such a media is not available, the biopsy can be submitted in saline but processing will need to occur within 2 days to prevent false negative results. Processing of specimens submitted in Michel's solution for direct immunofluorescence is generally recommended to occur within 5 days of biopsy, but studies have shown long-term (6 months) preservation of reproducible results [95].

Microscopically, PV demonstrates acantholysis of keratinocytes, resulting in an intraepidermal blister. Acantholysis can be recognized by the rounded borders of the keratinocytes. When the desmosomal protein complex fails, the cytoplasm tends to contract into the cell, resulting in a rounded epithelial cell with eosinophilic cytoplasm but preserved and intact nucleus. In contrast, a dyskeratotic keratinocyte may have pink and rounded cytoplasm but generally shows brighter dense pink cytoplasm and a pyknotic nucleus. Moreover, a blister resulting from spongiosis (edema) rather than acantholysis tends to show stellate looking (rather than uniformly rounded) keratinocytes as the desmosome proteins are still functional in spongiotic disorders and serve as the glue keeping keratinocytes adherent to one another. PV classically shows acantholysis that is most prominent in the spinous layers just above the basal layer, resulting in the so-called "suprabasilar" pattern of acantholysis (Fig. 2.28). This is due to the fact that desmoglein 3 is expressed in a gradient, with highest concentration in the suprabasilar keratinocytes. The autoantibodies generated in PV do the most damage to this area of the epithelium. In contrast, desmoglein 1 has higher expression in the superficial most layers of the epidermis, including the granular layer, and so the acantholysis that is observed in PF is typically in the superficial-most portions of the epidermis. Acantholysis in both variants may involve skin appendages, and acantholysis detected along the hair follicle epithelium may be a good clue to the diagnosis [96]. The preservation of intact basal keratinocytes with rounded cell borders in PV can lead to a pattern reminiscent of a row of tombstones [1]. Within the dermis, there is typically a moderately brisk inflammatory infiltrate comprised of lymphocytes, eosinophils, and neutrophils. Acantholytic cells may be detected on Pap smears and are recognized by their

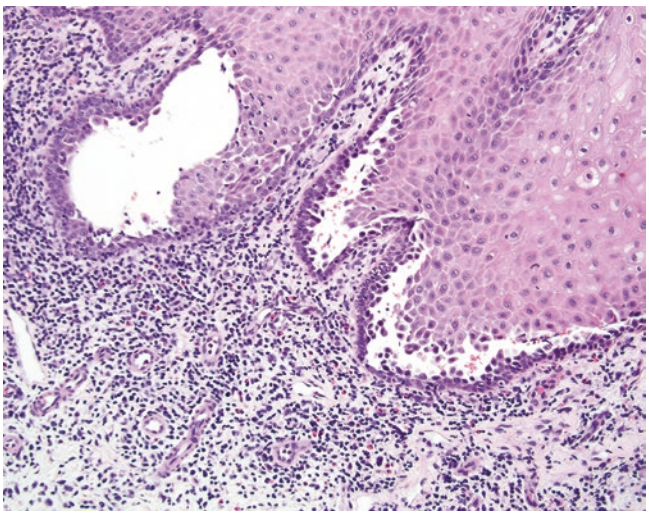

Fig. 2.28 Pemphigus vulgaris. Mucosal epithelium demonstrating suprabasilar acantholysis. The dermis shows a mixed infiltrate including eosinophils

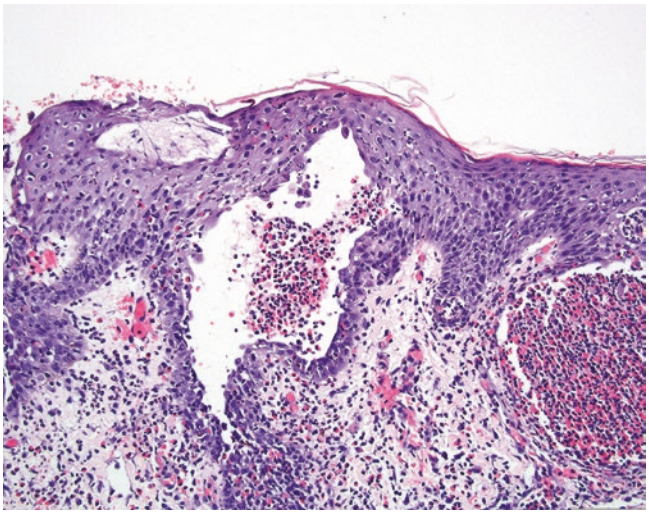

Fig. 2.29 Pemphigus vegetans. Acanthotic epidermis with large, intraepidermal eosinophilic microabscesses. Acantholysis can be appreciated at the edges of the microabscess

high nuclear-to-cytoplasm ratio but uniform, hypochromatic nucleus with small nucleoli [86, 87]. It is important to know the patient's disease to prevent misinterpretation of these findings as dysplasia [87].

PVeg has additional and often quite striking histologic features. Epidermal hyperplasia, which can be so exuberant as to be classified as pseudoepitheliomatous, correlates with the vegetative and verrucous appearance of clinical lesions. Eosinophilic microabscesses within the epidermis are also seen (Fig. 2.29). The acantholytic cells that identify the disease as pemphigus are often located within and therefore obscured by these intraepidermal eosinophilic microabscesses. Pathologists should be familiar with the expected histologic findings of PVeg so that this constellation of features prompts careful evaluation for acantholysis.

2.5.1.3 Immunohistochemical Features

While the histologic features of pemphigus are generally fairly diagnostic on routine examination, direct immunofluorescence studies provide an important adjunct test to definitively confirm the diagnosis. Application of fluorescent-conjugated antibodies to immunoglobulins will result in a characteristic pattern of staining matching the normal expression pattern of the target antigen, namely desmoglein 3 in PV. IgG and C3 decorate the cell membrane of keratinocytes (Fig. 2.30), with most prominent staining in the lower levels of the epithelium in PV. IgA is less commonly deposited [96, 97]. This intercellular pattern of staining has been described as "lace-like" or "fishnet-like." Usually the deposition is linear, as if a fine-tip marker is outlining each keratinocyte; however, a subset of patients will show a granular deposition pattern [97]. If a biopsy is encountered that does not show epidermis, a search for any hair follicles within the biopsy may provide the needed information, as follicular epithelium will show the same intercellular pattern of staining.

Other ancillary tests are not required for the diagnosis of PV. However, indirect immunofluorescence studies may provide information regarding disease activity. Indirect immunofluorescence is performed by incubating patient serum (containing the circulating autoantibodies) on a "normal" skin substrate (typically monkey esophagus is the preferred substrate). Serial dilutions of the serum can provide an estimated autoantibody titer, and high titers tend to correlate with severe disease [1, 86].

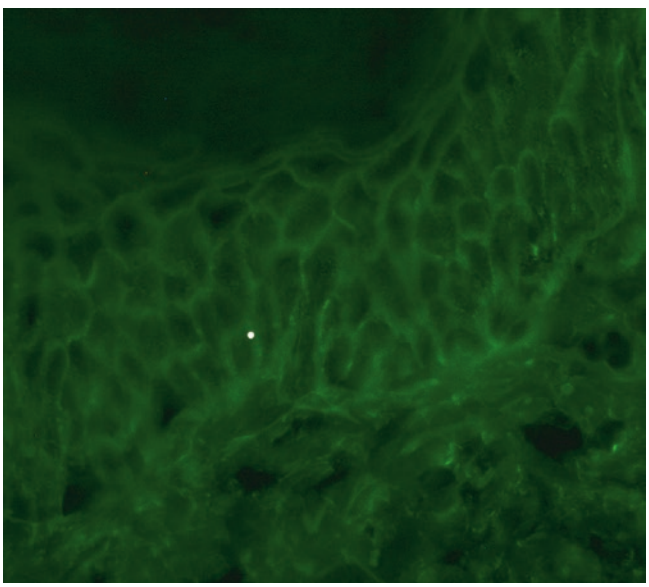

Fig. 2.30 Pemphigus. Intercellular deposition of IgG and C3 are seen in the pemphigus family of diseases

2.5.1.4 Differential Diagnosis

The histologic differential diagnosis of PV includes Hailey–Hailey disease, Darier disease, herpetic infection, and papular acantholytic dyskeratosis. Hailey–Hailey disease, Darier disease, and papular acantholytic dyskeratosis will also show variable degrees of acantholysis without (Hailey–Hailey) or with (Darier) dyskeratosis. Importantly, direct immunofluorescence studies will be negative in these inherited acantholytic disorders. Herpes virus infection usually shows the characteristic viral cytopathic effect of cellular molding, chromatin margination, and multinucleation and can be detected by immunohistochemical staining. Importantly, the topical anesthetic EMLA has been reported to cause intraepidermal acantholysis and can thus mimic pemphigus as well [98].

The histologic differential diagnosis of PF would include other diseases with more superficial blisters, including impetigo, staph-scalded skin, and tinea. Infectious stains coupled with cultures, negative immunofluorescence, and clinical history should help resolve this differential.

The histologic differential diagnosis of PVeg often includes infectious entities. Special stains for organisms and cultures are essential to detect the etiologic organisms. PVeg shares virtually identical histologic features with pyodermatitis vegetans, a disease with strong association to inflammatory bowel disease. Microscopically, pyodermatitis vegetans shows the same pseudoepitheliomatous hyperplasia with eosinophilic microabscesses, but will have a negative direct immunofluorescence study [99, 100].

Subepidermal blistering diseases such as mucous membrane pemphigoid and bullous pemphigoid may enter the differential diagnosis, either clinically or histologically. These disorders, which occasionally involve the vulva, are characterized by tense (rather than flaccid) blisters on an erythematous base and are due to autoantibodies generated against proteins in the hemidesmosome complex that links basal keratinocytes to the dermis. Microscopically, the blister split occurs at the junction of the epidermis/epithelium and dermis/subepithelium, rather than the intraepidermal blister that occurs in the pemphigus family of diseases. Mucous membrane pemphigoid and bullous pemphigoid have positive direct immunofluorescence findings as well, but immunoreactants (usually IgG and C3) are localized to the basement membrane zone in a linear distribution rather than the intercellular pattern seen in pemphigus.

2.5.2 Subepithelial Blistering Disease: Mucous Membrane Pemphigoid, Bullous Pemphigoid, and Linear IgA Bullous Dermatosis

Subepidermal/subepithelial blistering diseases, similar to the pemphigus family, are generally autoimmune mediated. The pemphigoid family of diseases, including mucous membrane pemphigoid (MMP) and bullous pemphigoid (BP), may occasionally involve the vulva, and are characterized by tense (rather than flaccid) blisters on an erythematous base. These diseases are due to autoantibodies (predominantly of the IgG subtype) generated against proteins in the hemidesmosome complex that links basal keratinocytes to the dermis. Linear IgA bullous dermatosis (LIGABD) and chronic bullous disease of childhood (CBDC) are likely the same disease presenting along a spectrum, with the age of presentation being the biggest difference between these two entities. Both LIGABD and CBDC arise from autoantibodies generated to similar antigens as in BP and MMP, but the antibodies are of the IgA subtype.

BP is one of the more common autoimmune-mediated blistering diseases and most often arises in older adults. BP uncommonly involves mucosal or genital surfaces, estimated around 10% of patients with the disease. A subset of BP arises in childhood however, and these children may have exclusively vulvar involvement [1, 101]. MMP affects preferentially mucosal sites such as conjunctiva, and oral and genital mucosa. MMP is also termed "cicatricial pemphigoid" due to the propensity for scarring sequelae of the disease. Older females are most commonly affected, with the vulva being a frequent site of involvement (in contrast to BP) [89]. The criteria for diagnosis of MMP include blisters on mucous membranes and positive direct immunofluorescence studies as described below [102]. LIGABD (or CBDC when occurring in children) is a relatively unusual blistering disease. When occurring in adults, middle age to older adults are affected and there is a slight predilection for the disease to occur in women [1]. LIGABD is often related to recent antibiotic usage (particularly vancomycin) [96]. CBDC typically presents in prepubertal children (with average age in the range of 4–6 years old) as blistering genital lesions that evolve to more widespread cutaneous involvement. Resolution is generally self-limited over a few months or years and is generally resolved by onset of puberty [1, 103]. CBDC occurs with equal frequency in children of both sexes and all races and is the most common acquired autoimmune blistering disease in childhood [104].

In all of these entities, autoimmunity against proteins making up the hemidesmosome—the protein complex that links the basal keratinocyte to the collagen framework of the superficial dermis—characterizes the disease. BP is characterized by autoantibodies generated to the BP230 (BPAg1, a plakin) or BP180 (BPAg2, also known as collagen XVII) protein antigens of the hemidesmosome [96, 105]. The autoantibodies in MMP are generated to a variety of hemodesmosomal proteins, including BP230, BP180, as well as laminin332, and α6β4 integrin [105]. LIGABD and CBDC generate an IgA autoantibody to fragments of the BP180 protein (collagen XVII), most commonly to the 97 and 120 kD fragments [104].

Similar to the pemphigus family of disease, these subepidermal blistering diseases are managed with aggressive immunosuppression, using corticosteroids and steroid sparing agents. Prednisone, cyclophosphamide, azathioprine, and mycophenolate mofetil have all been shown to have utility in the treatment of BP and MMP [102]. Rarely, mild or localized disease may be successfully managed with topical treatment alone [106]. LIGABD and CBDC may be managed with dapsone. MMP in particular, requires coordinated management with ophthalmologists and gastroenterologists or otolaryngologists due to the propensity for ocular, laryngeal, and esophageal involvement and the risk of scarring sequelae.

2.5.2.1 Clinical Features

BP rarely involves the vulva, although rare reports document convincing cases of exclusively vulvar involvement [101, 107]. BP presents as tense blisters on an erythematous base, most often involving the trunk and flexural sites. Blisters may be preceded by a nonspecific urticarial phase, in which clinical lesions are eczematous or urticarial-appearing. The mucosa is rarely involved. Blisters resolve without scarring. Patients often complain of pruritus.

MMP not uncommonly involves vulvar skin and mucosa, with the labia majora and minora both affected. Clinically, lesions resemble those seen in BP, with tense blisters arising on an erythematous base. However, in contrast to BP, scarring is a common sequelae as blisters resolve. Conjunctival and oral mucosal involvement is commonly also present upon examination.

LIGABD and CBDC have similar clinical appearances. Lesions are often annular or targetoid, with small clusters of blisters aligned along the perimeter. This has been often referred to as "clusters of jewels" or "string of pearls" sign [104]. The blisters, which are tense as in BP and MMP, may have serous or hemorrhagic fluid in them. The genital region is often involved (particularly in children), but the extremities, face (peri-oral), and rarely mucosa may also be involved by lesions. Complete skin examination and further workup is paramount, particularly as CBDC involving the vulva may be initially mistaken for childhood sexual abuse [106]. Healing of blisters often leaves pigmentary alteration but no scarring [104]. Clinical symptoms may include burning or itching, or they may be absent.

2.5.2.2 Histologic Features

Microscopically, the blister split for these diseases occurs at the junction of the epidermis/epithelium and dermis/subepithelium, rather than the intraepidermal blister that occurs in the pemphigus family of diseases. This subepidermal/subepithelial blister lacks epidermal necrosis and/or dyskeratosis. In BP, the blister cavity classically demonstrates an eosinophil-rich infiltrate. This eosinophil-rich infiltrate is also present in the dermis. BP should not show scarring in the dermis. In MMP, the blister cavity generally shows fewer inflammatory cells than in BP (Fig. 2.31). Neutrophils predominate in early blisters, with eosinophils and lymphocytes recruited in older blisters [106]. In some biopsies, scarring or dermal fibrosis may be evidence of a previous blistering episode. LIGABD and CBDC show identical histology, characterized by a subepidermal blister with a neutrophil-rich infiltrate in the blister cavity and superficial dermis. Neutrophils will often be aligned along the dermal–epidermal junction, often contiguously, but sometimes in a discontinuous pattern which will histologically mimic dermatitis herpetiformis.

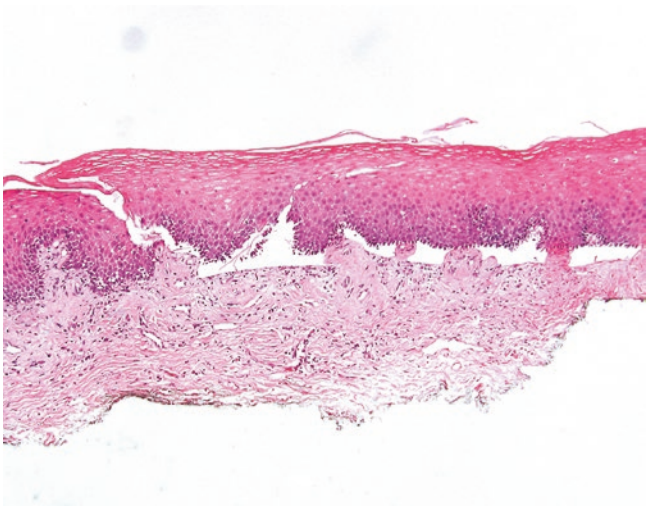

Fig. 2.31 Mucous membrane (cicatricial) pemphigoid. The mucosa demonstrates a subepithelial blister with minimal inflammation in the blister cavity or submucosa

2.5.2.3 Immunohistochemical Features

Direct immunofluorescence studies are imperative to confirm the diagnoses of MMP, BP, and LIGABD. In contrast to the intercellular pattern seen in pemphigus, these diseases have linear deposition of immunoreactants along the dermal–epidermal junction: in MMP and BP these immunoreactants are usually IgG and C3, and in LIGABD/CBDC the main immunoreactant is IgA (with C3 deposition also seen as a secondary immunoreactant) [96]. Direct immunofluorescence studies have been shown to have both a high sensitivity (nearly 91%) and a high specificity (98%) in the diagnosis of BP [108]; as such, most cases of suspected BP are captured through histology and direct immunofluorescence.

However, indirect immunofluorescence studies may also be of value in the diagnosis of subepidermal blistering diseases. The salt-split skin method involves inducing a subepidermal blister in normal skin substrate and incubating with patient serum. In the salt split skin test, autoantibodies will

bind to either the epidermal side (the "roof") or the dermal side (the "floor") of the blister. This pattern provides information regarding the exact location of the split within the hemidesmosomal complex and shows high specificity (although relatively low sensitivity) in the diagnosis of BP [108]. In BP, the antigens targeted are relatively superficial in the lamina lucida of the basement membrane zone, and therefore autoantibodies localize to the roof/epidermal side of the blister. This is in contrast to similar diseases such as epidermolysis bullosa acquisita (see differential diagnosis below), where the autoantibody is generated to an antigen in the superficial dermis, so the immunoreactants in the salt split skin test localize to the floor/dermal side of the blister.

The salt split skin concept can be exploited by immunohistochemical staining for collagen type IV (basement membrane collagen) in formalin-fixed patient biopsies. As the blister in BP generally occurs at a relatively superficial location in the hemidesmosome, collagen IV will stain the floor/dermal side of the blister. In epidermolysis bullosa acquisita, the blister roof/epidermal side will be stained by collagen IV [96].

Due to the varied nature of the autoantibody targets in MMP and their different location within the hemidesmosome complex, the abovementioned indirect studies and collagen IV staining may not be as helpful in confirming the diagnosis.

The indirect immunofluorescence studies using monkey esophagus as a substrate has historically been less useful in the diagnosis and management of the pemphigoid family than in the pemphigus family of disease. False negative results are frequently reported in BP and sensitivities are relatively low [108]. However, some authors suggest that testing for subclasses of IgG (rather that IgG as a whole) can improve the detection capabilities [109].

Immunoblotting of patient serum may also rarely be used in the diagnostic workup. Target antigens, which define the disease, are identified by molecular weight, and thus the exact target antigen (ex BP180 or BP230) can be identified. Immunoblotting has largely given way to less technically demanding techniques such as ELISA (enzyme-linked immunosorbent assay) designed to detect specific, commonly targeted antigens. ELISA assays show overall moderate sensitivity but high specificity in the diagnosis of BP [108].

2.5.2.4 Differential Diagnosis

The pemphigus family of diseases can be distinguished from the pemphigoid family of diseases by the presence of an intraepidermal, rather than a subepidermal, blister. The location of the blister formation and the distribution of immunoreactivity with direct immunofluorescence is distinctive.

Subepidermal or subepithelial blisters may also result from cytotoxic damage to the epidermis, as seen in robust examples of interface dermatitis. As such, bullous examples of lichen planus, fixed drug eruption, and Stevens Johnson syndrome/toxic epidermal necrolysis may sometimes mimic the pemphigoid diseases. Any of these interface dermatoses should show individual necrotic keratinocytes and vacuolar changes at the dermal–epidermal junction. The edge of a blister is the best place to appreciate these changes.

Well-established, advanced lichen sclerosus may sometimes induce an artifactual subepidermal blister due to marked dermal sclerosis. This should not be interpreted as a superimposed, secondary autoimmune blistering disease. Negative direct immunofluorescence studies coupled with a homogenized papillary dermal collagen framework and attenuated rete ridge pattern would support a diagnosis of lichen sclerosus over a true blistering disease.

Additional subepidermal blistering diseases that have histologic overlap with both BP and MMP include epidermolysis bullosa acquisita (EBA) and pemphigoid gestationis. EBA occurs in a similar demographic of patients (older to elderly adults) as BP and is often more refractory to treatment. Autoantibodies are generated against collagen VII, which is present as an anchoring fibril in the superficial dermis. Disruption at this site will frequently result in scarring as blisters resolve. This propensity for scarring is similar to MMP. Classically, the blisters in EBA are pauci-inflammatory, but inflammatory cells (eosinophils or neutrophils) may be present in a subset of cases. Although direct immunofluorescence studies show linear IgG and C3 along the basement membrane zone (identical to BP and MMP), the target of the autoantibodies is to a more deeply located antigen (collagen VII). As a result, indirect salt-split skin will show deposition of immunoreactivity along the dermal side (the floor) of the blister, which is in contrast to the pattern of epidermal deposition in most cases of BP. Pemphigoid gestationis is essentially the development of BP during pregnancy (most often the second or third trimester) [96]. Histologic features and direct immunofluorescence studies are identical to BP, and thus accurate diagnosis relies on knowledge of the patient's pregnancy status.

The primary histologic differential diagnosis of LIGABD and CBDC is dermatitis herpetiformis. Also characterized by a subepidermal blister, neutrophils aligned along the dermal–epidermal junction, and deposition of IgA along the basement membrane zone, dermatitis herpetiformis shares many histologic features of LIGABD and CBDC. However, the dermal neutrophils in dermatitis herpetiformis tend to cluster in the papillary dermal tips, whereas in LIGABD and CBDC, the neutrophils are generally dispersed continuously along the dermal–epidermal junction. The IgA deposition seen on direct immunofluorescence in dermatitis herpetiformis is more granular and patchy than the linear deposition seen in LIGABD and CBDC. However, clinical presentation is also helpful in the distinction: dermatitis herpetiformis essentially never involves the vulvar skin (preferring instead extensor surfaces) and has a strong association with celiac disease.

2.5.3 Hailey–Hailey Disease, Darier Disease, and Papular Acantholytic Dyskeratosis

Hailey–Hailey Disease (HHD), Darier Disease (DD), and Papular Acantholytic Dyskeratosis (PAD) are all united by the common presence of the histologic feature of acantholysis. As previously mentioned, acantholysis is the dissociation of keratinocytes due to insufficient cell–cell adhesion. These genodermatoses are distinguished clinically by their distribution of lesions and presence/absence of a family history of similar rashes. Although HHD and DD are inherited diseases, presentation may not occur until early adulthood.

HHD, also known as benign familial pemphigus, is an inherited genodermatosis transmitted in an autosomal dominant manner. The genetic defect is a mutation in *ATP2C1*, which encodes a calcium pump involved in maintaining normal cell–cell adhesion [96]. As there is incomplete penetrance, not all patients will report a family history. Patients with HHD generally present in the second to fourth decade of life with pruritic intertriginous papules and plaques. Erosion and maceration is common, leaving patients susceptible to secondary bacterial, fungal, or viral (particularly herpetic) infection. A case report exists regarding the development of squamous cell carcinoma in a patient with HHD without other predisposing or contributable factors [110]; this occurrence seems the exception and not the rule. The clinical manifestations may have a waxing and waning course, with exacerbations from hot weather and increased friction and ultimate improvement with age [1, 96].

DD, also known a keratosis follicularis, is another inherited genodermatosis. This disease, also inherited in an autosomal dominant fashion with incomplete penetrance, is due to a mutation in *ATP2A2*, which—similar to HHD—encodes a calcium pump integral to desmosome integrity. Patients generally present in mid to late childhood (often around puberty) with hyperkeratotic papules distributed on the face, chest, neck, back, ears, and groin. Similar to HHD, these lesions are prone to secondary infection.

PAD, which has been variably termed papular acantholytic dermatosis of the genital-crural (or vulvar-crural) folds or papular genitocrural acantholysis, is a third example of an acantholytic dermatosis affecting vulvar skin. These lesions have clinical and histologic overlap with both HHD and DD, but lesions are generally limited to the genital folds and may extend to the upper thighs. Family history is uncommonly reported. Some studies have shown genetic similarity to HHD or DD [111, 112], lending support to the idea that PAD may be a localized variant or mosaic expression of HHD or DD.

Management for all of these acantholytic processes is similar, with ablative therapies (cryosurgery, laser, excision, or electrocautery) being common. Topical steroids, topical antibiotics to minimize infectious complications, and retinoids have also been utilized as therapies [113].

2.5.3.1 Clinical Features

Patients with HHD present with eroded or macerated plaques in the axillae, inguinal folds, vulva, perineum, neck, and inframammary folds. True blisters are generally not visible, but skin is typically erythematous, eroded, and crusted. Verrucous papules are another reported clinical presentation; this presentation may mimic condylomas [114]. An accompanying foul odor may point to secondary infection of lesions [1]. Evidence of associated lichenification attests to the pruritic nature of lesions [115].

Patients with DD demonstrate skin lesions in a seborrheic distribution (face, neck, ears, chest, back, and groin). Skin lesions are verrucous and keratotic papules that have a rough appearance and feel and often coalesce into papillomatous plaques [116]. The color of lesions ranges from flesh colored to yellow to red to brown. In addition to skin lesions, nail dystrophy is frequent. Similar to HHD, lesions may be foul smelling due to secondary infection.

The lesions in patients with PAD are localized to the perigenital region. Lesions are described as distinct white to flesh colored papules most often occurring on the labia majora [117]. Most often lesions are asymptomatic, but may occasionally cause itching or burning.

Clinical distinction between these three disorders may be difficult. The distribution of lesions and a positive family history are some of the most helpful distinguishing features. In the absence of family history, distinction may be more difficult. Clinically, in theory, PAD is more likely than HHD to present as asymptomatic distinct papules, whereas HHD is generally pruritic and painful with more vesiculation [113]. Other entities within the clinical differential (particularly with the isolated lesions seen in PAD) include fungal and viral infections [115] and genital warts [114].

2.5.3.2 Histologic Features

Microscopic evaluation of HHD reveals an acanthotic epidermis with acantholysis likened to a "dilapidated brick wall." The entire span of the epidermis may show breakdown between keratinocytes, in contrast to the suprabasilar accentuation of acantholysis in pemphigus vulgaris (Fig. 2.32). Adnexal structures (hair follicles) generally do not show acantholysis, and classically there is minimal dyskeratosis, with corps ronds and grains usually absent. There may be slight to moderate inflammation in the dermis (particularly when secondarily infected), as well as surface erosion or ulceration with serum crusting.

Biopsies from DD show a combination of both acantholysis and dyskeratosis. There is often a thick layer or column of parakeratosis overlying the lesions (Fig. 2.33). Dyskeratosis is manifest by corps ronds (rounded acantholytic cells with a round nucleus surrounded by a pale halo) and grains (basophilic cells with hyperchromatic, elongated/flattened nuclei, usually in the granular layer). Acantholysis is most promi-

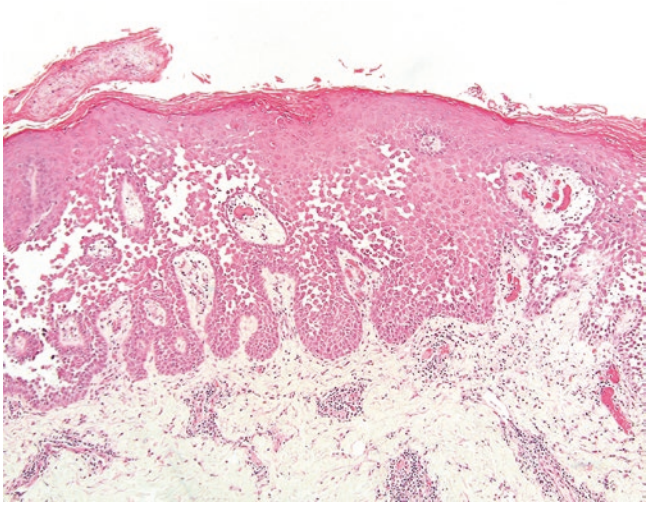

Fig. 2.32 Hailey–Hailey disease. The epidermis is acanthotic with prominent acantholysis but minimal dyskeratosis, recapitulating a "dilapidated brick wall"

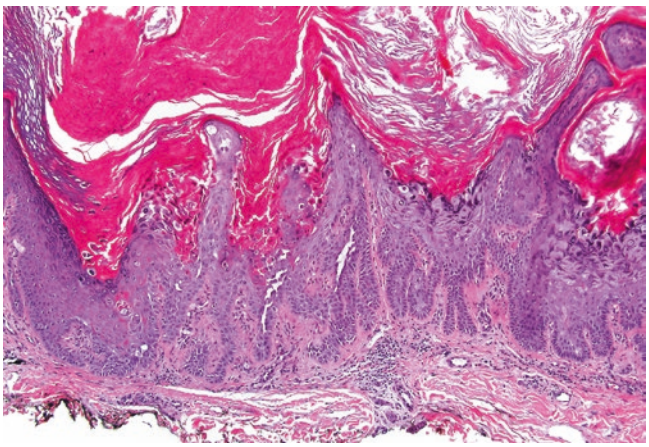

Fig. 2.33 Darier disease. Acantholysis and dyskeratosis is prominent within a papillomatous and acanthotic epidermis

nent in the suprabasilar layer, and all of the diagnostic features may be seen involving hair follicles. Typically there is scant dermal inflammation, unless there is secondary infection.

The histologic features of PAD may resemble either HHD or DD, and sometimes there may be features of both diseases in one biopsy specimen [113, 115, 118, 119]. The acantholysis in PAD may be more focal than in HHD [1].

Importantly, all three of these disorders should have negative direct immunofluorescence studies. Ancillary studies that may be performed in addition to direct immunofluorescence include stains for infectious organisms, should there be a histologic concern for secondary infection by bacterial, fungal, or viral (particularly herpetic) organisms.

The entities discussed above need to be differentiated from one another, and this is best accomplished through clinical–pathologic correlation. Predominant acantholysis without dyskeratosis and the correct distribution of lesions and/or family history favors HHD. Prominent dyskeratosis with corps ronds and grains and the correct distribution of lesions and/or family history favors DD. The other major histologic differential is pemphigus. Lesions of pemphigus are generally acquired and often (but not always!) present in an older cohort. Histologically, pemphigus generally shows suprabasilar acantholysis without significant dyskeratosis and will have positive direct immunofluorescence studies. If clinical history is not available, if there is histologic overlap with the different disorders discussed herein, and/or if direct immunofluorescence was not submitted, it may be prudent to sign out reports as "Acantholytic dermatosis (with or without dyskeratosis)" and give a differential that may variably include HHD, DD, PAD, or pemphigus. If pemphigus is within the differential diagnosis, direct immunofluorescence studies would be recommended as a follow-up test.

2.6 Granulomatous Reaction Pattern

2.6.1 Crohn Disease of the Vulva

Crohn disease (CD) involving the vulvar skin and mucosa is rare, but it is likely under-recognized and underreported. CD is a granulomatous process that affects the gastrointestinal (GI) tract, but may affect skin outside of the GI tract. CD may directly extend from the GI tract to the skin, presenting most often as fistulous tracts, or may present as discrete skin lesions. Referred to by some as "metastatic" lesions, this cutaneous involvement is perhaps more accurately referred to as noncontiguous involvement by CD [120].

Approximately one-third of patients with GI CD disease will have extracutaneous manifestations, including joint (arthritis), oral (aphthous ulcers), ocular (uveitis), and cutaneous lesions [120]. Cutaneous manifestations of CD include pyoderma gangrenosum, erythema nodosum, and noncontiguous cutaneous CD. Crohn disease in the vulva may precede the diagnosis of GI Crohn disease up to 50% of the time, depending on the study cited [120–122], and it may be possible to have CD limited to the vulva. In a single institution study of vulvar CD, the average age of presentation was 28 [120], while comprehensive literature reviews of CD of the vulva cite median presentation around age 34 [121, 123].

The precise pathogenesis of cutaneous CD remains unclear. Type IV hypersensitivity reactions, immune complex deposition, cross-reactivity between skin and gastrointestinal antigens, and genetic predispositions have all been proposed as possible mechanisms [124]. Cell-mediated immunity is thought to play a role as well in the development of granulomas specifically.

Depending on the presentation, clinical workup may require imaging to assess for enterocutaneous fistula formation. Therapeutic options include topical steroids, antibiotics, and TNF-α inhibitors, with surgical treatments reserved for refractory cases [120–123].

2.6.1.1 Clinical Features

Vulvar CD may present in several different and distinct manners. Although typically asymptomatic, patients may complain of pain/discomfort and less commonly pruritus. Labial edema is the most commonly observed manifestation, seen in approximately two-thirds of patients. This swelling is often asymmetrical and erythematous and may be the only physical finding. Ulcerations, often described as "knife-like" [121, 125] and of variable depth and distribution are also frequently encountered. Mass-forming lesions and abscesses are yet other presentations that may be encountered [1, 120]. Bulbous lesions clinically concerning for condylomata have also been detailed in the literature [121, 126] (Fig. 2.34).

The clinical differential diagnosis for vulvar CD includes infectious processes (namely a variety of sexually transmitted infections), hidradenitis suppurativa, pyoderma gangrenosum, and neoplastic entities. As such, a biopsy may be taken to help clarify the diagnosis.

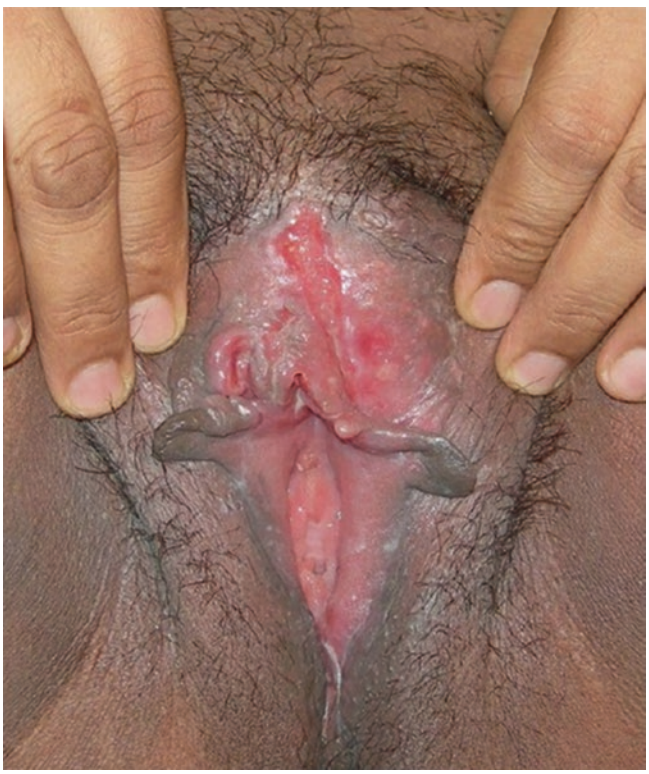

Fig. 2.34 Crohn disease involving the vulva. Edema and asymmetric ulcerations are present. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

2.6.1.2 Histologic Features

The classically described histologic pattern of cutaneous CD is a noncaseating granulomatous dermatitis (Fig. 2.35). The granulomas are epithelioid, variably loose to tight, without central necrosis or suppuration, and multinucleated giant cells and a rim of associated lymphocytes may be present. Granulomas may be closely aligned to the dermal–epidermal junction, but may be located deep in the subcutis as well [124]. The presence of eosinophils was seen in two-thirds of cases (Fig. 2.36), and seems to be a distinguishing feature from sarcoidosis, which typically lacks eosinophils [124]. Granulomatous vasculitis and granulomatous lymphangitis have also been described [127].

However, while granulomatous inflammation is a distinctive and recognizable histologic feature of cutaneous CD, at

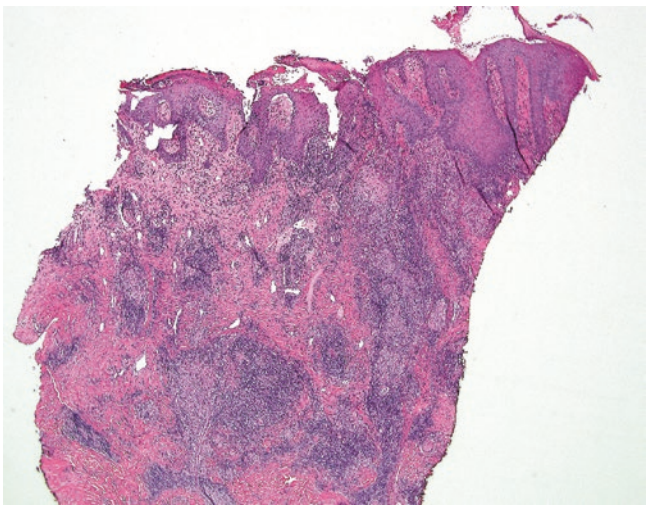

Fig. 2.35 Crohn disease. The epidermis is thickened and the dermis shows a noncaseating granulomatous dermatitis

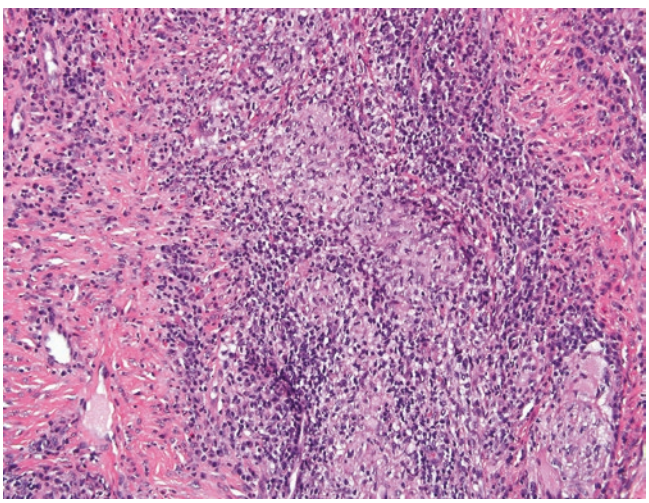

Fig. 2.36 Crohn's disease. Higher magnification shows noncaseating granulomas in the dermis with surrounding admixed eosinophils

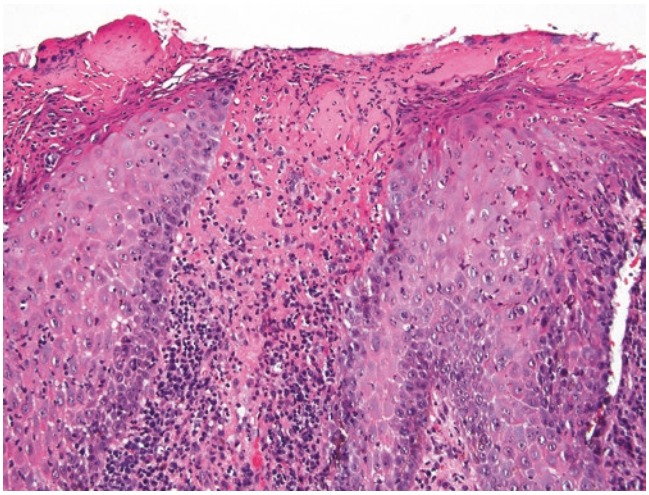

Fig. 2.37 Crohn disease. There is often surface ulceration or erosion, even in the absence of dermal granulomas

least one study suggested that granulomas are not requisite to make a diagnosis of noncontiguous/metastatic CD. In a single institutional study of clinically confirmed vulvar CD, only 38% of patient biopsies showed granulomatous inflammation, suggesting that requiring granulomas for a diagnosis of vulvar CD may be overly restrictive and thereby miss the diagnosis in a large subset of cases [126]. Another case series noted that two-thirds to three-quarters of patients with vulvar CD had biopsies which confirmed the diagnosis by documentation of granulomatous inflammation [120], suggesting the absence of such inflammation in the remaining patient biopsies.

Additional features seen in cutaneous CD include ulceration, lichenoid inflammation, and lymphatic dilatation. Ulceration of the epidermis is often appreciated in biopsies of cutaneous CD, corresponding to the frequently observed clinical ulceration, and may be present alone or with other inflammatory features (Fig. 2.37). Lichenoid inflammation may be seen with or without a granulomatous infiltrate [124, 126]. Dilated lymphatic spaces, thought to be a result of fibrosis from GI surgeries or from persistent chronic inflammation, have been documented and may prove to be an important clue to the diagnosis as it is less commonly described in entities that may be within the histologic differential diagnosis [126, 127]. Notably, a subset of patients demonstrated vulvar dysplasia or carcinoma on biopsy (particularly seen in the bulbous and exophytic lesions), further supporting the need for biopsy in these cases [126].

2.6.1.3 Immunohistochemical Features

Ancillary testing in cutaneous CD plays a minimal role. There are no diagnostic immunohistochemical stains. Special stains to include deep fungal and mycobacterial infections are generally performed as part of the workup, as with most granulomatous infiltrates confronting a pathologist.

2.6.1.4 Differential Diagnosis

Cutaneous CD may have histologic overlap with other ulcerating diseases such as hidradenitis suppurativa and pyoderma gangrenosum as well as infectious entities and granulomatous processes such as sarcoidosis. Hidradenitis, discussed below, presents with a rich, neutrophil-predominant inflammatory infiltrate centered around disrupted hair follicles and sweat glands. Pyoderma gangrenosum, as will be discussed later in this chapter, may be associated with inflammatory bowel disease, but involvement of the vulva is unusual. Infectious etiologies should be excluded with use of relevant special stains for organisms. Particularly as granulomatous diseases may herald a mycobacterial or deep fungal infection, acid fast and PAS or GMS stains are requisite to include infectious etiologies. Cultures and molecular techniques, coupled with a high index of suspicion, may be necessary to exclude some infections, particularly entities such as lymphogranuloma venererum, which may have nonspecific histologic features (coupled with characteristic lymphadenopathy) and negative special stains for organisms. Vulvar sarcoidosis may have considerable histologic overlap with CD and would be in the histologic differential diagnosis, particularly when granulomas are present and if the patient is presenting with vulvar disease alone in the absence of GI symptoms. Eosinophil-rich infiltrates are said to favor CD over sarcoidosis, and ulceration is common in CD but unusual in sarcoidosis [1, 124].

2.7 Vasculopathic Reaction Pattern

2.7.1 Behcet Disease

Behcet disease (BD) is a systemic disease that affects multiple organs and elicits considerable morbidity for patients. Considered by many to be an autoinflammatory disease requiring a genetic predisposition coupled with some exogenous triggering event, BD was initially characterized by the triad of oral, genital, and ocular lesions [128]. BD is now known to involve other organ systems, resulting in articular, neurologic, gastrointestinal, and cardiovascular signs and symptoms [128, 129]. Pulmonary artery aneurysm is a source of considerable morbidity and mortality. Involvement of the central nervous system and the ocular system generally predicts prognosis [128]. Expansion of spectrum of disease has led some authors to prefer that it be referred to as Behcet syndrome, as the constellation of features affecting different subgroups of patients may vary considerably [130].

BD is relatively rare in the United States and Western European countries. It has a higher prevalence in the Mediterranean, Central Asia, and the Far East, with Turkey having the highest incidence of affected patients, averaging approximately 400 per 100,000 in a few studies [129, 130].

BD affects men and women at similar frequencies, with an age of onset ranging from the mid-20s to mid-30s. Multiple studies have documented a more severe disease course in men, with higher rates of visceral involvement, morbidity, and mortality [128, 129, 131]. Women more often demonstrate genital ulcers and erythema nodosum and overall have been shown to have a better prognosis than their male counterparts [128]. Disease severity also seems to vary by geography, with milder disease reported in non-endemic regions such as the United States [130].

Proposed diagnostic criteria by an international Behcet disease study group include recurrent (>3 episodes per year) oral ulcers and two of the following minor criteria: recurrent genital ulceration, uveitis, cutaneous lesions, and/or a positive pathergy test [132]. Pathergy refers to the development of a hypersensitive clinical response to relatively minor trauma; typically, a papule or pustule develops in response to a minor skin irritation. The pathergy test used in the diagnosis of BD involves skin puncture with a sterile needle and evaluation for formation of an erythematous papule or pustule after 24–48 h and has a specificity of 87% and sensitivity of 60% for BD [1, 129]. One study found a positive test in nearly 60% of patients [131].

The pathogenesis of BD is complex and still under investigation. Currently, most experts believe BD results from a complex interplay between genetic predisposition, the activated immune system, and the possible contribution of infectious triggers. The presence of HLA-B51 allele of the major histocompatibility complex (MHC) class I has been strongly linked to BD in multiple studies [129, 130, 133] and has been estimated to account for about 20% of the genetic susceptibility to BD [129]. HLA-B51 genotype was noted to confer an increased risk of venous thrombosis [133]. Other MHC class I variants have also been investigated with regard to their relationship to various disease manifestations in BD [129, 133], as well as other genes encoding cytokines or regulators of cytokines [129]. Epigenetic events, particularly methylation (resulting in transcriptional silencing) of genes that affect T-helper cell function, have been proposed to play a role in BD [130]. Activation of Th-1 and Th-17 immune responses are thought to mediate much of the organ damage in BD, with cytokines related to these types of responses (IL-2, IFNγ, IL-6, IL-23, and others) being elevated in patients with BD [129, 130]. Hyper-activation of these immune responses may result from cross-reactivity with an infectious antigen, and innumerable viruses, bacteria, and mycobacteria have been proposed as inciting infectious agents in BD [129].

Treatment of BD requires a multidisciplinary approach, particularly when there is widespread organ involvement. Treatment is generally individualized and based on the severity of symptoms and organs involved [130]. Genital ulcerations in particular are generally treated with topical corticosteroid or steroid-sparing agents, systemic immunosuppressants such as corticosteroids, azathioprine, and cyclosporine, thalidomide, and colchicine [129, 130]. Anti-TNF-α therapies are commonly employed for visceral organ involvement [129].

2.7.1.1 Clinical Features

Ulcerations (both genital and oral) are generally some of the first manifestations of the disease and may be the only manifestations in up to one-half of patients [131] (Fig. 2.38a, b). Genital ulcers are typically large and deep, involve the labia majora, and heal over the course of several weeks with scarring. Lesions are generally large (often exceeding 1 cm in size), "punched out" appearing, and have a sharp border [129]. Ulcers may worsen in pregnancy [129]. Involvement of the cervix and vagina should prompt consideration of other ulcerative conditions as ulcerations at these sites are unusual in BD [130].

Diagnosis of BD remains predominantly a clinical one, and diagnostic laboratory tests are lacking. Biopsy may be supportive but is rarely specific. Additional skin examination should reveal the presence (or at least a history) of multiple, recurrent, painful mouth ulcers; the absence of mouth ulcerations strongly argues against a diagnosis of BD as this is a major criteria for diagnosis of the syndrome [130]. Erythema nodosum (painful subcutaneous nodules, frequently on the lower legs) may be seen in a subset of patients. Folliculitis or acneiform-like lesions are also relatively common cutaneous findings [129], and may be related to the pathergy that frequently is documented in BD [134].

The clinical differential diagnosis of genital ulcers in BD include infectious diseases (including herpes simplex virus, syphilis, chancroid, and lymphogranuloma venereum), ulcerative lichenoid processes such as fixed drug eruption, erosive lichen planus, or erythema multiforme, malignancy, and many of the other diseases discussed in this chapter than can present with genital ulceration [129].

2.7.1.2 Histopathologic Features

Biopsies of the ulcers in BD are relatively nonspecific. Ulcer with fibrin deposition along the dermal–epidermal junction is characteristic, with underlying mixed inflammation (Fig. 2.39). Neutrophils may predominate in early lesions, with transition to more lymphocytes, histiocytes, and plasma cells over time [1]. Vascular damage is a frequently documented event and fibrin rimming vascular walls may be seen (Fig. 2.40). Lymphocytic vasculitis (Fig. 2.41) has been suggested as being more common than a leukocytoclastic vasculitis [1]; however, distinction between a primary leukocytoclastic vasculitis and secondary neutrophilic inflammation of vessels in an ulcer bed can be difficult if not impossible.

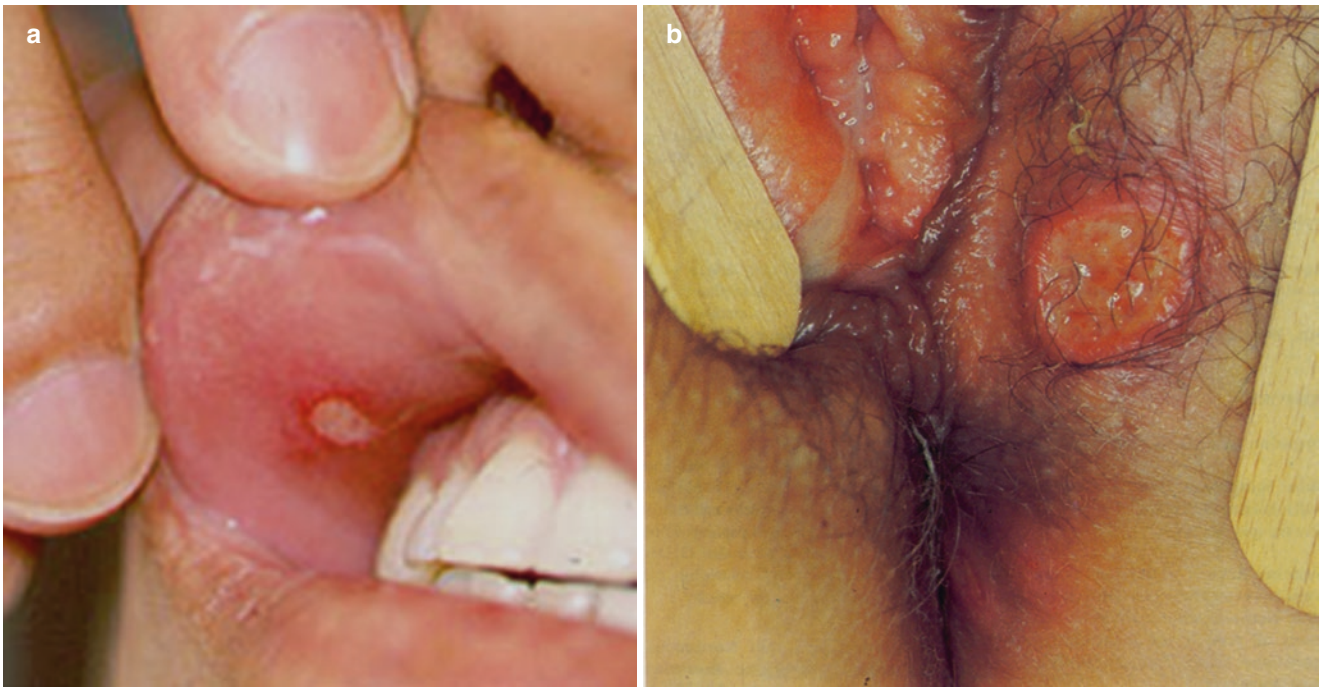

Fig. 2.38 Behcet's disease. (**a**) Oral ulcers are invariably part of the disease manifestations. (**b**) Ulceration of the labia majora is large and deep. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

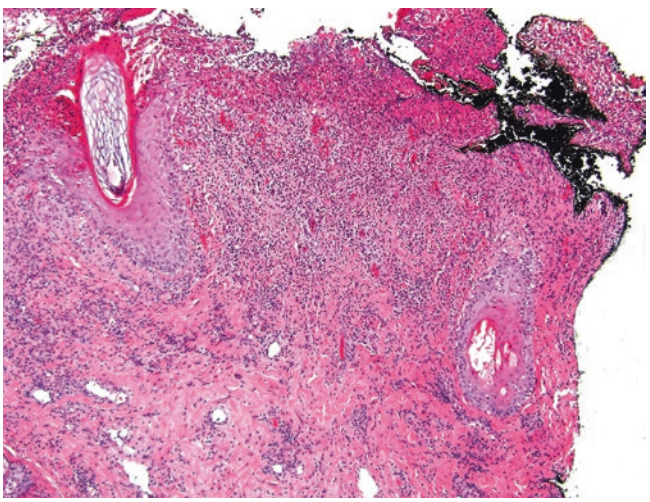

Fig. 2.39 Behcet disease. Surface ulceration with dermal inflammation is nonspecific but commonly seen in BD

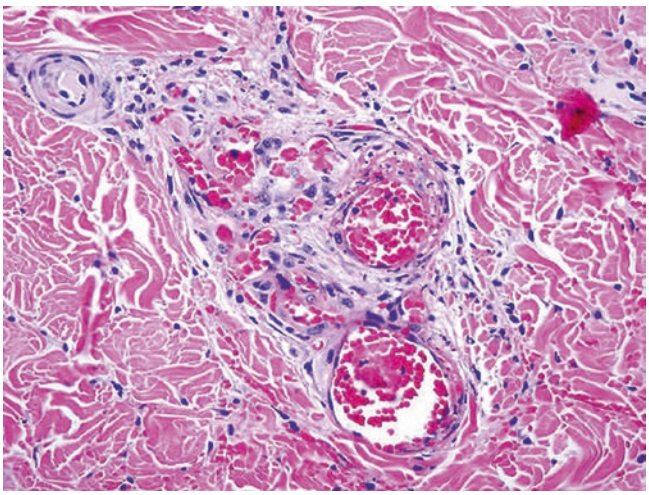

Fig. 2.40 Behcet disease. Vascular damage may be seen, with fibrin rimming vascular walls. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

2.7.1.3 Immunohistochemical Features

Ancillary testing performs a limited role in the workup of possible BD. Stains to exclude identifiable infectious etiologies are recommended.

2.7.1.4 Differential Diagnosis

The histologic differential diagnosis includes ulcers from other localized and systemic diseases. It is important for biopsy specimens to include some portion of intact epidermis to evaluate for the characteristic lichenoid infiltrate or vacuolar changes and cytotoxic damage to the epithelium that would characterize erosive lichen planus, fixed drug eruption, or erythema multiforme. Herpetic ulcers may be differentiated from those occurring in BD by recognition of nuclear molding, chromatin margination, and multinucleation in the adjacent epidermal keratinocytes; immunohistochemical stains for the viral antigens may be useful if viral cytopathic effect is not readily identified. Pyoderma gangrenosum may show ulcer with underlying zonal inflammation. Crohn disease can present with ulcerations and may

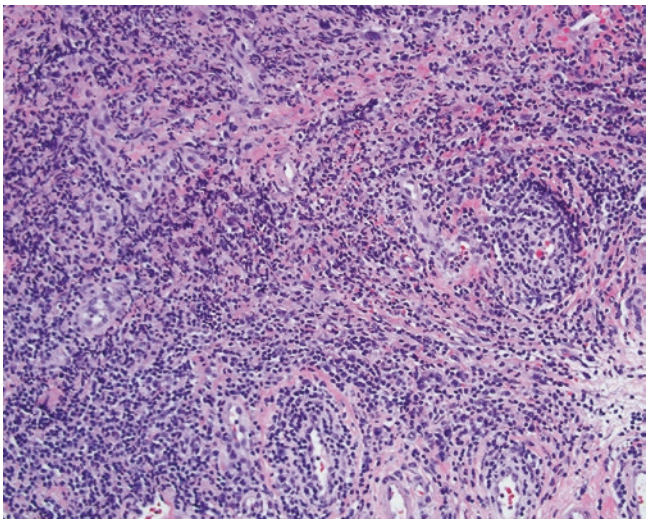

Fig. 2.41 Behcet disease. A lymphocytic vasculitis may be more common than a neutrophilic (leukocytoclastic) vasculitis. Note the layers of lymphocytes concentrically surrounding the vessels in this image

lack the characteristic and historically disease-defining granulomas, thus closely mimicking BD; the similarities between Crohn and Behcet disease in terms of clinical and histologic presentation and organ involvement have led to speculation about disease overlap [135].

Although the histopathologic features in BD are nonspecific, biopsies may be particularly useful to exclude other entities within the clinical differential. Autoimmune-mediated blistering disorders are often histologically distinct (and will show positive direct immunofluorescence studies), and malignancies can generally be detected with adequate sampling.

2.7.2 Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis that presents as nonhealing, sterile ulcerations. Ulcerations expand outward, are nonresponsive to antibiotics, and typically worsen rather than improve with surgical intervention due to pathergy. The vulva is rarely involved by PG; however, familiarity with the entity is important for clinicians and pathologists to prevent misdiagnosis and mistreatment. It can be misdiagnosed as infection (including necrotizing fasciitis), leading to inappropriate surgical intervention and subsequent long-term scarring sequelae [136, 137].

PG may present within any age group; vulvar involvement by PG is limited to case reports, with patients presenting anywhere from the late teens to late 70s [138–141]. PG has important associations with a variety of other diseases, and it is estimated that systemic disease association is present in approximately half of cases of PG [138]. The most common associations include rheumatologic disease, inflammatory bowel disease, or lymphoproliferative disorders.

PG is a diagnosis of exclusion and ruling out other causes of ulceration through careful history and physical exam, tissue cultures, and laboratory studies is imperative.

Treatment usually requires initiation of high dose topical and/or systemic corticosteroids or other immunosuppressive medications, although some lesions may be refractory to treatment. Debridement or surgical management should be avoided as it generally worsens the condition.

2.7.2.1 Clinical Features

Vulvar involvement by PG presents as large, painful ulcers, classically with a violaceous to gun-metal gray raised edge or rolled border [138, 141]. Ulcers often have jagged, irregular borders and may be surfaced by a purulent exudate and frank necrosis. Ulcers may also be multifocal and are often described as being "punched out" [138].

Patients may report that the lesion began as a small erythematous pustule or nodule which then ulcerated and expanded over time. Minimal trauma may further worsen the ulcer or precipitate new ones, a phenomenon known as pathergy. Lesions are generally exquisitely tender, with patients often reporting pain that seems out of proportion to exam findings [142]. With treatment and time, the ulcers flatten and heal leaving atrophic scars that have been described as cribriform.

The ulcerative variant of PG is most common; however, vegetative, bullous, and pustular variants are also reported [142].

The clinical differential diagnosis of PG is infection, other noninfectious ulcerating diseases such as Behcet syndrome, and less commonly malignancy [141]. For vulvar lesions, infections from numerous organisms may be considered. For the diagnosis of PG, a full infectious workup should be negative. Biopsy can support the diagnosis of PG, but the histologic features are not specific for the diagnosis. Biopsy will also help to rule out specific infectious etiologies or malignancy. The optimal biopsy technique to evaluate a patient with possible PG is via an incisional biopsy that encompasses the inflamed, rolled edge of the ulcer [142].

2.7.2.2 Histopathologic Features

Microscopically, biopsies of PG demonstrate an ulcer with underlying dense dermal inflammation (Fig. 2.42). As PG is a neutrophilic dermatosis, the dermis is filled predominantly with neutrophils, and vasculitis should be absent. There may be necrosis of the dermal collagen and leukocytoclasis (fragmented neutrophil debris). This histologic appearance will mimic an infectious abscess. There are no diagnostic features to confirm PG. However, if the rolled border of the ulcer has been appropriately sampled, the pathologist will be able to visualize "undermining" of the ulcer, that is, extension of the neutrophilic infiltrate under the edges of the ulcer bed and extending radially away from the ulcer. There have been some papers which suggest that very early lesions of PG may have a lymphocyte—rather than neutrophil—predominant inflammatory infiltrate [143].

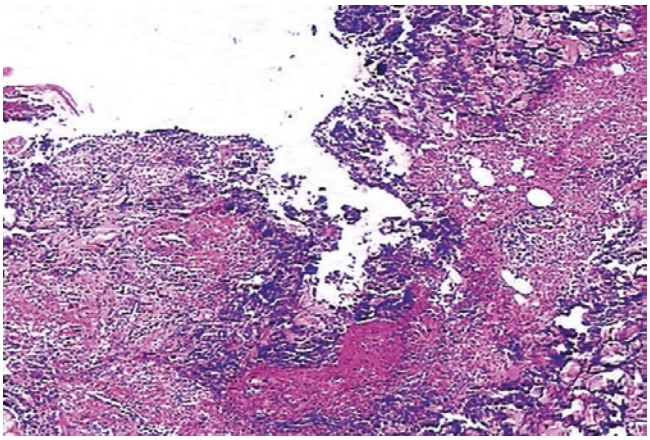

Fig. 2.42 Pyoderma gangrenosum. Histologic features are relatively nonspecific, showing ulceration with undermined borders and dermal neutrophils. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

2.7.2.3 Immunohistochemical Features and Differential Diagnosis

Ancillary testing is necessary to exclude infectious etiologies, which comprises the major histologic differential diagnosis. Special stains (Gram, PAS, GMS, and Fite or Ziehl-Neelsen) should be negative for bacterial, fungal, and mycobacterial organisms, respectively. If the above histologic features are present and stains for infectious organisms are negative, it is the author's habit to make a diagnosis of "Neutrophilic dermatosis," with a comment suggesting that if infectious etiologies have been excluded clinically and through microbial culture methods, then the features would be compatible with a clinical diagnosis of PG.

2.8 Folliculocentric/Follicular Occlusion Reaction Pattern

2.8.1 Fox–Fordyce Disease

Fox–Fordyce Disease (FFD) is a follicular-based dermatosis thought to be due to obstruction of the apocrine sweat duct, which empties directly into the hair follicle (as opposed to eccrine sweat ducts which empty directly onto the skin surface). FFD is also commonly referred to as "apocrine miliaria." As might be expected based on the presumed pathogenesis, this disease manifests in skin regions containing apocrine sweat glands, namely the genital skin, axillae, and areola. Exacerbation of disease occurs with activities that induce sweating including exercise, warm weather, sexual activity, and other physical or emotional stressors [144, 145]. The disease was first described in 1902 by Drs. Fox and Fordyce. A strong role for a hormonal influence can be argued, as this dermatosis occurs predominantly in women of reproductive age (up to 90% of cases are thought to arise in this population [145]). Fluctuations with menstruation and improvement during pregnancy, with oral contraceptive use, and after menopause also lend credence to the role of hormones in the pathophysiology of the disease [144].

The pathogenesis, as alluded to above, is thought to be initiated by plugging of the hair follicles. This plugging (correlating histologically with follicular hyperkeratosis) allows for accumulation of the mucin and lipid-rich apocrine sweat secretions which are then eliminated through the follicular epithelium and may incite an inflammatory response. Histiocytes phagocytose the material, imparting a foamy appearance that correlates with the xanthomatous infiltrate frequently seen in biopsies [146, 147].

2.8.1.1 Clinical Features

The hallmark presentation of FFD is relapsing and recurring pruritus of skin regions characterized by the presence of apocrine glands. While the axilla is most commonly involved, vulvar involvement alone has also been described [148]. Patients generally present with a history of itching in the axilla and perigenital regions. The clinical history will often reveal exacerbations during summer months, perimenstrually, and/or after exercise. Examination reveals small (1–3 mm), smooth, uniform, and equidistant follicular-based papules in the axillae and on the groin and areola (Fig. 2.43).

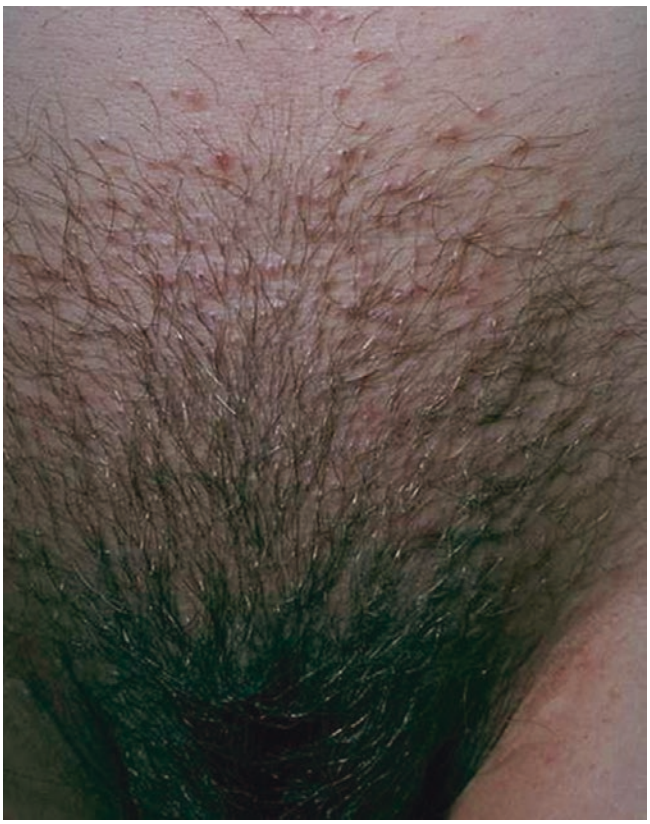

Fig. 2.43 Fox–Fordyce disease. Physical examination reveals follicular-based, uniform flesh-colored papules on mons pubis and external vulva. Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

The color of the lesions range from flesh colored to slightly erythematous to faintly yellow [146], and most papules lack an associated hair shaft [144].

Notably, although a hormonal influence is presumed based on the demographic patterns of affected patients, laboratory studies have not documented any consistent abnormalities in patients with FFD [144], and therefore are not indicated in the workup of this entity. The diagnosis is typically made clinically, although occasionally biopsy may be necessary to support the diagnosis and exclude other similarly appearing entities such as folliculitis (including acneiform eruptions and hidradenitis), lichen amyloidosis, lichen nitidus, and eruptive syringomas [145, 148].

Treatment of FFD is notoriously difficult. Avoidance of sweating may minimize exacerbations. Topical therapies including corticosteroids, retinoids, benzoyl peroxide, calcineurin inhibitors, and antibiotics are all mainstays of treatment. Systemic therapies include retinoids and oral contraceptive pills. Surgical excision or electrocautery have been reported in treatment-refractory cases [144, 145, 148].

2.8.1.2 Histopathologic Features

Early reports of the histology of FFD focused on the presence of a "retention vesicle" in the hair follicle in the region where the apocrine duct exits into the hair follicle (Fig. 2.44). Subsequent studies have expanded the features associated with the disease [146] and have abolished the requirement of a retention vesicle to be diagnostic. Some series have not convincingly identified retention vesicles in any cases [147]. As such, histopathologic examination of clinically presumed FFD may show a variety of features, many of which may be subtle. A nonspecific but nonetheless helpful clue will be the low-power observation of dilated apocrine glands [149]; however, this observation requires a punch biopsy as apocrine glands generally are not sampled in shave biopsies (Fig. 2.45). Most commonly observed and more specific features include spongiosis (edema) of the follicular infundibulum, follicular hyperkeratosis (follicular plugging by keratin), and dilation of the follicular infundibulum [146, 147, 150, 151] (Fig. 2.46). More contemporary series in the literature have focused on the presence of perifollicular foamy histiocytes, which in some cases may be subtle [145], and in other cases may be robust enough to form a frankly xanthomatous appearing zone [147, 151]. This perifollicular histiocytic infiltrate may also include lymphocytes and mast cells [147]. A less commonly observed feature is dyskeratosis within the follicular epithelium [146], which was seen in approximately one-quarter of cases in one study [147]. Cornoid lamellation (a narrow, vertical column of parakeratosis) and vacuolar changes in the epidermis have also been described occasionally [146] but were not seen in any of the seven cases examined of the largest series to date [147]. As the features may be subtle, serial sections may be necessary to find the described features that support the diagnosis;

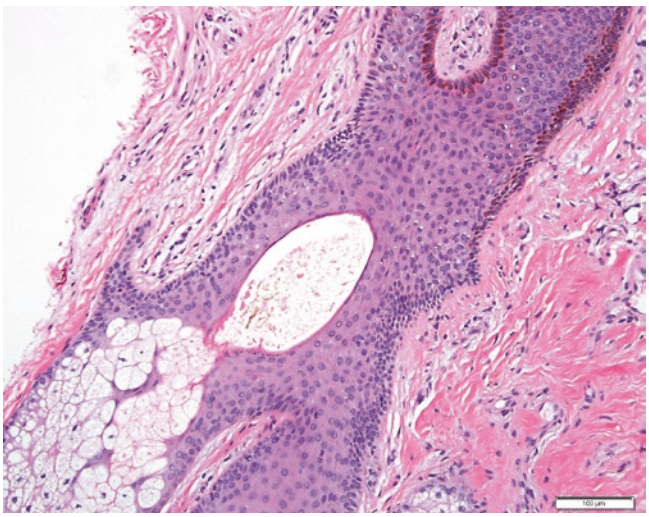

Fig. 2.44 Fox–Fordyce disease. A "retention vesicle" is seen in the follicle in the region where the apocrine duct enters the hair follicle

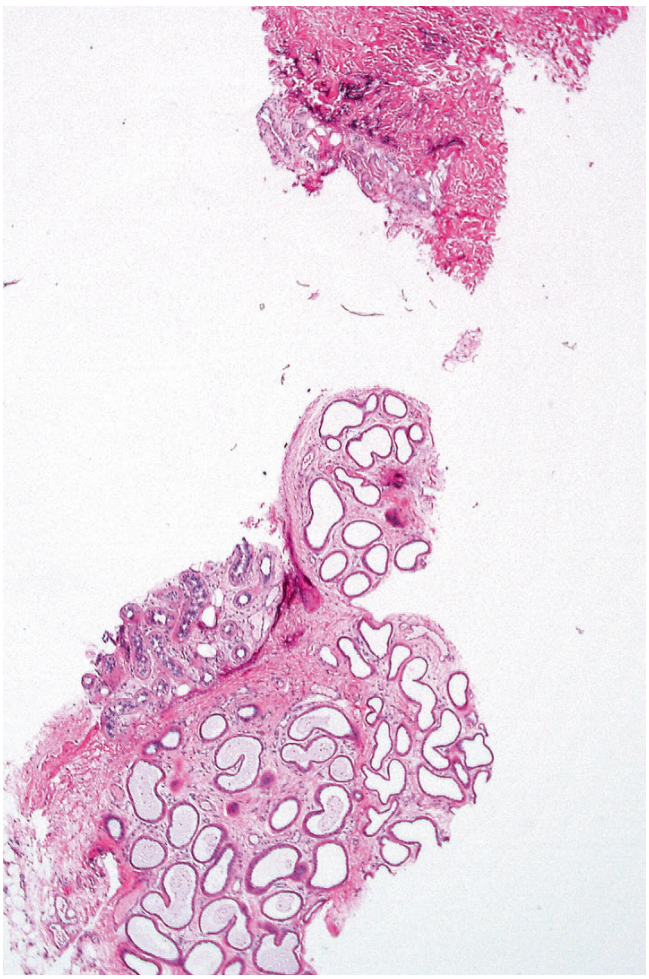

Fig. 2.45 Fox–Fordyce disease. Apocrine glands are often dilated, but not always sampled

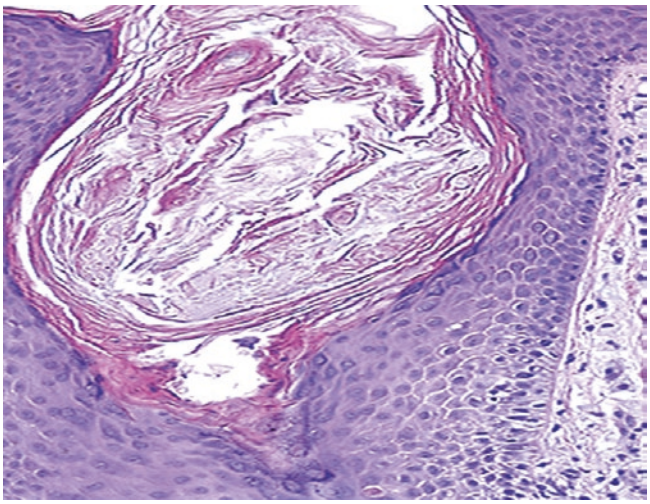

Fig. 2.46 Fox–Fordyce disease. The hair follicle is expanded and plugged by keratin (follicular hyperkeratosis). Photo provided courtesy of previous edition in Chinese (Science Press, Beijing, China)

alternatively, transverse sectioning (rather than the classical vertical sectioning of punch biopsies) can allow for evaluation of all hair follicles in the biopsy at once and has been advocated as the optimal method for diagnosis of FFD [150].

2.8.1.3 Immunohistochemical Features

Ancillary studies are not required to make the diagnosis. CD68 immunostaining will amplify subtle perifollicular histiocytes [145, 147]. The presence of PAS-positive, diastase-resistant material in the perifollicular zones has been used to support the notion that the perifollicular xanthomatous cells contain apocrine sweat secretions [151], but this finding has not been duplicated in other studies or cases [147, 149].

2.8.1.4 Differential Diagnosis

The histologic differential diagnosis includes xanthoma variants, granulomatous rosacea, and granulomatous perifolliculitis [147]. Xanthomas, which may occasionally involve similar sites as FFD, classically do not show preferential perifollicular location but are more interstitial. Serum lipid testing would reveal abnormalities in the case of xanthoma but would be expected to be normal in FFD. Granulomatous rosacea and granulomatous perifolliculitis would be unusual in the sites affected by FFD and are also typified by a granulomatous appearance that is less xanthomatous and may include multinucleated giant cells.

2.8.2 Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a complex disease causing considerable morbidity for patients due to disabling pain and scarring. It is a chronic disease with episodic flaring. Patients are typically misdiagnosed in early stages of the disease, experience frequent delays in diagnosis, and often are inadequately managed by physicians unfamiliar with treating HS. The disease presents more commonly in females than in males (ratio 3:1) as painful inflammatory nodules in the intertriginous skin folds. Between 1 and 4% of the population may be affected by HS [125, 152]. The disease usually presents after puberty and often remits after menopause, which supports assertions of a hormonal role in the disease.

The pathogenesis of HS is related primarily to hair follicle abnormalities; however, factors such as the immune system, hormonal effects, diet and obesity, and external factors such as smoking all have been found to play a role in the development of the disease. The term "hidradenitis" is somewhat misleading as the sweat glands are not the source of the disease. In fact, HS is considered to be one of four diseases within the "follicular occlusion tetrad"—the others being acne conglobata, pilonidal cysts, and dissecting cellulitis [153]. All of these entities are linked by a similar pathogenic mechanism, namely, the obstruction of hair follicles, leading to occlusion, rupture, and recruitment of inflammatory cells. One of the first histologic changes in HS is hyperplasia and hyperkeratosis of the follicle in the region of the infundibulum (near the opening to the surface) [154]. As the follicles become hyperproliferative, sebum production may be increased [125] and occlusion of the follicle opening may occur. Ultimately, the expanded follicles rupture, spilling sebum, hair shafts, and any resident bacteria into the dermis and eliciting a robust inflammatory reaction. Defective immune responses to common skin flora may heighten the inflammatory response and prevent resolution of inflammation [153]. Over time, deep-seated ruptured follicles can form epithelial sinuses which can coalesce to form draining sinus tracts and nodules that characterize the disease.

HS can be seen in association with inflammatory bowel disease (both Crohn disease and ulcerative colitis), spondyloarthropathies linked to HLA B27, and pyoderma gangrenosum [153]. The association of HS with the metabolic syndrome has been a source of recent research focus [152].

Treatment of HS involves multidisciplinary care. Supportive care, medical management, and surgical excisions may all play a role through the duration of this chronic disease [125]. Current efforts involve increasing awareness of the disease to allow for earlier diagnosis to prevent long-term scarring sequelae. Chronic lymphedema and development of squamous cell carcinoma due to persistent inflammation are rare complications [152].

2.8.2.1 Clinical Features

HS presents with inflammatory lesions in the axillary, inguinal, anogenital, and inframammary skin folds. Patients will report recurring, waxing, and waning skin infections involving these regions. Skin lesions are generally tender and painful, and may prompt presentation to emergency departments

rather than a primary care or gynecologic care center [125] (Fig. 2.47).

Physical examination during an acute episode may reveal large erythematous papules and nodules with fluctuance or bogginess distributed in the intertriginous sites. Acne-like lesions and pustules may be readily evident, as may ulcers and erosions. So-called "tombstone comedones" are characteristic of the disease. Inflammatory nodules may drain purulent, seropurulent, malodorous, and/or bloody fluid. Evidence of chronicity of the disease will be atrophic or hypertrophic scars, strictures, and contractures in these same areas [125]. Vulvar edema may be present as a result of inflammation elsewhere in the perigenital region.

Full body examination to include other sites that HS typically involves is imperative. Lymphadenopathy may sometimes be present as a result of the marked inflammation.

The clinical differential diagnosis of vulvar inflammatory nodules will include infections (including bacterial, mycobacterial, deep fungal, chronic herpetic, and other sexually transmitted infections), noncontiguous Crohn disease, and carcinoma. Cultures for microbial organisms are important to exclude infectious etiologies (whether primary or secondary). A skin biopsy (see histologic features below) is not always required to diagnose HS, but will be essential to exclude other more nefarious diagnoses.

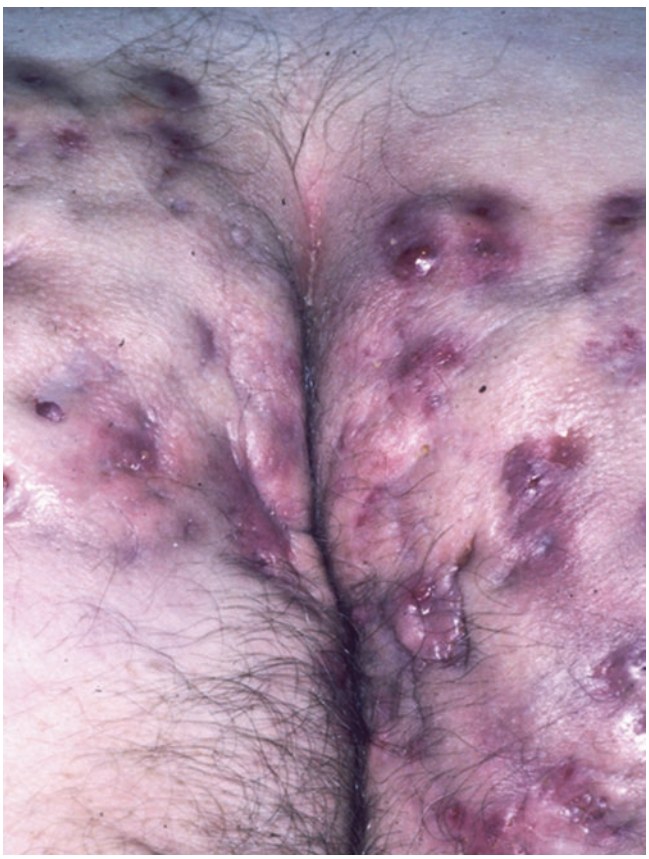

Fig. 2.47 Hidradenitis suppurativa. The vulva shows multiple erythematous and boggy lesions (Courtesy of Dr. Kenneth Hatch, University of Arizona)

2.8.2.2 Histopathologic Features

Skin biopsy is not requisite for a diagnosis of HS, and the features may differ depending on the stage and severity of the patient's disease.

Early lesions have been described as having both epidermal and follicular hyperplasia, perifolliculitis at the level of the infundibulum, and accumulation of keratin debris within the dilated follicle (follicular hyperkeratosis). These features were more common than actual follicular rupture or a neutrophilic-rich infiltrate, both of which were seen in only a quarter of early cases [155]. Follicular rupture and neutrophilic margination was postulated to be a later event in the sequence of lesional development (Figs. 2.48 and 2.49).

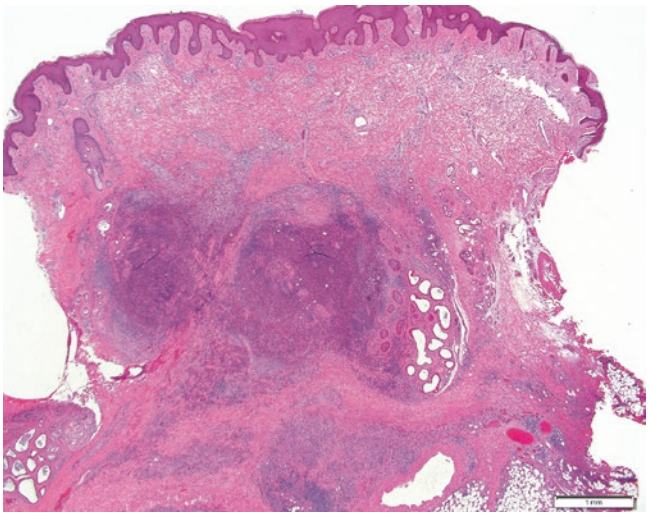

Fig. 2.48 Hidradenitis suppurativa. Scanning magnification shows a pan dermal infiltrate that destroys adnexal structures

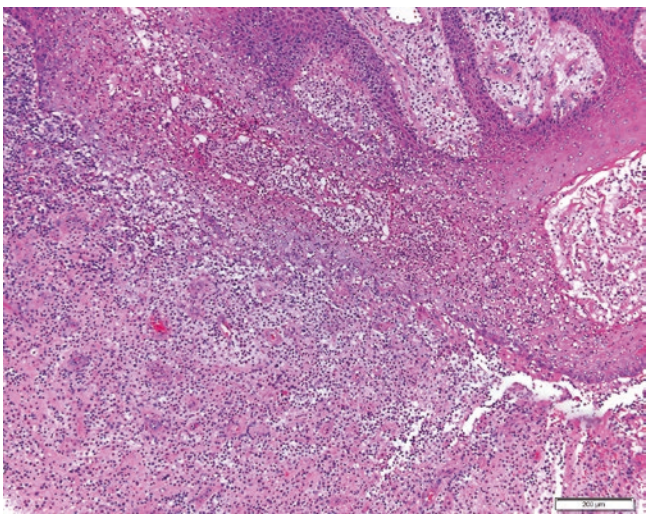

Fig. 2.49 Hidradenitis suppurativa. Follicular destruction and rupture mediated by neutrophils is commonly seen

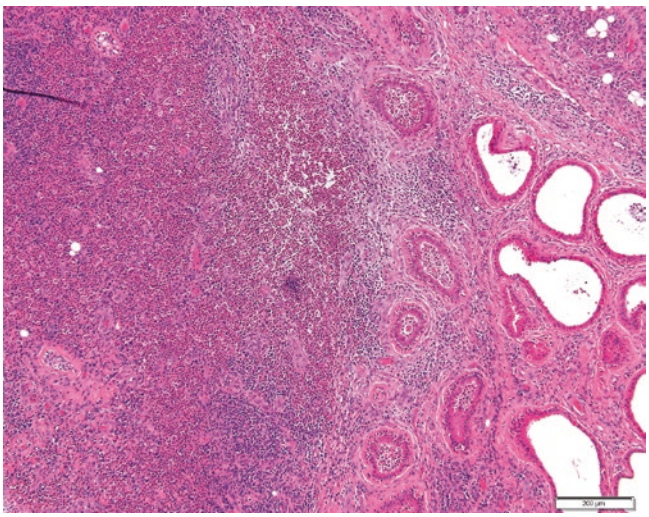

Fig. 2.50 Hidradenitis suppurativa. Less commonly, apocrine glands are invaded and destroyed by inflammation

Apocrine gland inflammation was seen in approximately half of cases [155] (Fig. 2.50), once again emphasizing that the term "hidradenitis" can be a misnomer.

The histologic features in well-established lesions (as may be seen in patients being surgically managed) are not particularly specific to the disease. However, the features seen are fairly characteristic and related to the pathogenesis. Dilated and ruptured hair follicles and follicular cysts are seen, with surrounding mixed inflammation and dermal fibrosis. Inflammation tends to be composed of neutrophils, lymphocytes, admixed polytypic plasma cells, histiocytes, and mast cells. Naked hair shafts surrounded by a granulomatous reaction and epithelial-lined sinus tracts are possible [156].

2.8.2.3 Immunohistochemical Features and Differential Diagnosis

The histologic differential diagnosis may include infection or nonspecific ruptured folliculitis. Special cytochemical or immunohistochemical stains to exclude infection may be useful, although microbial cultures will always provide a more sensitive mechanism to detect organisms. The presence of discrete, noncaseating granulomas may provide a clue to a diagnosis of metastatic/noncontiguous Crohn disease.

If tissue is provided without accompanying clinical information, it may be impossible to provide an outright diagnosis of HS. However, the astute pathologist, when confronted with a vulvar biopsy showing scarring, inflammation, and ruptured pilosebaceous units, may be able to suggest the possibility of HS.

Acknowledgements The author thanks Dr. Susi Jeffus for her generous editorial assistance during the preparation of this chapter.

References

1. Hoang MP, Selim MA. Vulvar pathology. 1st ed. New York: Springer; 2015.
2. Niamh L, Naveen S, Hazel B. Diagnosis of vulval inflammatory dermatoses: a pathological study with clinical correlation. Int J Gynecol Pathol. 2009;28:554–8.
3. Chan MP, Zimarowski MJ. Vulvar dermatoses: a histopathologic review and classification of 183 cases. J Cutan Pathol. 2015;42:510–8.
4. O'Keefe RJ, Scurry JP, Dennerstein G, et al. Audit of 114 non-neoplastic vulvar biopsies. Br J Obstet Gynaecol. 1995;102:780–6.
5. Koppes SA, Engebretsen KA, Agner T, et al. Current knowledge on biomarkers for contact sensitization and allergic contact dermatitis. Contact Dermatitis. 2017;77:1–16.
6. Schlosser BJ. Contact dermatitis of the vulva. Dermatol Clin. 2010;28:697–706.
7. Warner N, Salvaggio HL, Zaenglein AL. JAAD Grand Rounds quiz. An erosive vulvar rash. J Am Acad Dermatol. 2013;68:350–2.
8. O'Gorman SM, Torgerson RR. Allergic contact dermatitis of the vulva. Dermatitis. 2013;24:64–72.
9. Nardelli A, Degreef H, Goossens A. Contact allergic reactions of the vulva: a 14-year review. Dermatitis. 2004;15:131–6.
10. Pichardo-Geisinger R. Atopic and contact dermatitis of the vulva. Obstet Gynecol Clin N Am. 2017;44:371–8.
11. Rosa G, Fernandez AP, Vij A, et al. Langerhans cell collections, but not eosinophils, are clues to a diagnosis of allergic contact dermatitis in appropriate skin biopsies. J Cutan Pathol. 2016;43:498–504.
12. Willis CM, Young E, Brandon DR, et al. Immunopathological and ultrastructural findings in human allergic and irritant contact dermatitis. Br J Dermatol. 1986;115:305–16.
13. Taylor RM. Histopathology of contact dermatitis. Clin Dermatol. 1986;4:18–22.
14. Rosa G, Fernandez AP, Schneider S, et al. Eosinophils are rare in biopsy specimens of psoriasis vulgaris. J Cutan Pathol. 2017;44:1027–32.
15. Sharon VR, Konia TH, Barr KL, et al. Assessment of the 'no eosinophils' rule: are eosinophils truly absent in pityriasis lichenoides, connective tissue disease, and graft-vs.-host disease? J Cutan Pathol. 2012;39:413–8.
16. Ozalp SS, Telli E, Yalcin OT, et al. Vulval pruritus: the experience of gynaecologists revealed by biopsy. J Obstet Gynaecol. 2015;35:53–6.
17. Lynch PJ, Moyal-Barracco M, Scurry J, et al. 2011 ISSVD Terminology and classification of vulvar dermatological disorders: an approach to clinical diagnosis. J Low Genit Tract Dis. 2012;16:339–44.
18. Chibnall R. Vulvar pruritus and lichen simplex chronicus. Obstet Gynecol Clin N Am. 2017;44:379–88.
19. Lynch PJ. 2006 International Society for the Study of Vulvovaginal Disease classification of vulvar dermatoses: a synopsis. J Low Genit Tract Dis. 2007;11:1–2.
20. Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133:377–85.
21. Kapila S, Bradford J, Fischer G. Vulvar psoriasis in adults and children: a clinical audit of 194 cases and review of the literature. J Low Genit Tract Dis. 2012;16:364–71.
22. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370:263–71.
23. Andreassi L, Bilenchi R. Non-infectious inflammatory genital lesions. Clin Dermatol. 2014;32:307–14.
24. Guerrero A, Venkatesan A. Inflammatory vulvar dermatoses. Clin Obstet Gynecol. 2015;58:464–75.

25. Omland SH, Gniadecki R. Psoriasis inversa: a separate identity or a variant of psoriasis vulgaris? Clin Dermatol. 2015;33:456–61.
26. Woo YR, Cho DH, Park HJ. Molecular mechanisms and management of a cutaneous inflammatory disorder: psoriasis. Int J Mol Sci. 2017;18:2684.
27. Ogawa E, Sato Y, Minagawa A, et al. Pathogenesis of psoriasis and development of treatment. J Dermatol. 2018;45:264–72.
28. Geller S, Xu H, Lebwohl M, et al. Malignancy risk and recurrence with psoriasis and its treatments: a concise update. Am J Clin Dermatol. 2018;19:363–75.
29. Zamirska A, Reich A, Berny-Moreno J, et al. Vulvar pruritus and burning sensation in women with psoriasis. Acta Derm Venereol. 2008;88:132–5.
30. Chau T, Parsi KK, Ogawa T, et al. Psoriasis or not? Review of 51 clinically confirmed cases reveals an expanded histopathologic spectrum of psoriasis. J Cutan Pathol. 2017;44:1018–26.
31. Kocak M, Bozdogan O, Erkek E, et al. Examination of Bcl-2, Bcl-X and bax protein expression in psoriasis. Int J Dermatol. 2003;42:789–93.
32. Moy AP, Murali M, Kroshinsky D, et al. Immunologic overlap of helper T-cell subtypes 17 and 22 in erythrodermic psoriasis and atopic dermatitis. JAMA Dermatol. 2015;151:753–60.
33. Lotery HE, Galask RP, Stone MS, et al. Ulcerative vulvitis in atypical Reiter's syndrome. J Am Acad Dermatol. 2003;48:613–6.
34. Edwards L, Hansen RC. Reiter's syndrome of the vulva. The psoriasis spectrum. Arch Dermatol. 1992;128:811–4.
35. Lewis FM, Bogliatto F. Erosive vulval lichen planus—a diagnosis not to be missed: a clinical review. Eur J Obstet Gynecol Reprod Biol. 2013;171:214–9.
36. Kirtschig G, Wakelin SH, Wojnarowska F. Mucosal vulval lichen planus: outcome, clinical and laboratory features. J Eur Acad Dermatol Venereol. 2005;19:301–7.
37. Job AM, Kaimal S. Lichen planus hypertrophicus of the vulva—a rare entity. Int J STD AIDS. 2017;28:1048–50.
38. Cooper SM, Haefner HK, Abrahams-Gessel S, et al. Vulvovaginal lichen planus treatment: a survey of current practices. Arch Dermatol. 2008;144:1520–1.
39. Lewis FM. Vulval lichen planus. Br J Dermatol. 1998;138:569–75.
40. Terlou A, Santegoets LA, van der Meijden WI, et al. An autoimmune phenotype in vulvar lichen sclerosus and lichen planus: a Th1 response and high levels of microRNA-155. J Invest Dermatol. 2012;132:658–66.
41. Cooper SM, Kirtschig G, Jeffery KJ, et al. No association between hepatitis B or C viruses and vulval lichen planus in a UK population. BJOG. 2004;111:271–3.
42. Cooper SM, Ali I, Baldo M, et al. The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case-control study. Arch Dermatol. 2008;144:1432–5.
43. Halonen P, Jakobsson M, Heikinheimo O, et al. Cancer risk of lichen planus: a cohort study of 13,100 women in Finland. Int J Cancer. 2018;142:18–22.
44. Ball R, Ball KM, Reutter J. Epithelial vulvar neoplasms and their changing classification. Semin Cutan Med Surg. 2015;34:199–205.
45. Regauer S, Reich O, Eberz B. Vulvar cancers in women with vulvar lichen planus: a clinicopathological study. J Am Acad Dermatol. 2014;71:698–707.
46. Cooper SM, Wojnarowska F. Influence of treatment of erosive lichen planus of the vulva on its prognosis. Arch Dermatol. 2006;142:289–94.
47. Mauskar M. Erosive Lichen Planus. Obstet Gynecol Clin N Am. 2017;44:407–20.
48. Fruchter R, Melnick L, Pomeranz MK. Lichenoid vulvar disease: a review. Int J Womens Dermatol. 2017;3:58–64.
49. Helgesen AL, Gjersvik P, Jebsen P, et al. Vaginal involvement in genital erosive lichen planus. Acta Obstet Gynecol Scand. 2010;89:966–70.
50. Murphy R. Desquamative inflammatory vaginitis. Dermatol Ther. 2004;17:47–9.
51. Simpson RC, Thomas KS, Leighton P, et al. Diagnostic criteria for erosive lichen planus affecting the vulva: an international electronic-Delphi consensus exercise. Br J Dermatol. 2013;169:337–43.
52. Day T, Moore S, Bohl TG, et al. Comorbid vulvar lichen planus and lichen sclerosus. J Low Genit Tract Dis. 2017;21:204–8.
53. Day T, Bowden N, Jaaback K, et al. Distinguishing erosive lichen planus from differentiated vulvar intraepithelial neoplasia. J Low Genit Tract Dis. 2016;20:174–9.
54. Fung MA, LeBoit PE. Light microscopic criteria for the diagnosis of early vulvar lichen sclerosus: a comparison with lichen planus. Am J Surg Pathol. 1998;22:473–8.
55. Brix WK, Nassau SR, Patterson JW, et al. Idiopathic lymphoplasmacellular mucositis-dermatitis. J Cutan Pathol. 2010; 37:426–31.
56. Fistarol SK, Itin PH. Diagnosis and treatment of lichen sclerosus: an update. Am J Clin Dermatol. 2013;14:27–47.
57. Ball SB, Wojnarowska F. Vulvar dermatoses: lichen sclerosus, lichen planus, and vulval dermatitis/lichen simplex chronicus. Semin Cutan Med Surg. 1998;17:182–8.
58. Fischer G, Rogers M. Vulvar disease in children: a clinical audit of 130 cases. Pediatr Dermatol. 2000;17:1–6.
59. Vilano SE, Robbins CL. Common prepubertal vulvar conditions. Curr Opin Obstet Gynecol. 2016;28:359–65.
60. Smith YR, Haefner HK. Vulvar lichen sclerosus: pathophysiology and treatment. Am J Clin Dermatol. 2004;5:105–25.
61. Murphy R. Lichen sclerosus. Dermatol Clin. 2010;28:707–15.
62. Weyers W. Hypertrophic lichen sclerosus with dyskeratosis and parakeratosis—a common presentation of vulvar lichen sclerosus not associated with a significant risk of malignancy. Am J Dermatopathol. 2013;35:713–21.
63. Aide S, Lattario FR, Almeida G, et al. Epstein-Barr virus and human papillomavirus infection in vulvar lichen sclerosus. J Low Genit Tract Dis. 2010;14:319–22.
64. Weyers W. Hypertrophic lichen sclerosus sine sclerosis: clues to histopathologic diagnosis when presenting as psoriasiform lichenoid dermatitis. J Cutan Pathol. 2015;42:118–29.
65. Farrell AM, Dean D, Millard PR, et al. Cytokine alterations in lichen sclerosus: an immunohistochemical study. Br J Dermatol. 2006;155:931–40.
66. de Oliveira GA, de Almeida MP, Soares FA, et al. Metalloproteinases 2 and 9 and their tissue inhibitors 1 and 2 are increased in vulvar lichen sclerosus. Eur J Obstet Gynecol Reprod Biol. 2012;161:96–101.
67. van de Nieuwenhof HP, Bulten J, Hollema H, et al. Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma. Mod Pathol. 2011;24: 297–305.
68. Liegl B, Regauer S. p53 immunostaining in lichen sclerosus is related to ischaemic stress and is not a marker of differentiated vulvar intraepithelial neoplasia (d-VIN). Histopathology. 2006;48:268–74.
69. Li Q, Leopold K, Carlson JA. Chronic vulvar purpura: persistent pigmented purpuric dermatitis (lichen aureus) of the vulva or plasma cell (Zoon's) vulvitis? J Cutan Pathol. 2003;30:572–6.
70. Salopek TG, Siminoski K. Vulvitis circumscripta plasmacellularis (Zoon's vulvitis) associated with autoimmune polyglandular endocrine failure. Br J Dermatol. 1996;135:991–4.
71. Virgili A, Corazza M, Minghetti S, et al. Symptoms in plasma cell vulvitis: first observational cohort study on type, frequency and severity. Dermatology. 2015;230:113–8.
72. Kavanagh GM, Burton PA, Kennedy CT. Vulvitis chronica plasmacellularis (Zoon's vulvitis). Br J Dermatol. 1993;129:92–3.

73. van Kessel MA, van Lingen RG, Bovenschen HJ. Vulvitis plasmacellularis circumscripta in pre-existing lichen sclerosus: treatment with imiquimod 5% cream. J Am Acad Dermatol. 2010;63:e11–3.
74. Bharatia PR, Pradhan AM, Zawar VP. Plasma cell vulvitis. Indian J Sex Transm Dis. 2015;36:185–7.
75. Virgili A, Levratti A, Marzola A, et al. Retrospective histopathologic reevaluation of 18 cases of plasma cell vulvitis. J Reprod Med. 2005;50:3–7.
76. Thomson MA, Carr RA, Ganesan R, et al. Extensive mucinous metaplasia of the vulva arising within Zoon's vulvitis. Br J Dermatol. 2007;156:750–2.
77. Meneux E, Paniel BJ, Pouget F, et al. Vulvovaginal sequelae in toxic epidermal necrolysis. J Reprod Med. 1997;42:153–6.
78. Noel JC, Buxant F, Fayt I, et al. Vulval adenosis associated with toxic epidermal necrolysis. Br J Dermatol. 2005;153:457–8.
79. Bonafe JL, Thibaut I, Hoff J. Introital adenosis associated with the Stevens-Johnson syndrome. Clin Exp Dermatol. 1990;15:356–7.
80. Ciavattini A, Clemente N. Female genital tract chronic graft-versus-host disease: review of the literature. Anticancer Res. 2015;35:13–7.
81. Smith Knutsson E, Bjork Y, Broman AK, et al. Genital chronic graft-versus-host disease in females: a cross-sectional study. Biol Blood Marrow Transplant. 2014;20:806–11.
82. Kornik RI, Rustagi AS. Vulvovaginal graft-versus-host disease. Obstet Gynecol Clin N Am. 2017;44:475–92.
83. Zantomio D, Grigg AP, MacGregor L, et al. Female genital tract graft-versus-host disease: incidence, risk factors and recommendations for management. Bone Marrow Transplant. 2006;38:567–72.
84. Brahimi N, Routier E, Raison-Peyron N, et al. A three-year-analysis of fixed drug eruptions in hospital settings in France. Eur J Dermatol. 2010;20:461–4.
85. Fischer G. Vulvar fixed drug eruption. A report of 13 cases. J Reprod Med. 2007;52:81–6.
86. Kavala M, Topaloglu Demir F, Zindanci I, et al. Genital involvement in pemphigus vulgaris (PV): correlation with clinical and cervicovaginal Pap smear findings. J Am Acad Dermatol. 2015;73:655–9.
87. Akhyani M, Chams-Davatchi C, Naraghi Z, et al. Cervicovaginal involvement in pemphigus vulgaris: a clinical study of 77 cases. Br J Dermatol. 2008;158:478–82.
88. Malik M, Ahmed AR. Involvement of the female genital tract in pemphigus vulgaris. Obstet Gynecol. 2005;106:1005–12.
89. Bohl TG. Vulvar ulcers and erosions—a dermatologist's viewpoint. Dermatol Ther. 2004;17:55–67.
90. Esmaili N, Chams-Davatchi C, Valikhani M, et al. Pemphigus vulgaris in Iran: a clinical study of 140 cases. Int J Dermatol. 2007;46:1166–70.
91. Spindler V, Eming R, Schmidt E, et al. Mechanisms causing loss of keratinocyte cohesion in pemphigus. J Invest Dermatol. 2018;138:32–7.
92. Atzmony L, Hodak E, Gdalevich M, et al. Treatment of pemphigus vulgaris and pemphigus foliaceus: a systematic review and meta-analysis. Am J Clin Dermatol. 2014;15:503–15.
93. Saldanha CS, Shenoy MM, Shanthala PR, et al. Multiple vegetating lesions over the genitalia. Diagnosis: pemphigus vegetans. Indian J Dermatol Venereol Leprol. 2015;81:325–6.
94. Jain V, Jindal N, Imchen S. Localized pemphigus vegetans without mucosal involvement. Indian J Dermatol. 2014;59:210.
95. Vaughan Jones SA, Salas J, McGrath JA, et al. A retrospective analysis of tissue-fixed immunoreactants from skin biopsies maintained in Michel's medium. Dermatology. 1994;189(Suppl 1):131–2.
96. Wick MR. Bullous, pseudobullous, & pustular dermatoses. Semin Diagn Pathol. 2017;34:250–60.
97. Diercks GF, Pas HH, Jonkman MF. Immunofluorescence of autoimmune bullous diseases. Surg Pathol Clin. 2017;10:505–12.
98. Lewis FM, Agarwal A, Neill SM, et al. The spectrum of histopathologic patterns secondary to the topical application of EMLA(R) on vulvar epithelium: clinicopathological correlation in three cases. J Cutan Pathol. 2013;40:708–13.
99. Nigen S, Poulin Y, Rochette L, et al. Pyodermatitis-pyostomatitis vegetans: two cases and a review of the literature. J Cutan Med Surg. 2003;7:250–5.
100. Carvalho S, Sanches M, Alves R, et al. Pyodermatitis vegetans of the vulva. Dermatol Online J. 2016;22(6).
101. Farrell AM, Kirtschig G, Dalziel KL, et al. Childhood vulval pemphigoid: a clinical and immunopathological study of five patients. Br J Dermatol. 1999;140:308–12.
102. Goldstein AT, Anhalt GJ, Klingman D, et al. Mucous membrane pemphigoid of the vulva. Obstet Gynecol. 2005;105:1188–90.
103. Hamann ID, NC H, Hunter JA. Chronic bullous dermatosis of childhood: relapse after puberty. J R Soc Med. 1995;88:296P–7P.
104. Mintz EM, Morel KD. Clinical features, diagnosis, and pathogenesis of chronic bullous disease of childhood. Dermatol Clin. 2011;29:459–62, ix.
105. Mihalyi L, Kiss M, Dobozy A, et al. Clinical relevance of autoantibodies in patients with autoimmune bullous dermatosis. Clin Dev Immunol. 2012;2012:369546.
106. Hoque SR, Patel M, Farrell AM. Childhood cicatricial pemphigoid confined to the vulva. Clin Exp Dermatol. 2006;31:63–4.
107. Urano S. Localized bullous pemphigoid of the vulva. J Dermatol. 1996;23:580–2.
108. Sardy M, Kostaki D, Varga R, et al. Comparative study of direct and indirect immunofluorescence and of bullous pemphigoid 180 and 230 enzyme-linked immunosorbent assays for diagnosis of bullous pemphigoid. J Am Acad Dermatol. 2013;69:748–53.
109. Jankaskova J, Horvath ON, Varga R, et al. Increased sensitivity and high specificity of indirect immunofluorescence in detecting IgG subclasses for diagnosis of bullous pemphigoid. Clin Exp Dermatol. 2018;43:248–53.
110. Holst VA, Fair KP, Wilson BB, et al. Squamous cell carcinoma arising in Hailey-Hailey disease. J Am Acad Dermatol. 2000;43:368–71.
111. Pernet C, Bessis D, Savignac M, et al. Genitoperineal papular acantholytic dyskeratosis is allelic to Hailey-Hailey disease. Br J Dermatol. 2012;167:210–2.
112. Knopp EA, Saraceni C, Moss J, et al. Somatic ATP2A2 mutation in a case of papular acantholytic dyskeratosis: mosaic Darier disease. J Cutan Pathol. 2015;42:853–7.
113. Hadjicharralambous E, Diamond S, Mehregan D. Papular acantholytic dyskeratosis of vulva in setting of Hailey-Hailey. Int J Dermatol. 2017;56:e126–8.
114. Langenberg A, Berger TG, Cardelli M, et al. Genital benign chronic pemphigus (Hailey-Hailey disease) presenting as condylomas. J Am Acad Dermatol. 1992;26:951–5.
115. Wieselthier JS, Pincus SH. Hailey-Hailey disease of the vulva. Arch Dermatol. 1993;129:1344–5.
116. Salopek TG, Krol A, Jimbow K. Case report of Darier disease localized to the vulva in a 5-year-old girl. Pediatr Dermatol. 1993;10:146–8.
117. Baliu-Pique C, Iranzo P. Papular acantholytic dyskeratosis of the vulva in a woman with benign familial pemphigus. Actas Dermosifiliogr. 2017;108:78–9.
118. Cooper PH. Acantholytic dermatosis localized to the vulvocrural area. J Cutan Pathol. 1989;16:81–4.
119. Wong TY, Mihm MC Jr. Acantholytic dermatosis localized to genitalia and crural areas of male patients: a report of three cases. J Cutan Pathol. 1994;21:27–32.
120. Laftah Z, Bailey C, Zaheri S, et al. Vulval Crohn's disease: a clinical study of 22 patients. J Crohns Colitis. 2015;9:318–25.
121. Barret M, de Parades V, Battistella M, et al. Crohn's disease of the vulva. J Crohns Colitis. 2014;8:563–70.

122. Boxhoorn L, Stoof TJ, de Meij T, et al. Clinical experience and diagnostic algorithm of vulval Crohn's disease. Eur J Gastroenterol Hepatol. 2017;29:838–43.
123. Andreani SM, Ratnasingham K, Dang HH, et al. Crohn's disease of the vulva. Int J Surg. 2010;8:2–5.
124. Emanuel PO, Phelps RG. Metastatic Crohn's disease: a histopathologic study of 12 cases. J Cutan Pathol. 2008;35:457–61.
125. Stewart KMA. Challenging ulcerative vulvar conditions: hidradenitis suppurativa, Crohn disease, and aphthous ulcers. Obstet Gynecol Clin North Am. 2017;44:453–73.
126. Foo WC, Papalas JA, Robboy SJ, et al. Vulvar manifestations of Crohn's disease. Am J Dermatopathol. 2011;33:588–93.
127. Ishida M, Iwai M, Yoshida K, et al. Metastatic Crohn's disease accompanying granulomatous vasculitis and lymphangitis in the vulva. Int J Clin Exp Pathol. 2013;6:2263–6.
128. Tursen U, Gurler A, Boyvat A. Evaluation of clinical findings according to sex in 2313 Turkish patients with Behcet's disease. Int J Dermatol. 2003;42:346–51.
129. Bulur I, Onder M. Behcet disease: new aspects. Clin Dermatol. 2017;35:421–34.
130. Yazici H, Seyahi E, Hatemi G, et al. Behcet syndrome: a contemporary view. Nat Rev Rheumatol. 2018;14:107–19.
131. Gurler A, Boyvat A, Tursen U. Clinical manifestations of Behcet's disease: an analysis of 2147 patients. Yonsei Med J. 1997;38:423–7.
132. International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. Lancet. 1990;335:1078–80.
133. Kaya TI, Dur H, Tursen U, et al. Association of class I HLA antigens with the clinical manifestations of Turkish patients with Behcet's disease. Clin Exp Dermatol. 2002;27:498–501.
134. Maia S, Martins A, Santos C, et al. Genital ulcers: do not forget Behcet disease. BMJ Case Rep. 2012;2012.
135. Kim ES, Chung WC, Lee KM, et al. A case of intestinal Behcet's disease similar to Crohn's colitis. J Korean Med Sci. 2007;22:918–22.
136. Wong WW, Machado GR, Hill ME. Pyoderma gangrenosum: the great pretender and a challenging diagnosis. J Cutan Med Surg. 2011;15:322–8.
137. Slocum AMY. A surgeon's nightmare: pyoderma gangrenosum with pathergy effect mimicking necrotising fasciitis. BMJ Case Rep. 2017;2017.
138. Sau M, Hill NC. Pyoderma gangrenosum of the vulva. BJOG. 2001;108:1197–8.
139. Reed BG, Shippey S, Kremp A, et al. Vulvar pyoderma gangrenosum originating from a healed obstetric laceration. Obstet Gynecol. 2013;122:452–5.
140. Sripathi H, Rao R, Prabhu S, et al. Pyoderma gangrenosum affecting the vulva. Indian J Dermatol Venereol Leprol. 2008;74:506–8.
141. Valmadre S, Gee A, Dalrymple C. Pyoderma gangrenosum of the vulva. Aust N Z J Obstet Gynaecol. 2002;42:548–9.
142. Dabade TS, Davis MD. Diagnosis and treatment of the neutrophilic dermatoses (pyoderma gangrenosum, Sweet's syndrome). Dermatol Ther. 2011;24:273–84.
143. Brooklyn T, Dunnill G, Probert C. Diagnosis and treatment of pyoderma gangrenosum. BMJ. 2006;333:181–4.
144. Yost J, Robinson M, Meehan SA. Fox-Fordyce disease. Dermatol Online J. 2012;18:28.
145. Kao PH, Hsu CK, Lee JY. Clinicopathological study of Fox-Fordyce disease. J Dermatol. 2009;36:485–90.
146. Boer A. Patterns histopathologic of Fox-Fordyce disease. Am J Dermatopathol. 2004;26:482–92.
147. Bormate AB Jr, Leboit PE, McCalmont TH. Perifollicular xanthomatosis as the hallmark of axillary Fox-Fordyce disease: an evaluation of histopathologic features of 7 cases. Arch Dermatol. 2008;144:1020–4.
148. Gurusamy L, Jegadeesan M, Jayakumar S. Fox-Fordyce disease of the vulva. Indian J Sex Transm Dis. 2016;37:65–7.
149. Macarenco RS, Garces SJ. Dilation of apocrine glands. A forgotten but helpful histopathological clue to the diagnosis of axillary Fox-Fordyce disease. Am J Dermatopathol. 2009;31:393–7.
150. Stashower ME, SJ K, Turiansky GW. Fox-Fordyce disease: diagnosis with transverse histologic sections. J Am Acad Dermatol. 2000;42:89–91.
151. Brau Javier CN, Morales A, Sanchez JL. Histopathology attributes of Fox-Fordyce disease. Int J Dermatol. 2012;51:1313–8.
152. Ergun T. Hidradenitis suppurativa and the metabolic syndrome. Clin Dermatol. 2018;36:41–7.
153. Scheinfeld N. Diseases associated with hidranitis suppurativa: part 2 of a series on hidradenitis. Dermatol Online J. 2013;19:18558.
154. Schneider MR, Paus R. Deciphering the functions of the hair follicle infundibulum in skin physiology and disease. Cell Tissue Res. 2014;358:697–704.
155. von Laffert M, Stadie V, Wohlrab J, et al. Hidradenitis suppurativa/acne inversa: bilocated epithelial hyperplasia with very different sequelae. Br J Dermatol. 2011;164:367–71.
156. Martorell A, Garcia-Martinez FJ, Jimenez-Gallo D, et al. An update on hidradenitis suppurativa (part I): epidemiology, clinical aspects, and definition of disease severity. Actas Dermosifiliogr. 2015;106:703–15.