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Lichenoid dermatoses involving the vulva: A clinical-pathologic correlation☆

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ABSTRACT

The lichenoid tissue reaction pattern generally signifies cytotoxic damage to the epithelium. When such reaction pattern occurs on vulvar skin or mucosa, the effects can result in considerable morbidity. None of the entities discussed in this review are entirely unique to the vulva, however, some entities may classically occur at this site, while others tend to be widespread diseases that may incidentally affect vulvar skin and mucosa. Given the complex anatomy of the vulva and the bridging of a site showing both keratinizing squamous epithelium and non-keratinizing squamous mucosa, histopathologic features may display variation in presentation. Although identification of a "lichenoid reaction pattern" alone may provide insight into the disease process, understanding of clinical presentation and specific sites of involvement, along with recognition of the nuanced features of the disease entities can help establish a specific diagnosis. Accurate histopathologic diagnoses by pathologists can improve the ability for treating clinicians to implement timely and effective treatment.

Introduction

Lichenoid dermatitis is a pattern of inflammation that blurs the normally crisp interface of dermis and epidermis (or mucosa and submucosa). The lichenoid tissue reaction pattern signifies cytotoxic damage to the epithelium which is visualized as keratinocyte death, generally through the process of apoptosis.[1]

Many dermatopathologists divide the lichenoid reaction pattern into a vacuolar change predominant category or an inflammatory predominant pattern. The vacuolar change subset is recognized by vacuolization of basal keratinocytes that disturbs the typical clear demarcation between epithelium and sub-epithelium; this pattern tends to have only sparse to moderate associated lymphocytic inflammation. The classic lichenoid inflammatory pattern shows a moderate to dense band of lymphocytic inflammation that tightly oppositions the dermal-epidermal junction. In both cases, lymphocytes mediate damage to keratinocytes, producing apoptotic and dyskeratotic keratinocytes that carry such names as Civatte bodies (if located within the epithelium) or cytoid or colloid bodies (if located in the papillary dermis). Certain disease entities are more likely to display a vacuolar pattern of damage (such as lupus erythematosus, erythema multiforme) while other diseases more classically show the inflammatory band pattern of damage (such as lichen planus). Of course it should be noted that these patterns are not absolute, and therefore careful clinicopathologic correlation is necessary to arrive at the correct diagnosis.

When a lichenoid reaction pattern occurs on vulvar skin or mucosa, the effects can result in considerable morbidity. None of the entities discussed in this review are entirely unique to the vulva, however, some entities may classically occur at this site, while others tend to be widespread diseases that may incidentally affect the vulvar skin and mucosa. Given the complex anatomy of the vulva and the bridging of a site showing both keratinizing squamous epithelium and non-keratinizing squamous mucosa, histopathologic features may display variation in presentation, particularly with regard to their classic features on cutaneous skin. Although identification of a "lichenoid reaction pattern" alone may provide insight into the disease process for our clinical colleagues, understanding the clinical presentation and specific sites of involvement, along with recognition of the nuanced features of the disease entities can help establish a more specific diagnosis. Accurate histopathologic diagnoses by pathologists can improve the ability for treating clinicians to implement timely and effective treatment. This review article focuses on some of the most common lichenoid dermatoses that involve the vulva- lichen sclerosus and lichen planus- as well as less frequent inflammatory conditions that can affect female genital skin and mucosa (Table 1).

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Table 1
Lichenoid Dermatoses affecting vulvar skin and mucosa.

	Clinical	Distinguishing Histopathologic features
Lichen sclerosus	Pale atrophic patches, "Figure of eight" appearance, does not involve vagina or cervix	Band of dermal homongenization/sclerosis in established disease; wiry collagen with horizontally aligned lymphocytes
Lichen planus	Can be erosive; will involve vagina and/or cervix	Hypergranulosis, saw tooth changes of basilar epidermis, band of inflammation
Fixed drug eruption	Annular, erythematous to violaceous patch; helpful if heals with hyperpigmentation; Often bilateral, symmetric in vulva	"Acute on chronic" features (orthokeratosis and pigment incontinence), mixed dermal inflammation with eosinophils and neutrophils
Graft vs Host disease	Erythema, red and white spots, fissures, adhesions, distorted vulvar architecture	Satellite cell necrosis, can resemble lichen sclerosis or lichen planus; dermal sclerosis with chronicity
Erythema Multiforme	Acral predominance, +/- mucosal lesions, targetoid and atypical targetoid appearance	Dyskeratosis at all levels of epidermis; more inflammatory than SJS/TEN
SJS/TEN	Painful erythema and epidermal sloughing Dusky erythema and atypical targetoid lesions that spread	Pauci-inflammatory compared to degree of keratinocyte death
Lupus/ CTD	Hyperkeratotic plaques or ulcers/erosions	Follicular plugging; Dermal mucin deposition
Zoon vulvitis	Glistening erythematous mucosal lesions, +/- "cayenne pepper" spots	Plasma cell rich infiltrate Mucinous metaplasia possible
Paraneoplastic pemphigus	Oral ulcerations, mix of lichenoid and blistering lesions; sometimes mimics SJS/TEN	Lichenoid dermatitis plus acantholysis; Positive direct immunofluorescence
Syphilis	Primary lesion is a painless chancre; secondary syphilis shows generalized copper colored macules and papules, often involving palms and soles	Psoriasiform and lichenoid reaction pattern, with plasma cells Positive immunostaining for T. *pallidum*

Lichen sclerosus

Perhaps the most recognized lichenoid dermatitis affecting the vulvar skin and mucosa is lichen sclerosus (LS). Previously known and sometimes still referred to as "lichen sclerosus et atrophicus", this autoimmune mediated disorder confers considerable morbidity if not detected and aggressively treated. Preferentially affecting the genital and perigenital regions of women with a biphasic age distribution, LS is one of the most commonly mentioned clinical indications for biopsy of vulvar skin, and represents about one third of complaints at vulvar specialty clinics.[2] LS most commonly affects post-menopausal women, however, young girls may also be affected and, by some estimates, represent about 10–15% of all cases of LS.[3,4] The pathogenesis of this complex disorder has yet to be completely elucidated. Longstanding and untreated LS leads to architectural alterations of normal vulvar architecture, resorption of sensitive genital tissues, and diffuse sclerosis. Additionally, there is a small but well-recognized risk of progression to invasive squamous cell carcinoma in long standing LS,[5] often preceded by the development of differentiated type vulvar intraepithelial neoplasia. This risk of invasive squamous cell carcinoma is linked to p53 driven mechanisms rather than human papilloma virus (HPV) dependent mechanisms.[6]

Background/ pathogenesis

There is reasonable agreement that LS represents an autoimmune phenomenon, particularly given its predominance in women. Moreover, the incidence of other autoimmune disorders, including vitiligo, alopecia areata, celiac disease, rheumatoid arthritis, and thyroid disease are higher in patients with LS than in nonaffected populations.[4,5,7] Autoantibodies directed against antigens in the lower half of the epidermis have been suggested as contributory.[5,8,9]

Other possible mechanisms may affect the development of LS. Infectious triggers, namely *Borrelia Burgdorferi* infection in European cohorts, have been posited to be contributory to the development of LS.[5] Hormonal influences have also been postulated to contribute to LS given the bimodal presentation of LS in prepubertal girls and postmenopausal women, however definitive mechanisms by which hormones affect the development of the disease have yet to be defined.[4,10] Trauma and chronic irritation from the moist genital environment have also been proposed as factors affecting LS development.[5]

The mechanism by which the dermal-epidermal interface is damaged and dermal collagen is remodeled remains a subject of investigation. CD4 and CD8 expressing T-cells have shown to be present in comparable numbers in some studies,[10] while in other studies CD8+ lymphocytes predominate.[11] CD57 positive cytotoxic (CD8+) T-cells that represent terminally differentiated antigen specific T-cells were shown to be elevated in cases of LS. It was not clear whether these cells, which are thought to work to minimize tissue damage, were a response to the dermal sclerosis or a mediator of it.[11] Matrix metalloproteinases 2 and 9,[12,13] other extracellular matrix proteins,[14] and connective tissue growth factor[14] have been shown to be expressed in cases of vulvar LS and may contribute to the remodeling of collagen and elastic tissue framework of the dermis. Cytokines that promote fibrosis and favor a Th2 response such as interleukins (IL) 4 and 6 and TGF-beta have been shown to be elevated in LS compared to lichen planus in some studies,[10] while other studies have demonstrated a Th1 cytokine profile in LS that is similar to that seen in lichen planus, with elevations in staining for interferons (IFN), tumor necrosis factors (TNF), and IL-1.[15]

P53-dependent mechanisms have been linked to the development of subsequent vulvar SCC arising in longstanding LS. Accordingly, several studies have investigated and documented higher levels of p53 immunoreactivity in vulvar biopsies of LS with adjacent SCC[16,17] and point mutations in p53 in biopsies of vulvar LS.[18]

Clinical presentation

Any age group may be affected by LS. Classically, a bimodal distribution of cases involving prepubertal girls and postenopausal women is described; only 5–15% of cases present prior to puberty.[19] The most common complaint of patients with LS is severe vulvar pruritus, often more intense at night and possibly interfering with sleep. Patients may also mention vulvar irritation or discomfort, burning, and pain during sexual intercourse.[8,10] Up to 39% of patients with LS are asymptomatic,[20] and the disease may be noticed during routine gynecologic exams.

LS presents clinically as small lichenoid, flat-topped papules that may coalesce to become ivory to white atrophic plaques with a parchment paper- like appearance (Fig. 1). The most commonly involved areas of the vulva include the labia minora and inner labia majora, clitoris, perineal body, and perianal region. With established disease involving all of these areas, the vulva may acquire a "figure of eight" appearance (Fig. 2). LS may also extend into the labiocrural folds or gluteal cleft. Importantly and in contradistinction to lichen planus (LP), LS does not typically involve the cervical or vaginal mucosa.[21]

Over time, lesions become progressively more hypopigmented and

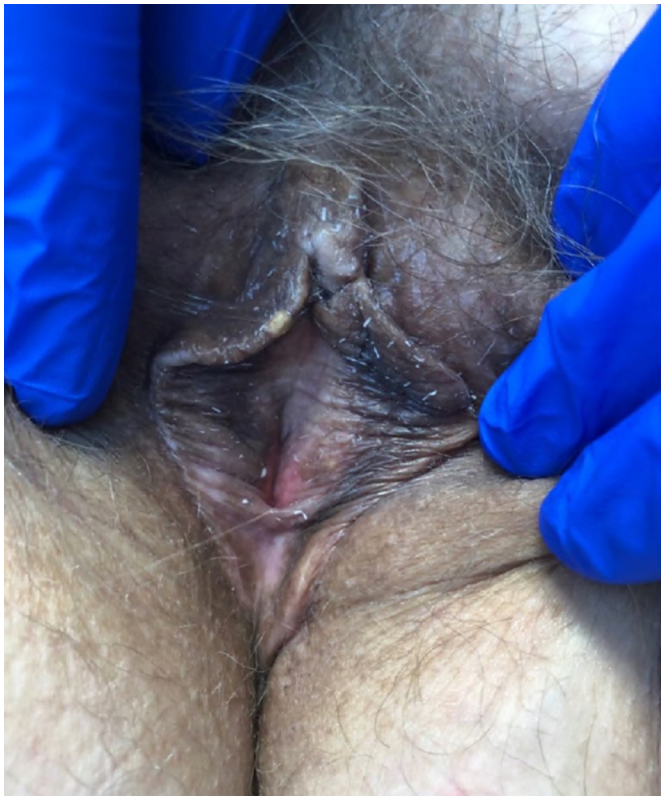

Fig. 1. Clinical presentation of early lichen sclerosus. White discoloration along the edge of the right labium minus with associated agglutination of the interlabial sulcus. There is white discoloration of the clitoral prepuce, the perineal boday, and mild clitoral phimosis.

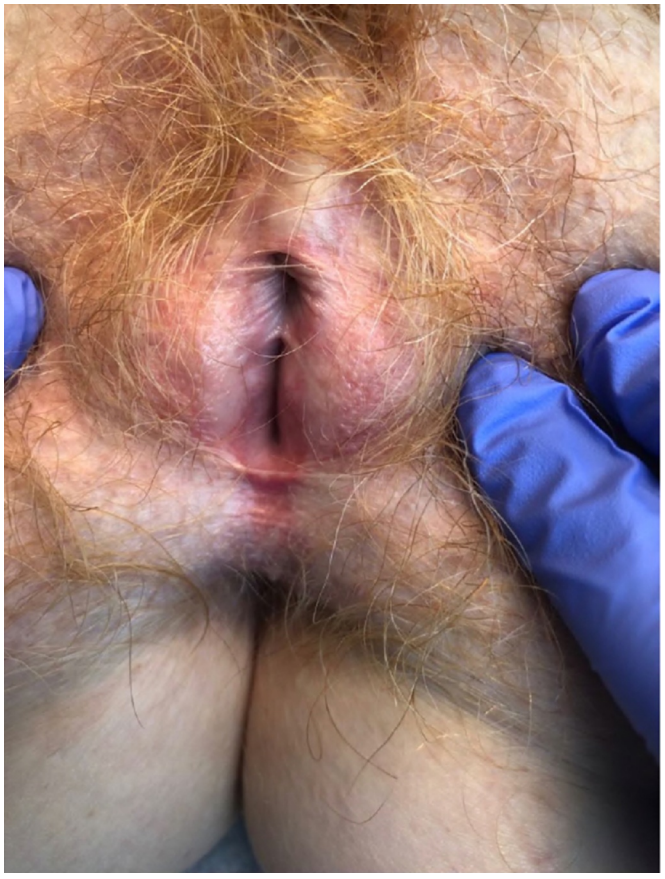

Fig. 2. Clinical presentation of established lichen sclerosus. Complete loss of bilateral labia minora, clitoral phimosis, parchment like skin changes, and vaginal stenosis.

the diffuse sclerosis can lead to vascular fragility with easy bruising and development of purpura. The fragile vulvar skin, often compared in appearance to “cigarette paper,” and modified mucosa becomes predisposed toward development of erosions, fissures, and ulcerations. Excoriations may also be present in patients who scratch. In long-standing lesions of LS, the identification of new hyperkeratotic or white thickening should be targeted for biopsy as it may herald the development of dysplasia or carcinoma. Advanced disease may reveal considerable anatomic distortion, including fusion of the labia, phimosis of the clitoris, stenosis of the vaginal introitus, and resorption of vulvar landmarks.[4] Early diagnosis and treatment is crucial to minimize long term sequelae.

Clinical exam of patients may be otherwise unremarkable. In contrast to patients with LP, oral and cutaneous lesion are uncommon. LS *can* arise in extragenital sites, but it is much less common and does not necessarily occur in patients with co-existing vulvar disease.

Super-potent topical steroids, in addition to avoidance of irritation and skin emollients, are the gold standard for treatment of vulvar LS. Treatment failure with topical steroids is uncommon. If a patient is not improving, evaluation for confounding factors including poor adherence to recommendations, secondary infection (bacterial or fungal) and possible misdiagnosis should be sought. Intralesional steroid injections may be considered in some patients. If the patient is truly steroid resistant or unable to tolerate topical steroids, second line therapy is a topical calcineurin inhibitor. This medication generally causes burning and discomfort after application and is sometimes discontinued for this reason. One randomized control trial comparing topical calcineurin inhibitor to topical steroid for treatment of LS demonstrated that while both treatments are efficacious, topical steroid was superior.[22] Other recognized therapies for LS include acitretin, methotrexate and phototherapy.[523] Various lasers, mesenchymal stem cells, and platelet-rich plasma are investigational treatment options; however, further study is still needed. Long term maintenance therapy with topical steroids or calcineurin inhibitors is recommended even after remission is established[24] due to the chronic nature of LS. Yearly gynecologic examinations should be continued after remission given the 2–6% risk of developing squamous cell carcinoma, and any changes in symptomatology should be evaluated.

Histopathologic findings

Early/inflammatory LS

The inflammatory pattern of LS is generally considered to represent "early" disease, however occasionally biopsies obtained with clinically advanced disease may show this more inflammatory pattern. This inflammatory pattern of LS demonstrates a variably dense lichenoid inflammatory infiltrate that obscures the dermal epidermal junction at least focally. Vacuolar interface changes affect the basilar keratinocytes, with exocytosis of lymphocytes into the epithelium and occasional scattered dyskeratosis (generally limited to the lower portion of the epidermis). The epidermis tends towards some degree of atrophy with diminishment of rete ridges. There is generally hyperkeratosis and less likely parakeratosis. Homogenized, bright pink papillary dermal sclerosis may be only focally evident in this stage, but should be searched for diligently as it helps secure the diagnosis (Fig. 3). Thickened basement membrane zone, the presence of this homogenized material in the papillary dermis, individual thickening of papillary dermal collagen fibers and lymphocytes arranged linearly among "wiry" collagen fibers have been listed as particular clues to the diagnosis in this early/inflammatory phase.[9,25,26] Elastic fiber stains (Verhoeff van Giesen) can illustrate the loss of papillary dermal elastic fibers,[13,25] although in early lesions of LS this change may be focal and difficult to appreciate.

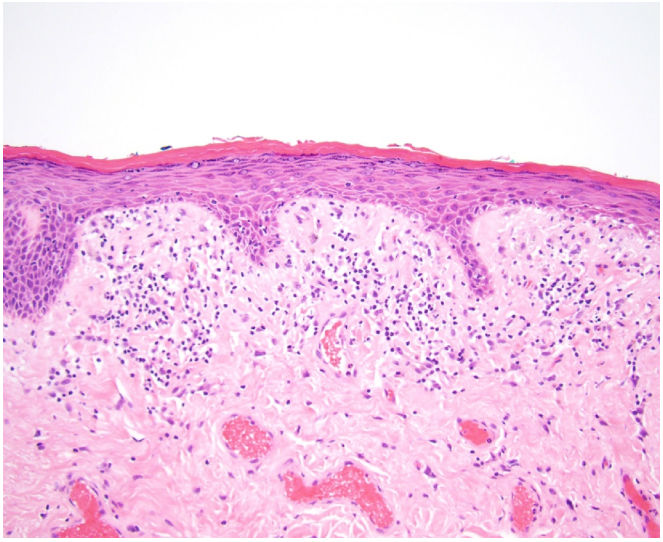

Fig. 3. Early/ inflammatory lichen sclerosus. There is compact orthokeratin, early atrophy of the epidermis, and slight vacuolar interface alteration. The papillary dermal collagen is wiry and dense with only focal homogenization (H&E, 200X).

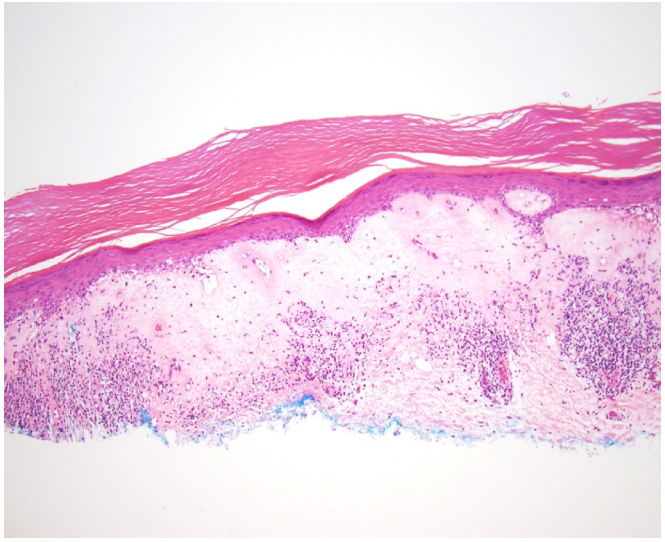

Fig. 4. Established features of lichen sclerosus with epidermal atrophy, overlying hyperkeratosis and significant homogenization of the papillary and superficial dermis. Vacuolar interface alteration is still seen, and beneath the homogenized collagen is a dense band of lymphoplasmacytic inflammation (H&E, 100X).

The differential diagnosis of biopsies of early/inflammatory LS include many of the other entities listed in this review. Lichen planus in particular may have considerable overlap, and thus knowledge of the extent and distribution of lesions and of extragenital cutaneous findings are important to arrive at the correct diagnosis. Fixed drug eruptions can be distinguished from inflammatory LS by the presence of neutrophils and eosinophils within the dermal infiltrate; when present, melanin incontinence is also a helpful clue but is often absent in vulvar fixed drug eruptions. In cases in which clinical information is limited, a diagnosis of "lichenoid dermatitis" with a comment listing histologic considerations may be most appropriate for the patient.

Established LS

Established or late LS has classic findings that are rarely confused for other lichenoid dermatoses. Epidermal changes range from atrophy to acanthosis, often with compact or orthohyperkeratosis and follicular plugging and follicular hyperkeratosis. Loss of a well-defined rete ridge pattern (effacement) may be seen with some squamatization of the basal keratinocytes. Apoptotic keratinocytes may be noted but are rare. The papillary dermis, and often the superficial reticular dermis, is replaced by homogenized and amorphous eosinophilic sclerosis (Fig. 4). This altered dermis is hypocellular, and entrapped normal vessels may show vascular dilatation and hemorrhage. There may be scattered inflammatory cells and pigmented macrophages. Beneath this zone of homogenized sclerosis, there is usually some degree of chronic inflammation. This lymphocyte predominant infiltrate may be sparse or dense and lichenoid. The presence of eosinophils and spongiosis may signify a superimposed hypersensitivity and/or allergic contact component.[13,26,27] Multinucleated giant cells and elastophagocytosis is exceedingly rare in genital LS, although this phenomenon has been reported as relatively common in biopsies from extragenital LS.[13,28]

Established LS has some histologic overlap with radiation dermatitis and chronic graft-versus-host disease. Full understanding of the clinical history can help distinguish between these possibilities.

Hypertrophic LS

Several variants of LS have been reported. Hypertrophic LS shows a more acanthotic epidermis than the atrophic epidermis of classic LS (Fig. 5 and 6). Hyperkeratosis and hypergranulosis accompany the acanthosis. Parakeratosis may be present in narrow columns, sometimes with underlying dyskeratotic keratinocytes.[9] The dermal sclerosis

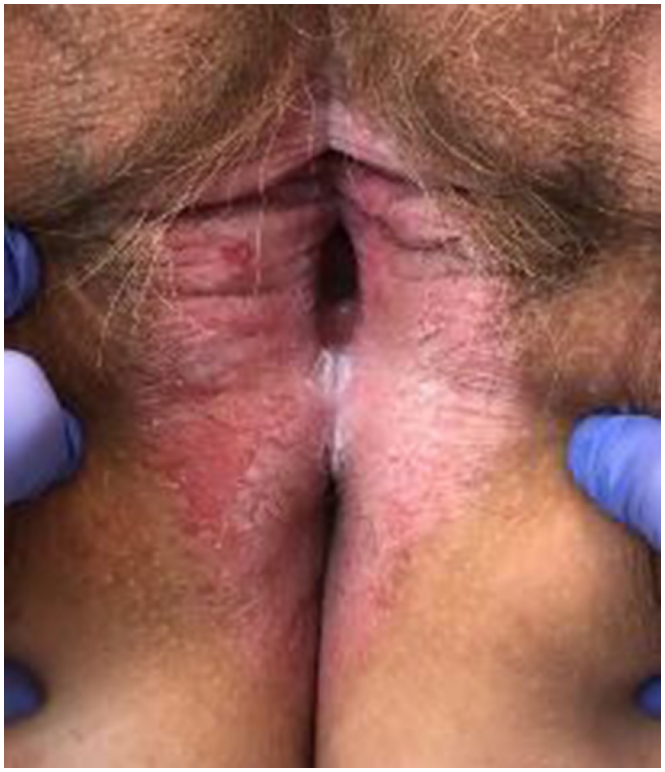

Fig. 5. Clinical presentation of hypertrophic Lichen Sclerosus. Thick waxy plaques overlying both inner labia majora, complete resorption of the labia minora, complete clitoral phimosis, and perianal involvement are seen.

may be less apparent than in classic LS, acquiring more of a "fibrotic" appearance.[29] Some authors believe hypertrophic LS represents LS with secondary lichen simplex chronicus (i.e. chronic itching, scratching, and manipulation of the vulvar skin). Notably, hypertrophic LS shares histologic overlap with differentiated vulvar intraepithelial neoplasia (dVIN), including acanthosis and parakeratosis. However, differentiated VIN will show nuclear atypia, crowding of basilar keratinocytes, keratinocyte mitotic activity, and bridging of rete ridges, while

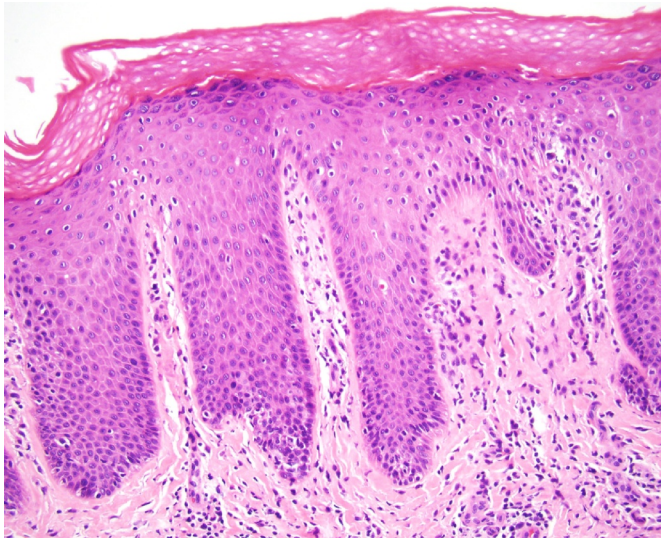

Fig. 6. Hypertrophic lichen sclerosus. Psoriasiform acanthosis of the epidermis with foci of vacuolar interface alteration seen at the tips of the rete ridges and rare dyskeratosis. Basal layer atypia is notably lacking. Papillary dermal collagen is "wiry" and somewhat homogenized, with thickening of basement membrane (H&E, 200X).

hypertrophic LS should lack all of these features. Although diffuse p53 immunostaining of basilar and supra basilar keratinocytes often supports dVIN,[17] p53 expression can also be similarly expressed in hypertrophic LS, thought to be due to ischemia resulting from the dermal sclerosis.[30]

Bullous LS

Bullous LS is a rare variant and seems to occur more commonly at extragenital sites.[31] On vulvar skin, vesicles, erosions, and hemorrhagic blisters are the presenting signs. Subepidermal blister without significant inflammation is typically seen microscopically, sometimes with extravasated erythrocytes.[32] Direct immunofluorescence studies should be negative, thus distinguishing it from other autoimmune mediated blistering disorders such as pemphigoid.[33]

Lichen planus

Lichen planus (LP) is an immune-mediated inflammatory condition that can affect skin as well as mucosal surfaces (including esophagus, conjunctiva, and vagina). Generalized cutaneous LP is a relatively uncommon condition, with an estimated prevalence of 1–2% in the general population.[34] Vulvar involvement by LP is even less common. Its exact prevalence is unknown,[35] but has been reported to represent approximately 1% of new cases seen in dermatology offices in some studies.[36,37] Vulvar LP may occur in isolation, but is often preceded or accompanied by LP elsewhere on the body.[35] Fifty percent of women with generalized cutaneous LP also have genital involvement, and many women with genital LP will also have oral involvement.[35] The typical age of presentation for women with vulvar LP is in the peri- or post- menopausal period, however, reports include presentations anytime from the third to ninth decade of life.[35] Vulvar LP is thought to be an under-recognized and under-diagnosed dermatosis affecting the vulva that carries significant morbidity and mortality implications for women. Unfortunately, it is common for women to present in advanced stages of disease due to a reluctance to disclose symptoms or submit to genital exam. There are three recognized forms of LP that affect the vulva: erosive, classic/papular, and hypertrophic. Each will be discussed separately here.

Background/ pathogenesis

LP is a T-cell mediated inflammatory dermatosis that can affect both keratinized and non-keratinized squamous (mucosal) epithelium. Either or both epithelial types can be affected in individuals.[38] The Th-1 pathway in particular has been implicated in the pathophysiology of LP with upregulation of pro-inflammatory cytokines such as IL1, IL6, IL7, IL15, IFN-γ and TNF-α, and down-regulation of anti-inflammatory cytokines such as IL11 critical for pathogenesis.[38] In accordance with an upregulated Th-1 pathway, there are higher numbers of CD4+, CD8+, and FOXP3+ *T*-regulatory cells in skin biopsies of LP when compared to control skin.[38] Additionally, T-cells that are autoreactive against the basement membrane have been demonstrated in numerous studies,[38–42] lending credence to a theory that LP itself may be an autoimmune disorder. It has been noted that vulvar LP is frequently diagnosed in patients with other autoimmune disorders (most often autoimmune thyroid disorders, alopecia areata, and celiac disease[7]), but LP itself is not currently classified as an autoimmune condition.

Vulvar LP, aside from the impact on patients' quality of life, also carries a 1–3% risk of developing squamous cell carcinoma.[43] As with lichen sclerosus (LS), carcinogenesis is independent from that of the human papillomavirus (HPV) pathway. One study found that SCC is more likely to develop in longstanding LP affecting non-hair-bearing parts of the vulva, with a particular predilection for the mucosa located between the clitoris and the urethra.[34] One of the major obstacles to preventing the development of cancer, or recurrence of a surgically excised cancer despite negative margins in the setting of LP, is the difficulty of treating the LP itself. Without resolution of the chronic inflammatory condition, the carcinogenic risk is anticipated to persist.[34]

EROSIVE LP

Clinical presentation

Of the three variants of LP that affect the vulva, erosive lichen planus (ELP) is the most common.[44,45] ELP typically presents on the mucosal sites of the vulva and/or vagina with well-demarcated pink to red glazed erosions (Fig. 7).[45] Erosions may also have a white, hyperkeratotic border or surrounding white striae.[45] The specific areas most affected are introitus (90%), vagina (20–38%), vulva (37%) and perianal skin (8%).[45–47] Early erosions may be subtle, and thorough clinical examination is needed to detect lesions in early stages. Early detection of ELP is of significant importance, as this variant can progress to significant scarring. Loss of vulvar architecture is in a similar pattern to that of LS with resorption of the labia minora, clitoral phimosis, and introital narrowing. Complete or partial vaginal agglutination can occur with vaginal LP.[45–48] Patients with ELP more often complain of pain than pruritus.[45,49] The pain is often described as burning, and may progress to dyspareunia, dysuria and/or pain with defecation.[45]

As with the other forms of LP affecting the vulva, topical steroid ointments are the appropriate first line therapy for ELP, along with reduction in irritants and use of emollients.[35,45] Similarly to LS, ultrapotent topical steroids are first line choices for vulvar LP. Topical calcineurin inhibitors have also been shown to have good effect in treating oral and genital ELP.[46,48,50–52] Ultrapotent topical steroids should not be used intravaginally; when vaginal disease is present, a medium to high potency steroid should be used on the vaginal mucosa. Patients should also be encouraged to use vaginal dilators regularly in order to prevent vaginal shortening.

Unfortunately, 25–40% of patients respond inadequately to topical therapy and will require systemic intervention.[45,47,53,54] Systemic treatment should also be considered in women with concurrent vulvar and extragenital disease. The four most common oral systemic agents used to treat ELP include prednisone, methotrexate, mycophenolate mofetil and hydroxychloroquine.[47] There is insufficient evidence to

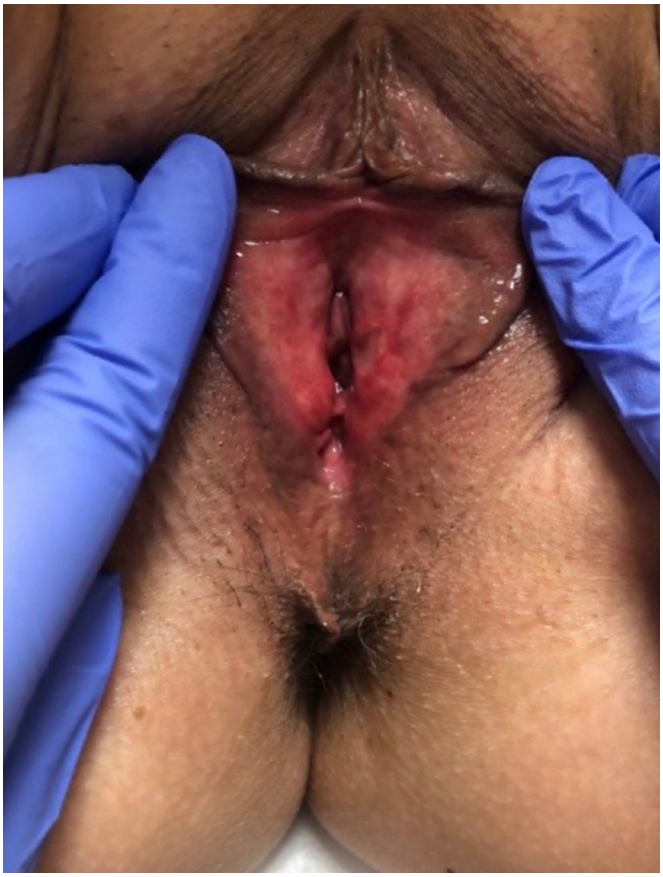

Fig. 7. Clinical presentation of lichenoid dermatitis, likely Erosive Lichen Planus (ELP). Exam demonstrates normal vulvar architecture with glazed erythema of the vestibule. Gingival erosions were also present. Although the biopsy results were nonspecific lichenoid dermatitis, the clinical presentation was consistent with ELP.

recommend one of these treatments over another at this time. Surgical intervention for release of vaginal agglutination is only indicated when the patient desires to be sexually active and has established control of vulvar disease. Once vaginal patency has been restored, intravaginal steroids and regular use of vaginal dilators should be recommended to prevent re-occlusion.[19] Intravaginal estrogen should also be considered in postmenopausal women.

Histopathology

The histologic features of ELP can range to non-specific erosion and ulceration to more specific changes similar to those seen in classic LP (Fig. 8). Depending on the area that is biopsied, the epidermal changes may not be as pronounced as the other variants, due to the erosions. However, the underlying band of inflammation, vacuolization/liquefactive degeneration of the basal layer, and dyskeratosis should all be present to some degree.[45] The histologic features are listed among the newly established criteria for the diagnosis of erosive lichen planus (Table 2). Three out of the nine newly established criteria must be met in order to diagnose ELP.[47]

CLASSIC LP

Clinical presentation

In the vulva, “classic” LP does not usually have the “classic” presentation of purple, pruritic, polygonal papules that is commonly associated with the diagnosis of cutaneous LP. On keratinized, hair-bearing skin of the vulva, classic LP has a wide variety of presentations. Clinical descriptions range in color from dusky red to brown, purple, or

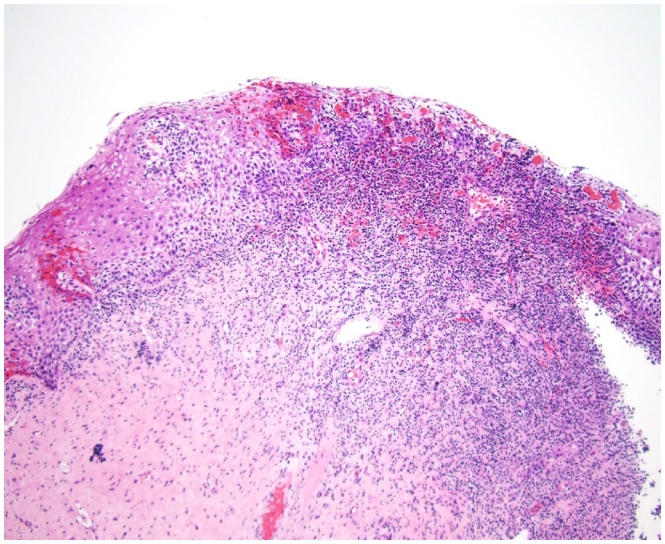

Fig. 8. Erosive lichenoid mucositis, suggestive of erosive lichen planus. Vulvar squamous mucosa with central erosion and lichenoid band of inflammation obscuring the junction between epithelium and submucosa (H&E, 100X).

Table 2
Diagnostic Criteria for Erosive Lichen Planus Affecting the Vulva.

Criteria
1. Presence of well-demarcated erosions or glazed erythema at the vaginal introitus
2. Presence of a hyperkeratotic white border to erythematous areas/erosions ± Wickham striae in surrounding skin
3. Symptoms of pain/burning
4. Scarring/loss of normal architecture
5. Presence of vaginal inflammation
6. Involvement of other mucosal sites
7. Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermoepidermal junction
8. Presence of an inflammatory band that consists predominantly of lymphocytes
9. Signs of basal cell layer degeneration, for example, Civatte bodies, abnormal keratinocytes, or basal apoptosis

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even gray-white. Lesions are most often unilateral, well-demarcated papules or plaques.[48,55] On the mucosal surfaces of the vulva, classic LP most often presents as white, reticulate, lacy or fern-like striae- resembling the classic Wickham's striae associated with cutaneous (extragenital) lichen planus.[55] Classic LP of the vulva is often pruritic but may also be completely asymptomatic.[35]

Before any treatment is initiated for lichen planus, a thorough review of a patient's current medications is recommended, as many common medications can produce a lichenoid drug eruption. Common offending medications include beta-blockers, NSAIDs, hydrochlorothiazide diuretics, and others.[35] Classic LP is more responsive to treatment that erosive LP. Typical treatment involves a two week course of moderately potent topical steroids in an ointment form and emollients[35] and is likely to result in quick remission.

Histopathology

Many of the pathognomonic histologic features of LP seen on extragenital skin are shared with LP affecting the vulva (Fig. 9). These classic features include hyperkeratosis, wedge-shaped hypergranulosis, acanthosis with an irregular “saw-tooth” or “spikey” contour to the dermal-epidermal junction, basal layer vacuolar change/liquefactive degeneration with dyskeratosis, and an underlying band-like infiltrate

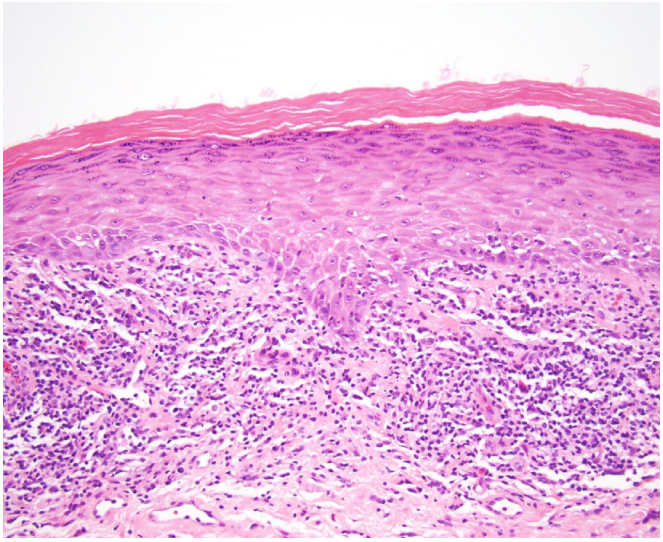

Fig. 9. Lichen planus. Acanthosis of the epidermis with overlying hyperkeratosis and a prominent, accentuated granular layer is seen. The rete ridges are irregular and somewhat spikey with a dense underlying band of lymphoplasmacytic inflammation that directly abuts and involves the dermal-epidermal junction (H&E, 200X).

of inflammatory cells within the dermis.[56] Some features seen more often in vulvar LP include parakeratosis (along with the usual hyperkeratosis), secondary spongiosis in the epidermis (especially at mucosal sites), a prominent plasma cell component in the band of inflammation seen in the dermis, and an absence or inconspicuousness of cytoid or Civatte bodies.[56] Although eosinophils are typically absent in LP at cutaneous sites, at least one study of vulvar LP has documented their presence with reasonable frequency.[55]

HYPERTROPHIC LP

CLINICAL PRESENTATION

Hypertrophic lichen planus (HLP) is one of the least described LP variants in the literature, despite its often striking clinical appearance (Fig. 10). HLP is typically sharply circumscribed from surrounding normal skin, with beefy red erythema and edema centrally, transitioning to a thick gray-pink, rind-like, lichenified border at the edge of the lesions[55] . HLP often spans the entire vulva circumferentially affecting the bilateral labia majora and can affect vulvar structures in between as well as the perineum.[55] These thick red plaques often show maceration and sometimes ulceration in the center, and can be confused clinically for psoriasis, extramammary Paget disease and high grade squamous intraepithelial lesions. .[55] Some examples of HLP display marked hyperkeratosis and verrucous changes that may resemble squamous cell carcinoma clinically.[35]

Hypertrophic lichen planus may also be treated with topical steroids, but a higher potency than those used for classic lichen planus is advised; typically an ultrapotent topical steroid ointment is recommended. Intralesional injection of corticosteroid may be indicated as penetration of topical steroids through the thickened stratum corneum is often limited.[35] Clinical suspicion for development of malignancy should be high when lesions do not respond to steroid therapy, and biopsy is recommended to exclude this possibility.[35]

Histopathology

As the name implies, the histologic features of hypertrophic lichen planus, involve a pronounced hypertrophy or acanthosis of the epidermis, as well as the stratum corneum (hyperkeratosis). The acanthosis should be pronounced, and is especially noticeable in follicular epithelium which is often expanded and bulbous. Some cases of HLP have

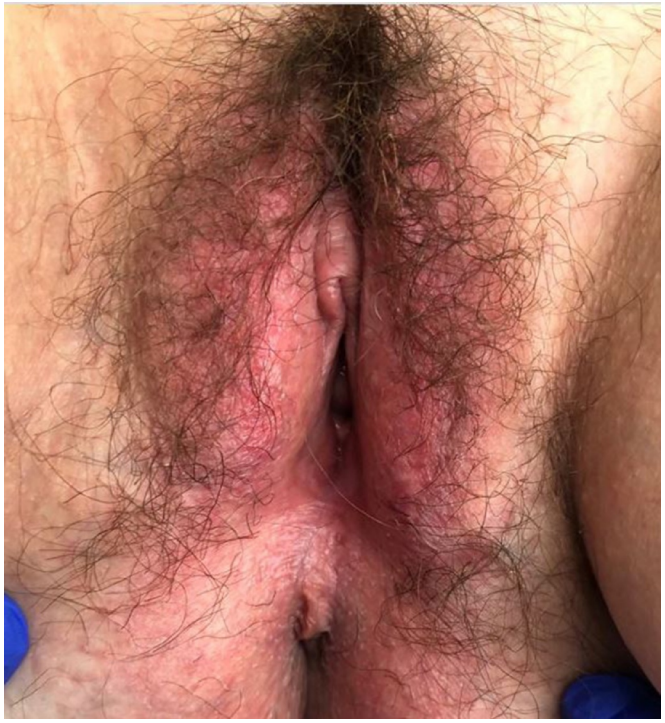

Fig. 10. Clinical presentation of hypertrophic lichen planus. Hypertrophic erythematous plaques of the bilateral labia majora are seen, extending into the interlabial sulci and coalescing over the anterior commissure. The labia minora are preserved but partial clitoral phimosis is present. There are no vestibular erosions.

dramatic hypertrophy of the epidermis that is better classified as pseudoepitheliomatous hyperplasia, and depending on the depth of the biopsy sample, may be mistaken for squamous cell carcinoma.[57] The spiky, irregular dermal-epidermal junction seen in classic LP is not as pronounced in HLP, and may be limited to the tips of expanded rete ridges.[55,57] HLP by definition shows liquefactive degeneration of the basal layer with dyskeratotic keratinocytes. This feature may be confluent and diffuse, limited to the tips of expanded rete ridges, or seen within the tops of the dermal papillae, which is somewhat in contrast to description of HLP at other sites, where basal vacuolization and dyskeratosis is confined to the tips of rete ridges.[55] The dermal inflammatory infiltrate in HLP is still band-like and composed primarily of lymphocytes, however the presence of eosinophils is not uncommon and more readily expected than in classic LP.[57] Scale crust and plasma cells in the infiltrate are more frequently noted in HLP than in classic LP.[55]

Fixed drug eruption

Fixed drug eruption (FDE) is a peculiar, localized hypersensitivity reaction. Exposure to a drug results in a reproducible, localized (single or multifocal) eruption on mucocutaneous surfaces. Repeated exposure to the drug elicits a response at the same anatomic site(s), often more quickly than the first exposure.[58] Any anatomic site may be affected by FDE, and mucosal sites (genital and oral) are not uncommon. Vulvar skin or mucosa may be affected by FDE, but accurate identification may be delayed and hampered by unusual presentation and unfamiliarity with the diagnosis. Moreover, although FDE has classic histopathologic features on cutaneous skin, the features on mucosal epithelium may be less specific and more difficult to recognize. The reason for the predilection of FDE to occur at specific sites remains unknown.

Background/ pathophysiology

Type IV hypersensitivity reactions are cell mediated, delayed reactions. Initial exposure to the offending medication may take up to a few weeks to present, but subsequent exposures to the drug result in a rapid (within several hours) return of symptoms and sometimes additional sites of involvement.[58,59] FDEs are reasonably common, with common culprits including non-steroidal anti-inflammatory drugs, antibiotics, and sedatives.[60–62] In one of the largest case series (of 13 women), vulvar FDE seemed to be linked most commonly to COX-2 inhibitors and statin medications,[59] but eruptions affecting vulva have also been reported to other common medications as well, such as fluconazole.[63]

The mechanism by which a drug produces a FDE is not completely understood. The possibility of a small molecule drug reacting with a protein in the epidermis or dermis to form an antigen recognized by the immune system is one possibility.[64] Cross reactivity to drugs within the same class can occur with FDE, which could support this theory.[59] Once activated, cellular responses mediated by cytotoxic (CD8 positive) lymphocytes with an effector memory phenotype evoke the damage to the dermal-epidermal junction that is seen on histopathology and resultant erythema and blistering.[58,65] These effector-memory T-cells are thought to be normal residents of the epithelium but at very low levels; biopsies from active and quiescent FDEs have increased numbers of these cells and are thought to contribute a protective immune function. These cells are activated upon drug ingestion, resulting in interferon release and a gain of cytotoxic activity against keratinocytes, along with recruitment of other cytotoxic T-cells and cytokines.[58] Fas/Fas ligand-mediated signaling has been described as critical to the downstream events that result in keratinocyte apoptosis in FDE.[66]

There may be some genetic susceptibility to the formation of FDE, as some HLA genotypes have been associated with a predisposition to develop such eruptions to certain specific medications.[67]

Clinical presentation

FDE classically presents as an annular, hyperpigmented patch that becomes erythematous to violaceous upon exposure to the offending medication. However, FDE may also present as multifocal lesions, and when presenting on mucosal sites, it is unlikely to be pigmented.[21,59] Vulvar involvement in particular has a tendency to be bilateral, symmetric, and can be blistering, ulcerating, or erosive.[59] When the vulvar mucosal epithelium is involved, lesions may be more irregular in shape and tend to be erosive.[21] Patients will report a localized burning, itching, or stinging sensation at the involved site(s), but systemic symptoms are unusual. Lesions can appear anywhere from 30 min to 8 h after drug exposure – although some cases have been reported after 2 weeks of exposure.[68]

The diagnosis of FDE, particularly if multifocal and involving mucosal sites, may be elusive if the relationship to the offending medication is not established. Diagnosis of vulvar FDE may be further complicated by its tendency to be non-pigmenting. For this reason it is essential to keep FDE within both the clinical and histopathologic differential diagnosis.

Treatment of FDE involves cessation and avoidance of the offending medication. Resolution occurs within 7–10 days after withdrawal of the medication, often with persistent slight hyperpigmentation.[68] Re-exposure is likely to result in recurrence of FDE at the same site.

Histopathology

Under the microscope, FDE classically demonstrates a lichenoid and vacuolar interface dermatitis. Basal keratinocytes demonstrate vacuolar changes and there is a band of inflammation aligned near the dermal-epidermal junction (Fig. 11). Intraepidermal lymphocytes mediate keratinocyte cell death and dyskeratosis, resulting in nuclear pyknosis and eosinophilic cytoplasmic condensation. This feature may be limited

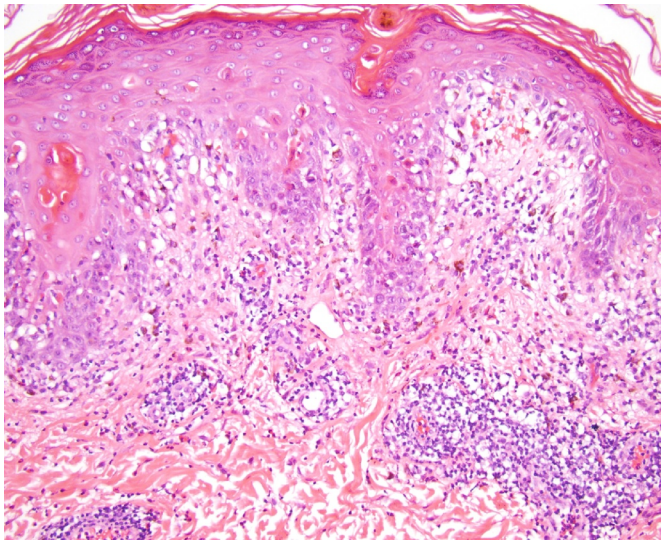

Fig. 11. Fixed drug eruption. Robust vacuolar interface alteration with prominent dyskeratosis is present, along with numerous eosinophils and prominent melanophages in the superficial dermis (H&E, 200X).

to individual cells, but with significant vacuolar interface alteration, there can be partial or confluent epidermal necrosis, with sub-epidermal clefting and blister formation. Cytoid bodies may be present in the dermis. The density of inflammation can be variable, but typically extends more deeply into the dermis than do other lichenoid processes and generally includes a mixed complement of inflammatory cells: lymphocytes, histiocytes, neutrophils, and eosinophils. The epidermis maintains an acute stratum corneum (i.e. orthokeratosis) while the dermis shows melanin pigmentary incontinence. This apparent paradox of an “acute but chronic” process should be a tip off to the diagnosis; however, dermal melanophages may be decreased or absent altogether in vulvar FDE, which are often non-pigmenting. In a case series of 13 vulvar FDEs, most biopsies were noted to display overall non-specific features and frequent superimposed spongiosis.[59] Neutrophil (rather than lymphocyte) predominant FDEs have been reported as a variant,[69] although to date, no reports of this variant have occurred on the vulva.

The histopathologic differential diagnosis of vulvar FDE includes many of the entities discussed within this article. On a strictly histopathologic basis, the depth (and often the density) of the infiltrate and presence of eosinophils helps distinguish FDE from other vacuolar interface-predominant eruptions such as erythema multiforme, SJS/TEN, or GVHD. Clinically, FDE is generally one or several lesions, while the other entities are more widespread, however generalized FDE can be clinically difficult to distinguish from SJS/TEN. [58] Vulvar FDE with associated spongiosis could be mistaken for spongiotic dermatoses such as allergic or irritant contact dermatitis, both of which are not uncommon on genital skin. Although the clinical considerations for a localized recurrent vulvar eruption can include herpetic and other infectious etiologies, these can be differentiated on biopsy by the absence of an acantholytic blister and viral cytopathic effect. Blistering disorders that can affect mucosa such as pemphigus vulgaris and cicatricial pemphigoid will typically show suprabasilar or subepithelial clefting respectively without accompanying vacuolar interface alteration and epithelial dyskeratosis; direct immunofluorescence studies should be positive in immune mediated blistering disorders but negative in FDE.

Graft vs host disease

Bone marrow and stem cell transplant patients are at risk for systemic complications resulting from donor-derived T-cells that attack the hosts’ tissues. Most often affecting the skin, mucosal tissues, liver, and gastrointestinal system, graft versus host disease (GVHD) can result in

considerable morbidity when the vulvar skin and mucosa is affected. Genital involvement may be a presenting or the only site of involvement for a minority of patients.[70,71] Chronic GVHD and genital involvement is not limited to adults; pediatric and adolescent cases are also reported. Pediatric patients may be less symptomatic despite clinical evidence of advanced disease.[72] GVHD has been historically separated into "acute" (<100 days from transplantation) and "chronic" (>100 days from transplantation) forms, but in reality, clinical and histopathologic changes may overlap considerably. Most of the literature regarding GVHD affecting vulvar skin and mucosa focuses on chronic GVHD changes. Genital symptoms involving the female reproductive tract typically begin within the first year of transplant but are reported up to two years after transplantation.[70] The incidence of vulvo-vaginal involvement by GVHD varies in the literature, but seems more common in patients receiving peripheral stem cell transplant compared to those receiving allogeneic bone marrow transplants.[70,73] Best estimates suggest that at least one quarter but up to one half of patients with GVHD have genital involvement.[70,74] However, genital involvement by GVHD may be underestimated in the literature due to underreporting; in one prospective study of patients receiving stem cell transplant, 27 of 41 women (66%) were diagnosed with genital GVHD by the end of three years, with most being diagnosed in the first year.[74] Genital involvement impacts sexual functioning and quality of life, and is best addressed with multidisciplinary management and early intervention.[70]

Background/Pathophysiology

In oversimplified terms, GVHD results when donor T-cells from the immunocompetent graft recognize the patient's (the host) tissue antigens as foreign and mount a cytotoxic attack against them.[70] Cytokine release, activation of T-cells, and stimulation of pro-inflammatory signaling cascades all contribute to the development of GVHD, and both cell-mediated immunity and humoral immunity play important roles.[73] Chronic inflammation and cytotoxic damage to tissue generally progresses to fibrosis and sclerosis of involved tissues.

Clinical presentation

Reported incidence of vulvar chronic GVHD is likely an underestimate. Presenting symptoms include dryness, pain, itching or burning, pain during urination and pain during intercourse. As these symptoms can overlap with the hypoestrogen state that is induced by many myeloablative therapies prior to transplant, it can be difficult to recognize that the symptoms may actually be related to GVHD.[70,75] Careful gynecologic examination is important to recognize clinical features specifically associated with chronic GVHD; some of these signs include synechiae (adhesions), the combination of red and white spots, reticular white lines, and fissures.[74] Vulvar skin and mucosal atrophy is frequently present but is not by itself a specific feature of genital GVHD.

There is a scoring system for chronic genital GVHD based on 2005 National Institutes of Health consensus criteria. This scoring system takes into account clinical signs as well as symptomatology and ranges from score 0 (asymptomatic even if clinical signs are present) to score 3 (frequent symptoms and widespread vulvar or vaginal adhesions with stenosis).[71,73,74] Clinical exam findings supportive of the mild or early disease include erythema and telangiectasias. Erosions, fissures, and focal adhesions are classified as moderately severe disease. Typically the vulva shows changes before the vagina becomes involved, but this is not always the case. The most commonly affected areas include the labia minora, perineum, clitoral prepuce, and vestibule; the labia majora is often unaffected.[73]

Vulvar GVHD may mimic lichen sclerosis or lichen planus clinically. White reticulated patches will mimic the Wickham striae of lichen planus. Chronic vulvar GVHD will more often be erosive and involve mucosal epithelium, in contrast to typical lichen sclerosus.[73] Correlation with a history of transplant is essential, and although a biopsy may help differentiate these entities, considerable histologic overlap may also exist.

Of note, patients who have received bone marrow or stem cell transplantation are at risk for reactivation of human papilloma virus infection and related dysplasia and carcinoma.[71,76] Chronic immunosuppression also predisposes to other infections such as herpesvirus. Clinical monitoring of patients should also take this into account.

Treatment involves topical steroids, non-steroidal immunosuppressants (such as calcineurin inhibitors), and topical estrogen therapy. Goal of treatment is to improve symptoms of pain by healing mucosal erosions and ulcerations, and to prevent the need for surgical management of stenotic complications.[71] Early identification and treatment can help prevent and minimize long term sequelae such as vaginal stenosis and vulvar sclerosis, although progressive fibrosis and altered vulvar architecture can occur even in spite of therapy. In several studies, between one quarter and one third of women were asymptomatic when they first developed clinical signs of early GVHD.[74,77] This supports the need for early and consistent gynecologic examinations as part of routine care following transplantation.

Histopathology

The decision to biopsy is not always an easy one. The highest likelihood of obtaining useful diagnostic information depends on the timing of the biopsy (biopsying a sufficiently developed lesion), the location of the biopsy (non-eroded or ulcerated skin/mucosa), and providing the pathologist with adequate and appropriate clinical information. Even still, biopsies may not be able to provide definitive diagnostic information.[73,78]

Biopsies of GVHD show a vacuolar interface reaction pattern, typically with a pauci-cellular dermal infiltrate (Fig. 12), but more inflammatory, lichenoid patterns are also recognized. Given that patients undergoing transplant have received numerous ablative and immunosuppressant medications, there may be associated changes of epidermal dysmaturation. These changes include nuclear enlargement and/or slight pleomorphism and partial impairment of the normal maturation gradient of the epithelium. There may be epidermal/ epithelial atrophy with a prominent granular layer and compact hyperkeratosis. Dyskeratosis is the hallmark feature of GVHD and may be

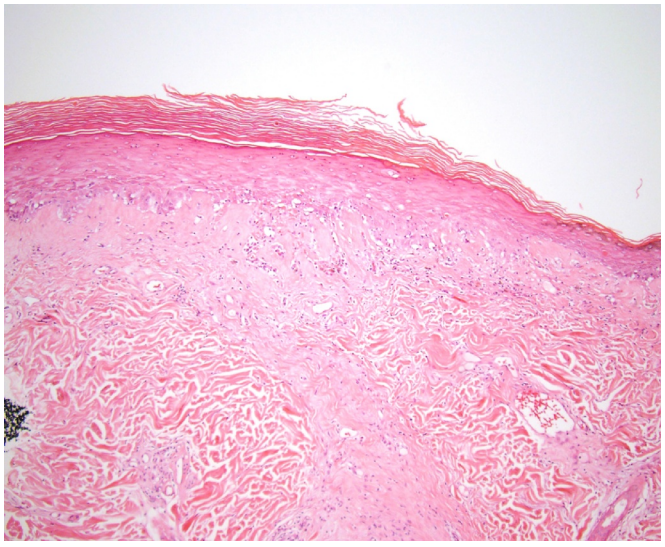

Fig. 12. Graft versus host disease. There is vacuolar interface alteration with abundant dyskeratosis. There is moderate exocytosis of lymphocytes into the lower half of the epidermis, with sparse lymphocytes surrounding dyskeratotic cells. The papillary dermis is sclerotic with a subtle band of lymphocytic inflammation (H&E, 100X).

seen at any and all layers of the epithelium. Satellite cell necrosis describes the identification of intraepidermal lymphocytes surrounding a dying keratinocyte.[78] Although usually described in the context of GVHD, this phenomenon is not unique to GVHD and may be seen in other vacuolar interface processes that result in cytotoxic damage to keratinocytes. Early or mild GVHD may show exceedingly subtle examples of dyskeratosis and vacuolar change. Severe GVHD can result in zonal or confluent epidermal necrosis, subepidermal clefting, and artifactual blistering.

The dermal infiltrate in GVHD is typically sparse, consisting predominantly of lymphocytes, but may be variable with increasing severity. Eosinophils are uncommon in GVHD but not always entirely absent.[79] Lichenoid GVHD may show a denser band of inflammation, with squamatization and saw-tooth changes of the dermal-epidermal junction in a manner that mimics lichen planus. Chronic GVHD also results in dermal/ subepithelial fibrosis and sclerosis.

The pathology consensus paper regarding the diagnosis of GVHD in the skin requires at a minimum the presence of keratinocyte apoptosis in the lower aspects of the epithelium.[78] Recommendation for the reporting of skin biopsies with clinical concern for GVHD include phrases such as "no evidence of GVHD", "possible GVHD", "probable GVHD", and "GVHD", based on a complete evaluation of histopathologic features and clinical data.[78]

Biopsies showing GVHD are often obtained with a clinical differential of drug eruption. As such, numerous studies have attempted to differentiate between these two possibilities. While some earlier studies considered features such as involvement of hair follicle epithelium or eccrine duct epithelium to be more supportive of GVHD or drug eruption respectively, there are conflicting results. Similarly, while the presence of eosinophils within the dermal infiltrate may be seen in a drug eruption, their presence does not exclude the possibility of GVHD.[79,80] Overall, the summary of evidence finds no consistently reproducible histopathologic changes to distinguish GVHD from drug eruption[81] and there is an absolute necessity to correlate with other systemic symptoms and laboratory values.

Chronic sclerotic GVHD, which involves dermal or subepithelial fibrosis and sclerosis, generally occurs in a top-down fashion. Although often preceded by an inflammatory phase, occasionally sclerosis and dermal homogenization may occur in the absence of an earlier lichenoid phase.[78] Chronic sclerotic GVHD may have histopathologic overlap with lichen sclerosus, as well as with chronic radiation dermatitis. In these cases, correlation with clinical history is essential but even still the absolute distinction may not be possible. Both chronic GVHD and lichen sclerosus can result in obliteration of normal vulvar architecture through fusion of labia and narrowing of genital openings, and thus the clinical presentation of both diseases may be quite similar.

Lupus erythematosus

Lupus erythematous (LE) is a heterogenous, multi-organ systemic disease with numerous and varied cutaneous manifestations. An exhaustive description of LE, its pathogenesis, and the myriad of clinical presentations is beyond the scope of this review. Cutaneous lesions of lupus have variable association with systemic disease. Chronic cutaneous (or discoid) lupus (DLE) is infrequently associated with positive serologies and systemic disease, although there is a subset of patients that will progress to systemic lupus (SLE), which may involve pulmonary, cardiac, brain, kidney, joint and other organ systems.[82] Conversely, approximately 70% of patients with SLE will have cutaneous lesions.[83] Genital (and even more specifically, vulvar) LE appears to be uncommon, although this may reflect underreporting or underdiagnosis. Approximately 5% of women with some type of cutaneous lupus (DLE or SLE) are estimated to have vulvar mucosal involvement[84]; the incidence of vulvar skin involvement has not been reported but appears to be rare based on isolated case reports in the literature.

Background/ pathophysiology

LE is an autoimmune disease that can affect multiple organ systems including the skin, and in some cases, it may be limited to the skin. Cutaneous manifestations of lupus span acute and chronic variants, each with different clinical and histopathologic presentations. The pathogenesis of LE includes a complex interaction of cell-mediated and innate immunity, genetic predisposition, hyperactivity of B-cells, cytokines and chemokines, and external and environmental stimuli.[83,85] Women are affected more frequently than men. Autoantibody formation against a variety of antigens assists in the subclassification of disease.[85]

As many cutaneous manifestations of LE are present in photo-distributed regions, the role of UV light has been investigated as causative, however the presence of oral and genital involvement suggests that other mechanisms also play a role in induction of lesions.[86] Skin lesions of DLE have been shown to have activation of Th22, Th17, and Th1 pathways.[83] Plasmacytoid dendritic cells have also been shown to be an important upregulator of Type- 1 interferon in skin lesions of LE,[85] and dysregulated type-1 interferon is thought to recruit the excess inflammation that typifies cutaneous lupus.[87,88]

Clinical presentation

Most of the (limited) literature reporting vulvar involvement in LE suggests that it almost always arises in women with previous diagnosis of LE, either DLE or SLE, rather than arising as an isolated finding or new diagnosis.[89] Skin and mucosal lesions may consist of atrophic erythematous plaques with scarring (as seen in typical lesions of DLE on sun-exposed skin) or present as erosions and ulcerations of mucosal epithelium. Sites of genital involvement by LE include the keratinized skin of the labia majora, mons pubis, and perianal skin, as well as the modified mucosal epithelium of the labia minor and introitus.[86] When hair-bearing skin is involved, there is typically scarring and permanent hair loss.[90,91] Patients may report itching, burning, pain with intercourse or urination, or may be asymptomatic.

Treatment of LE requires input from multiple specialties, including rheumatology, dermatology, and gynecology. Vulvar LE is treated similarly to other cutaneous lesions, which generally involves systemic hydroxychloroquine and topical corticosteroids.[86] Emerging and investigative treatments showing some promise for the treatment of cutaneous LE include monoclonal antibodies directed against interferon-α, B-lymphocyte stimulators, and Janus kinase (JAK) inhibitors.[88]

Histopathology

The histopathologic features of LE vary depending on the variant being sampled. While DLE and SLE and variants in between share some features (namely inflammation, basal vacuolar change at the dermal-epidermal junction, and dermal mucin deposition), the density, intensity, and amount of these features varies considerably.

DLE has fairly characteristic constellation of features; case reports suggest that vulvar DLE resembles DLE at other anatomic sites (Fig. 13).[89,91] Biopsies will show atrophic or mildly acanthotic epidermis with overlying hyperkeratosis, keratin plugged follicles, and a prominent granular layer. Lichenoid inflammation is present at the dermal–epidermal junction, with scattered dyskeratotic or apoptotic keratinocytes within the epidermis and generally scattered melanophages in the superficial dermis. Basement membrane zone thickening is a helpful feature if identified. In addition to the superficial band of inflammation, a lymphoplasmacytic infiltrate may extend more deeply into the dermis, generally surrounding eccrine glands and hair follicles. Dermal mucin deposition may be appreciated, but this feature may be subtle. Hypertrophic LE is a variant of DLE that typically demonstrates more verrucous to vegetative lesions; microscopically hypertrophic LE shows acanthotic epidermis with hair follicles expanded by marked

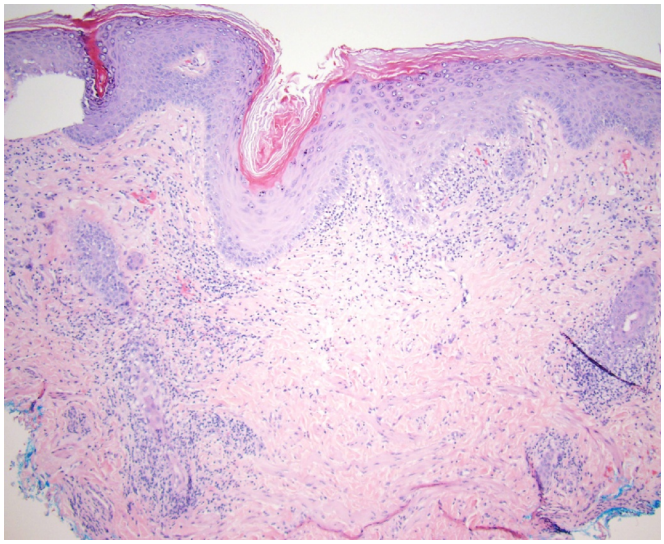

Fig. 13. Discoid lupus erythematosus. There is hyperkeratosis with a slightly acanthotic epidermis, follicular plugging, and a lymphoplasmacytic inflammatory infiltrate at both the superficial and deep aspects of the biopsy (H&E, 100X).

hyperkeratosis. CD123 expressing plasmacytoid dendritic cells clustered and located near the dermal-epidermal junction have been reported as a useful parameter to differentiate hypertrophic DLE from some of its mimickers.[92] Hypertrophic LE has been reported once involving the vulva in a patient with generalized DLE.[89]

Biopsies of skin involved by SLE is much more subtle and may sometimes be non-specific. Epidermal atrophy and hyperkeratosis with subtle vacuolization of keratinocytes at the dermal-epidermal junction is appreciated. Dermal inflammation is typically sparse and limited to superficial perivascular lymphocytes and occasionally a few plasma cells. Dermal mucin is increased, often to the point that special stains are not required to appreciate its presence. Mucosal biopsies may show only epithelial erosion or ulceration; these biopsies may be non-specific and non-diagnostic in isolation.[84]

Historically there has been a role for direct immunofluorescence in the diagnosis of cutaneous lupus. Granular deposition of multiple immunoreactants (IgM, IgA, IgG, C3, or some combination) along the dermal-epidermal junction is supportive of a diagnosis of LE. The utility and specificity of a positive result increases when sun-protected, non-lesional skin is biopsied.[93] While direct immunofluorescence studies are still utilized today, autoantibody serologies offer a sensitive and specific means of diagnosis and classification.

Descriptions of the other histopathologic manifestations of LE are beyond the scope of this article, particularly as some of the variants (namely subacute cutaneous LE, tumid LE, bullous LE, chilblains LE, and LE panniculitis) have not been reported in genital sites.

Erythema multiforme

Erythema multiforme (EM) is a hypersensitivity reaction with a particular and characteristic clinical presentation of annular to target-toid lesions. EM is typically triggered by a preceding infection (most commonly herpes virus or *Mycoplasma* infection) or by medication ingestion. Skin or mucosa may be involved. About one quarter of patients with EM are thought to have involvement of genital skin or mucosa.[94]

Background/ pathophysiology

EM is a delayed type hypersensitivity reaction. Frequently related to herpes virus infection (usually HSV type 1), and less likely to drug exposure, EM occurs most often in young adults of all ethnicities and races.[95] EM is less commonly linked to medication ingestion, with nonsteroidal anti-inflammatory drugs, antibiotics, and anticonvulsant medications most frequently implicated. Recurrent EM refers to patients who experience multiple episodes of EM per year over multiple years; recurrent EM has a very strong association with HSV infection although other infections or exposures have rarely been linked to this.[95] Research focused on HLA allele frequencies has found that certain alleles may predispose to the development of EM.[95]

EM, in particular HSV–associated EM, is thought to develop from fragments of viral DNA that are transported via the blood to the skin where they elicit release of cytokines (interferon appears to be especially important) and trigger activation of T cells, resulting in cytotoxicity to basal keratinocytes.[95,96]

Clinical presentation

EM presents as symmetric round/ annular skin lesions less than 3 cm, resembling a target with a central bull's eye. The classic target lesion is zonated with a central area of dusky erosion surrounded by pale edema and bright erythema (3 zones). Atypical targetoid lesions are also described in EM; these tend to be raised with only two distinct zones of outer erythema and central edema.[97,98] Lesions can involve any part of the skin, but involvement of acral skin (palms and soles) is classic and facial involvement is not uncommon. Erythema on skin of color may be difficult to appreciate and targetoid lesions as seen in EM and other skin diseases may be harder to recognize.[99] Involvement of mucosa places patients into the category of EM “major”, but total body surface areas affected should not exceed 10%.[95,97,98] Vulvar involvement is usually ulcerative and painful.

Patients with EM report pain and stinging of the skin, and may feel systemically unwell with fever and malaise, but are generally less sick than those with SJS/TEN. [100] Episodes last for approximately one week before resolution, but may be recurrent, particularly related to reactivation of herpes simplex virus infection.[95] Therapy is supportive and focused on eliminating any contributory infections or exposures. Mucosal disease can be managed with topical anesthetics and corticosteroids.[95] Suppression of HSV through the use of antivirals may prevent recurrence of EM episodes in patients predisposed to this.[94]

Histopathology

EM is the prototypic vacuolar interface reaction pattern (Fig. 14). Basal keratinocytes show vacuolization, disrupting the normally sharp demarcation between epidermis and dermis. Lymphocytes may exocytose within the epithelium, and individual dyskeratotic keratinocytes are present at all layers of the epidermis, in contrast to the basilar preference of dyskeratosis seen in lichen planus and the inflammatory phase of lichen sclerosus. Spongiosis may part of the earliest features seen,[21] and basal vacuolization may be subtle. The epidermis is not acanthotic and the corneum preserves a basketweave appearance, testifying to the acute nature of the eruption. Dermal inflammation can vary as either band like or perivascular, but the density is generally less than seen in lichen planus. T-lymphocytes predominate in lesions of EM,[101] and eosinophils are sometimes part of the infiltrate.[102] EM in the vulvar region may show more spongiosis and may tend toward erosive and ulcerative lesions.[21]

Stevens Johnson Sydrome/ Toxic Epidermal Necrolysis

Similar to EM, Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) also represent hypersensitivity reactions but a more severe disease with systemic symptoms, considerable morbidity, and risk of mortality. While historically viewed on a clinical spectrum with EM, SJS and TEN are now favored to be clinically distinct from EM.[97,98,100] SJS/TEN arises almost always as an adverse medication effect, with the disease most commonly linked to sulfa-type antibiotics,

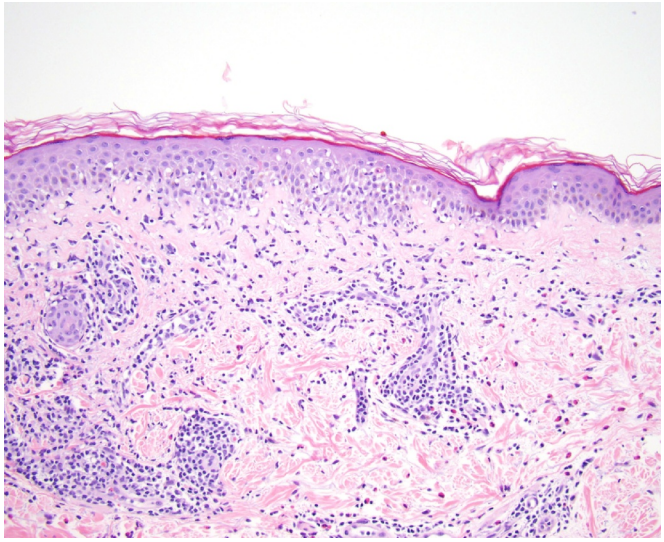

Fig. 14. Erythema multiforme. Acute, basket-weave stratum corneum with underlying vacuolar interface alteration and dyskeratosis of the epidermis is present with an underlying dermal inflammation of lymphocytes, plasma cells, and eosinophils (H&E, 200X).

anti-convulsants, and anti-inflammatory drugs.[103] SJS/TEN is a true dermatologic emergency that needs to be recognized quickly and accurately in order to implement aggressive supportive care to decrease likelihood of poor outcome, long term complications, and death.

Background/ pathophysiology

SJS/TEN is a delayed type hypersensitivity reaction almost exclusively related to ingestion of an offending medication. Most patients present between 4 and 28 days after exposure.[104] Various cytokines, including TNF alpha, interferon, and various interleukins, are thought to be important in the pathogenesis of SJS/TEN, ultimately resulting in activation of cytotoxic T and NK cells. These cytotoxic lymphocytes stimulate keratinocyte apoptosis through Fas/Fas ligand, granulysin, and perforin- mediated pathways,[104,105] leading to keratinocyte death and epidermal detachment. Necrosis, in addition to apoptosis, may play a role late in the disease.[106]

As in EM, patients with certain HLA alleles may be more susceptible to development of SJS/TEN when exposed to certain medications.[104]

Clinical presentation

In SJS/TEN, patients present with painful erythema and blisters with skin and mucosal sloughing following a febrile and “flu-like” prodromal phase of 1–3 days. Earliest symptoms may involve the mucous membranes; these generally appear as non-specific erosions and ulcerations with underlying erythema. Cutaneous involvement usually follows close behind, presenting as erythematous to dusky irregular macules and patches with purpuric edges.[104] Although some of the lesions in SJS/TENS may appear targetoid, they may be distinguished from EM by their expansion too large irregular lesions with blistering over several days. Patients are systemically unwell, and mucosal involvement may preclude the ability to eat/swallow. Distinction between SJS and TEN is based on percent of body surface involved by epidermal detachment: SJS has $<10\%$ and TEN has $>30\%$ involved.[98,104]

The clinical differential of SJS/TEN is staphylococcal scalded skin syndrome (SSSS), particularly in pediatric patients. SSSS results in superficial epidermal sloughing (rather than full-thickness epidermis) due to bacterial produced exfoliative toxins.[81] As only the superficial most portion of the epidermis is lost in SSSS, the prognosis is much better. Distinction between SJS/TEN and SSSS is frequently a reason for performing a biopsy in patients presenting with skin sloughing, and histopathologic evaluation should readily determine the location of the blister.

Diffuse epidermal detachment poses risks for dehydration, temperature volatility, and secondary infectious complications, and these represent causes of mortality in the acute stage. The SCORTEN severity scoring system can be used to assess prognosis and mortality risk; it incorporates seven parameters which independently have correlated with prognosis. These parameters include patient age, heart rate, serum urea level, serum bicarbonate level, and serum glucose levels.[81,104]

Treatment of SJS/TEN focuses on immediate identification and cessation of the offending medication and implementation of aggressive supportive care. Other therapies that may have a role in treating severe disease include intravenous immunogloblulin, tumor necrosis factor alpha inhibitors, cyclosporine, and plasmapheresis.[107] Long term consequences of TEN include vulvovaginal adhesions and stenosis in a subset of women.[108]

Histopathology

Similarly to EM, TEN/SJS shows a vacuolar interface reaction pattern, with dyskeratosis prominent within the epidermis. The dermal inflammatory infiltrate tends to be sparse, particularly in relation to the degree of cytotoxicity within the epidermis (Fig. 15), and lesser in degree than lesions of EM.[97] In comparison to the lymphocyte -rich infiltrate in EM, the sparse inflammatory infiltrate in SJS/TEN is made up of macrophages and dermal dendrocytes.[101] However, a few cases have attempted to characterize blister fluid in SJS/TEN and have detected predominance of CD8 expressing T-cells.[109] One study has found a trend toward fewer eosinophils in biopsies of SJS/TEN than in EM, but otherwise similar histologic features.[102] Other studies have linked a denser infiltrate with eosinophils, neutrophils, and extravasated erythrocytes with drug-induced cases of SJS/TEN.[110]

Notably, marked cell death of keratinocytes can lead to confluent epidermal necrosis, often with subsequent subepidermal separation and blistering. This feature may occur in any single biopsy of EM, SJS, or TEN, depending on the timing and location of the biopsy. The degree of epidermal necrosis does not always correlate with disease severity; full thickness skin necrosis does not always equate to a diagnosis of TEN,

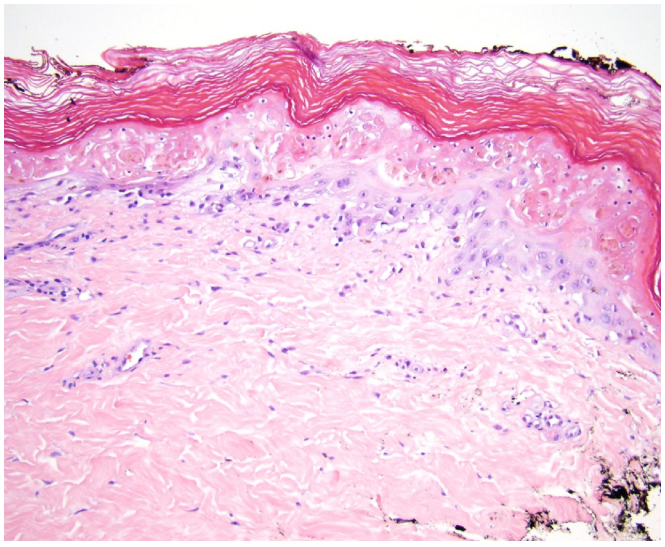

Fig. 15. Stevens Johnson Syndrome/ toxic epidermal necrolysis. Acute, basket-weave stratum corneum with underlying, near-complete necrosis of the epidermis. The remaining viable basal layer of the epidermis shows vacuolar interface alteration with scattered dyskeratosis. The dermis is notably pauci-inflammatory (H&E, 200X).

and the absence of full thickness skin necrosis should not preclude the diagnosis. The accurate diagnosis is made through correlation with clinical distribution of lesions and the amount of body surface affected.

Although EM, SJS, and TEN may involve the mucosal and skin surfaces of the vulva, as these entities are usually a widespread eruption, biopsies from the vulva would be unusual when other, less anatomically sensitive areas are available for biopsy. The relatively recently described entity *Mycoplasma pneumoniae*- Induced Rash and Mucositis (MIRM), on the other hand, will almost exclusively involve mucosal surfaces and biopsies from an oral or genital site is more likely. MIRM is a relatively recently defined entity linked to recent infection with *Mycoplasma psneumoniae*. Occurring more often (but not exclusively) in children and adolescents, MIRM presents as a severe mucocutaneous blistering eruption usually one week after respiratory symptoms. Clinical lesions are described as vesicobullous, targetoid, papular, or macular. Oral involvement is almost universal, ocular symptoms somewhat less and genital mucosa affected in about two thirds of cases.[111] Despite the alarming clinical appearance and marked mucosal involvement, patients with MIRM have a good prognosis, with most making a complete recovery without sequelae, in contrast to true SJS/TEN.[111,112] Diagnostic criteria for MIRM include at least two affected mucosal sites, less than or equal to 10% of body surface skin sloughing, vesiculobullous or atypical targetoid lesions, and clinical evidence of atypical pneumonia with detection of positive *Mycoplasma* titers.[111] Despite the overlapping clinical presentation and identical histology of a vacuolar interface dermatitis, the pathophysiology of MIRM is thought to depend on immune complex deposition from proliferating clones of B-cells and subsequent complement activation, rather than the cytotoxicity that predominates in EM and SJS/TEN.[111,113] Many of the cases previously described in the literature as *Mycoplasma* associated EM may actually be better classified as MIRM. Treatment consists of administration of immunosuppressants and antibiotics and supportive care.[111]

OTHER (SOMETIMES) lichenoid DERMATOSES

A review would be incomplete without brief mention of a few more entities that may, on occasion, present with a lichenoid reaction pattern. Although these entities are typically classified as different primary reaction patterns, inclusion of these diagnoses within your differential diagnosis of a lichenoid dermatosis will preclude misdiagnosis.

Zoon vulvitis

Zoon vulvitis is generally classified as a vasculopathic inflammatory reaction pattern. However, there is frequently a band-like inflammatory associated with this entity, and therefore it has some overlap with the lichenoid reaction pattern.

Zoon vulvitis (also termed plasma cell vulvitis or vulvitis circumscripta plasmacellularis) is a mucosal inflammatory reaction of unclear etiology. Chronic irritation, moisture, friction, suboptimal hygiene, and excessive perspiration have all been postulated to predispose to the condition.[114] Autoimmune contributions have also been considered.[115] Zoon vulvitis involves exclusively the mucosal lined portions of the vulva, with the introitus, interface of the labia minora, periurethral region, vulvar vestibule, and clitoris listed as the most common sites of involvement in decreasing frequency.[116] Zoom vulvitis appears as single or multiple well-circumscribed erythematous to glistening patches on the mucosal surface (Fig. 16). Lesions are generally described as being bright red, red-orange, or red-brown, and erosion is common. Pinpoint bright red spots resembling cayenne pepper are said to be a distinctive clue.[114,117] Many patients are asymptomatic but some may complain of pain, burning, itching, or dyspareunia. The clinical differential often includes erosive lichen planus, fixed drug eruption, or squamous intraepithelial neoplasia.[117]

Microscopically, biopsies demonstrate attenuated, atrophic

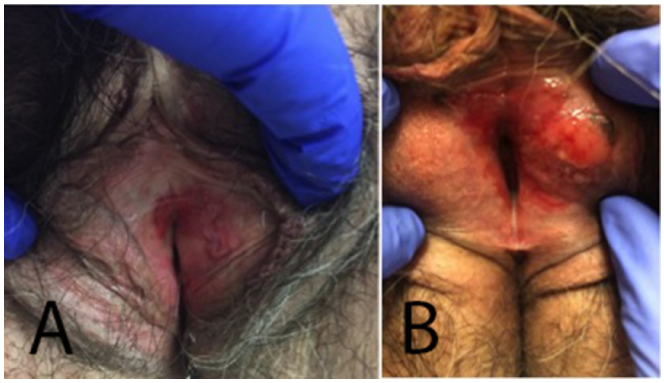

Fig. 16. Clinical presentation of Zoon vulvitis and ELP. A: Initial presentation with focal erythema without erosion and normal vulvar architecture consistent with Zoon vulvitis. B: Presentation three years later showed diffuse glazed erythema, loss of labia minora and clitoral phimosis, which was more consistent with erosive lichens planus. Biopsy of left labium minus revealed a poorly differentiated squamous cell carcinoma.

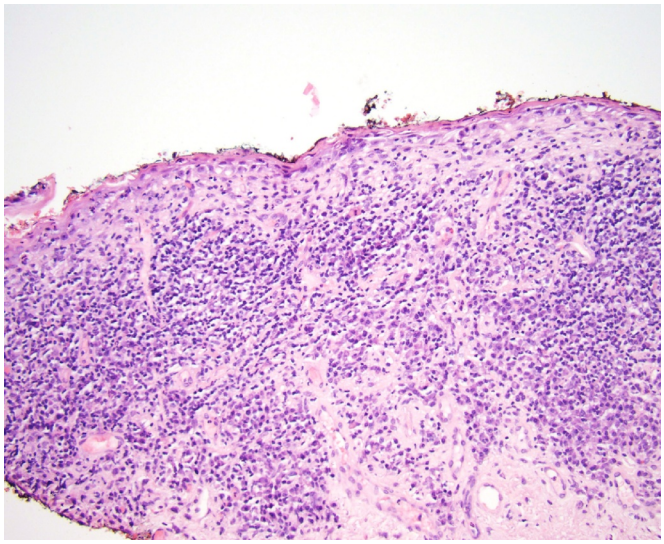

Fig. 17. Zoon vulvitis. There is marked atrophy of the mucosa with a dense underlying plasmacytic inflammatory infiltrate (H&E, 100X).

epithelium with erosion and occasionally full-thickness ulceration (Fig. 17). There may be focal vacuolar change in basilar keratinocytes, as well as exocytosis of neutrophils and lymphocytes into the epithelium. Uniform, mild intraepidermal edema described as “watery spongiosis” may be seen.[118] The finding of "lozenge" shaped keratinocytes in the suprabasilar layer of epithelium has been described as a relatively specific (but not sensitive) feature in Zoon vulvitis.[119] The lozenge shaped keratinocyte is defined as a keratinocyte that is wider than it is tall, imparting a diamond shaped appearance. Depending on the report, these distinctive keratinocytes may be rare[120] or seen in half of cases.[119] An additional rare and presumably metaplastic epithelial change is the presence of mucinous metaplasia.[121,122] Mucinous metaplasia in Zoon vulvitis should show uniform replacement of surface keratinocytes by single units or strips of confluent epithelium with mucin containing cells. These mucinous cells should lack cytologic atypia and individual scattered pagetoid spread, thus distinguishing it from extramammary Paget disease.[121,122]

The submucosa in Zoon vulvitis is characterized by a superficially located, dense band of inflammation rich in plasma cells. This lymphoplasmacytic infiltrate will obscure and blur the mucosal/submucosal demarcation. By definition, the majority of the inflammatory infiltrate should be composed of plasma cells for a confident diagnosis

of Zoon vulvitis.[120] As plasma cells are frequently encountered in biopsies from vulvar skin and mucosa, the presence of plasma cells alone should not trigger consideration of this diagnosis. The remainder of the infiltrate will be composed of admixed neutrophils, eosinophils, lymphocytes, and mast cells. Red blood cell extravasation and hemosiderin deposition is also characteristically identified; these consistent features have led some authors to classify Zoon vulvitis as a vasculopathic rather than lichenoid reaction pattern and to propose that Zoon vulvitis is a mucosal manifestation of cutaneous pigmented purpura.[123]

Treatment of Zoon vulvitis is often fraught with difficulty. Topical therapies, including high potency steroids, tacrolimus, and imiquimod have all been tried and represent the mainstay of treatment options.[124–128] Platelet rich plasma injection has been reported as a potential novel therapy with efficacious results[129] but is still under investigation.

Paraneoplastic pemphigus

Paraneoplastic pemphigus is an immune-mediated blistering disease typically arising in the setting of underlying malignancy. Although the disease usually arises in adults, children have also been reported to be affected.[130,131] Presentation may precede, coincide with, or follow the diagnosis of underlying malignancy. The most common associated malignancies include non-Hodgkin lymphoma, Castleman disease, thymoma, and other hematologic and solid malignancies.[130–132] In paraneoplastic pemphigus, tumor antigens are thought to cross-react with multiple varying antigens found within the epidermis, and autoantibodies are generated to desmogleins, the plakin family of proteins, and other components of cell-cell adhesion.[132,133] Desmoglein 3 autoantibodies have been correlated with genital lesions in one study.[132] Autoantibody formation to these proteins results in an intraepidermal or sometimes subepidermal blister. However, lichenoid tissue reactions are commonly seen and may often predominate in paraneoplastic pemphigus. Humoral immunity through the production of autoantibodies plays an etiopathogenic role, as does cellular immunity and cytotoxic T- lymphocytes. The dominant arm of the immune system (humoral vs cell mediated) in each individual patient may contribute to the variability in clinical and histopathologic presentation.[131,134,135]

Patients with paraneoplastic pemphigus classically present clinically with impressive oral mucosal lesions (intractable stomatitis) as well as cutaneous and mucosal blisters and polymorphic, erythematous lesions. The clinical concern is often for Stevens Johnson Syndrome, which makes sense given the considerable clinical and histopathologic overlap. About a third of patients are reported to have genital involvement.[132] Under the microscope, biopsies from patients with paraneoplastic pemphigus may show an erythema multiforme-like pathology, with vacuolar interface alteration, dyskeratosis at any level of the epidermis, and an associated band of lymphoid inflammation in the dermis. Evidence of intraepidermal (usually suprabasilar) or less likely subepidermal blistering may be present in the same biopsy; blister formation may be a minor component or may predominate the biopsy findings. Presence of dyskeratosis in association with suprabasilar acantholysis should suggest the diagnosis.[133,136] Lesions more closely resembling lichen planus have also been reported.[135] Direct immunofluorescence is critical to the diagnosis, as it will show *both* intercellular and basement membrane zone staining of immunoreactants (generally C3 and IgG, but additional immunoreactants are not uncommon). Indirect immunofluorescence studies performed on rat bladder epithelium have historically been used as confirmatory tests, with higher specificity and sensitivity than on normal skin substrate.[131] In one study of 104 patients, indirect immunofluorescence was positive in nearly 80% of patients.[132] However, ELISA and immunoblotting techniques have become more prevalent and offer more specific diagnostic information, high sensitivity, and reliablability.[131,132]

Treatment of paraneoplastic pemphigus focuses on treatment of the underlying associated malignancy, as well as immunosuppressive methods to suppress auto-antibody production.[132]

Syphilis

Syphilis is a sexually-transmitted infection caused by the spirochetal bacterial organism Treponema *pallidum*. The incidence of syphilis has increased since 2000, with increasing infections being attributed to HIV infection, intravenous drug use and abuse, and unprotected sexual intercourse.[137] Primary syphilis classically presents as a painless solitary ulcer in the genital region which may go undetected. The primary lesion will heal and within weeks to months the secondary stage will present as a disseminated skin rash. Referred to as “the great mimicker” due to the wide variety of clinical presentations reported, this secondary stage may be flat (macular), raised (papular), ulcerative, pustular, or a mix of presentations. The “copper” hue to lesions and the presence of lesions on palms and soles are clinical clues to the diagnosis.[137] If undiagnosed and untreated, secondary syphilis may progress to the latent and tertiary phases, leading to long-term, multi-organ involvement and damage. Similar to the range of clinical morphologies, the histopathologic features of this infection can also vary. The secondary stage of syphilis in particular is likely to demonstrate a lichenoid tissue reaction pattern. Slender, irregularly elongated rete ridges comprise the epidermal changes, and classically a lymphoplasmacytic band of inflammation will hug the dermal epidermal junction, with vacuoles along the dermal-epidermal junction that each contain a lymphocyte (Fig. 18).[138] Despite the band-like appearance of the infiltrate, dyskeratosis is usually not a prominent feature. Of course, vulvar skin and mucosa normally exhibit plasma cells as part of the inflammatory milieu, so the presence of plasma cells alone does not signify the diagnosis, and plasma cells may also be present in other similar-appearing skin rashes.[138] Endothelial swelling and deep extension of the inflammatory infiltrate can be helpful clues. However, histologic patterns of inflammation are well reported to be variable,[139] so pathologists should have a low threshold for considering syphilis within the differential diagnosis. The diagnosis can be confirmed in tissue with immunohistochemistry directed against T. *pallidum*, which will demonstrate spirochetal organisms in the epithelium and endothelial cells, often – but not always!!- abundant in number. Laboratory serologies provide further proof of infection. Penicillin remains the preferred treatment for patients.[137]

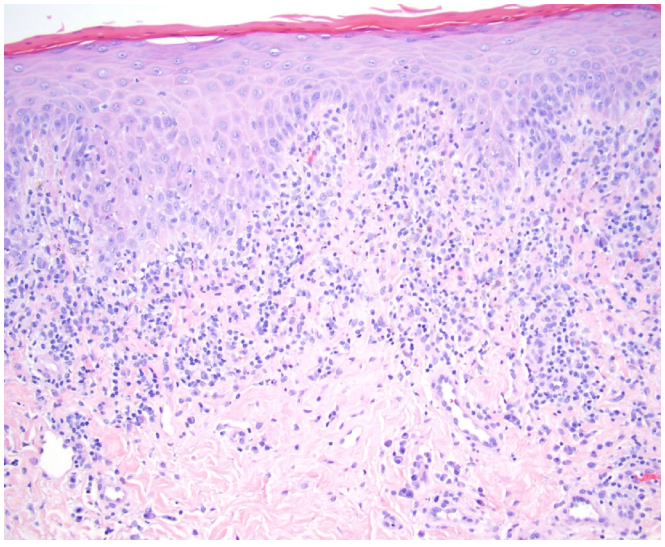

Fig. 18. Syphilis. Irregular acanthosis with somewhat thinned and elongated rete ridges, obscured by dense lymphoplasmacytic inflammation and scattered vacuolar interface alteration is seen. A prominent plasma cell component can be seen near the bottom of the figure (H&E, 200X).

References

1. Gru AA, Salavaggione AL. Lichenoid and interface dermatoses. *Semin Diagn Pathol.* 2017;34:237–249.
2. Ball SB, Wojnarowska F. Vulvar dermatoses: lichen sclerosus, lichen planus, and vulval dermatitis/lichen simplex chronicus. *Semin Cutan Med Surg.* 1998;17:182–188.
3. Vilano SE, Robbins CL. Common prepubertal vulvar conditions. *Curr Opin Obstet Gynecol.* 2016;28:359–365.
4. Smith YR, Haefner HK. Vulvar lichen sclerosus: pathophysiology and treatment. *Am J Clin Dermatol.* 2004;5:105–125.
5. Fistarol SK, Itin PH. Diagnosis and treatment of lichen sclerosus: an update. *Am J Clin Dermatol.* 2013;14:27–47.
6. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol.* 2014;67:290–294.
7. Cooper SM, Ali I, Baldo M, Wojnarowska F. The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case-control study. *Arch Dermatol.* 2008;144:1432–1435.
8. Murphy R. Lichen sclerosus. *Dermatol Clin.* 2010;28:707–715.
9. 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;35:713–721.
10. Funaro D. Lichen sclerosus: a review and practical approach. *Dermatol Ther.* 2004;17:28–37.
11. Carlson JA, Grabowski R, Chichester P, Paunovich E, Malfetano J. Comparative immunophenotypic study of lichen sclerosus: epidermotropic CD57+ lymphocytes are numerous–implications for pathogenesis. *Am J Dermatopathol.* 2000;22:7–16.
12. 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.
13. Fancher K, Gardner JM, Shalin SC. Elastophagocytosis and interstitial granulomatous infiltrate are more common in extragenital vs genital lichen sclerosus. *J Cutan Pathol.* 2020.
14. Gambichler T, Skrygan M, Czempiel V, et al. Differential expression of connective tissue growth factor and extracellular matrix proteins in lichen sclerosus. *J Eur Acad Dermatol Venereol.* 2012;26:207–212.
15. Farrell AM, Dean D, Millard PR, Charnock FM, Wojnarowska F. Cytokine alterations in lichen sclerosus: an immunohistochemical study. *Br J Dermatol.* 2006;155:931–940.
16. Carlson JA, Amin S, Malfetano J, et al. Concordant p53 and mdm-2 protein expression in vulvar squamous cell carcinoma and adjacent lichen sclerosus. *Appl Immunohistochem Mol Morphol.* 2001;9:150–163.
17. Chiesa-Vottero A, Dvoretsky PM, Hart WR. Histopathologic study of thin vulvar squamous cell carcinomas and associated cutaneous lesions: a correlative study of 48 tumors in 44 patients with analysis of adjacent vulvar intraepithelial neoplasia types and lichen sclerosus. *Am J Surg Pathol.* 2006;30:310–318.
18. Tapp RA, Feng J, Jones JW, Carlson JA, Wilson VL. Single base instability is promoted in vulvar lichen sclerosus. *J Invest Dermatol.* 2007;127:2563–2576.
19. Fischer GB, J., Margesson L. *The Vulva: A Practical Handbook for Clinicians.* 2nd ed. Cambridge: Cambridge University Press; 2016.
20. Goldstein AT, Marinoff SC, Christopher K, Srodon M. Prevalence of vulvar lichen sclerosus in a general gynecology practice. *J Reprod Med.* 2005;50:477–480.
21. Hoang MP, Selim MA. *Vulvar Pathology.* 1st ed. New York: Springer; 2015.
22. Goldstein AT, Creasey A, Pfau R, Phillips D, Burrows LJ. A double-blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosus. *J Am Acad Dermatol.* 2011;64:e99–104.
23. Nayeemuddin F, Yates VM. Lichen sclerosus et atrophicus responding to methotrexate. *Clin Exp Dermatol.* 2008;33:651–652.
24. Neill SM, Lewis FM, Tatnall FM, Cox NH. British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. *Br J Dermatol.* 2010;163:672–682.
25. 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;22:473–478.
26. Chan MP, Zimarowski MJ. Vulvar dermatoses: a histopathologic review and classification of 183 cases. *J Cutan Pathol.* 2015;42:510–518.
27. Carlson JA, Lamb P, Malfetano J, Ambros RA, Mihm Jr MC. Clinicopathologic comparison of vulvar and extragenital lichen sclerosus: histologic variants, evolving lesions, and etiology of 141 cases. *Mod Pathol.* 1998;11:844–854.
28. Abbas O, Chatrath V, Goldberg LJ. Elastophagocytosis in extragenital lichen sclerosus. *J Cutan Pathol.* 2010;37:1032–1037.
29. Weyers W. Hypertrophic lichen sclerosus sine sclerosis: clues to histopathologic diagnosis when presenting as psoriasiform lichenoid dermatitis. *J Cutan Pathol.* 2015;42:118–129.
30. 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;48:268–274.
31. Sauder MB, Linzon-Smith J, Beecker J. Extragenital bullous lichen sclerosus. *J Am Acad Dermatol.* 2014;71:981–984.
32. Kavak A, Erdoğan B, Topkarc Z, Sönmezler H, Sakız D. Bullous lichen sclerosus: isolated vulvar involvement. *Dermatol Online J.* 2018:24.
33. Leonard N, Biswas A, Hickey S, Bell H. Eosinophilic spongiosis in a case of lichen sclerosus: a marker for superimposed bullous pemphigoid. *Histopathology.* 2008;52:885–887.
34. 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.
35. McPherson T, Cooper S. Vulval lichen sclerosus and lichen planus. *Dermatol Ther.* 2010;23:523–532.
36. Lewis FM. Vulval lichen planus. *Br J Dermatol.* 1998;138:569–575.
37. Schmidt H. Frequency, duration and localization of lichen planus. A study based on 181 patients. *Acta Derm Venereol.* 1961;41:164–167.
38. 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;132:658–666.
39. Oyama N, Chan I, Neill SM, et al. Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. *Lancet.* 2003;362:118–123.
40. Howard A, Dean D, Cooper S, Kirtshig G, Wojnarowska F. Circulating basement membrane zone antibodies are found in lichen sclerosus of the vulva. *Australas J Dermatol.* 2004;45:12–15.
41. Cooper SM, Dean D, Allen J, Kirtschig G, Wojnarowska F. Erosive lichen planus of the vulva: weak circulating basement membrane zone antibodies are present. *Clin Exp Dermatol.* 2005;30:551–556.
42. Baldo M, Bailey A, Bhogal B, Groves RW, Ogg G, Wojnarowska F. T cells reactive with the NC16A domain of BP180 are present in vulval lichen sclerosus and lichen planus. *J Eur Acad Dermatol Venereol.* 2010;24:186–190.
43. Ruocco V, Satriano RA, De Rosa G, Pettinato G, Gombos F. Malignancy in lichen planus. *Int J Dermatol.* 1989;28:542–544.
44. Gorouhi F, Davari P, Fazel N. Cutaneous and mucosal lichen planus: a comprehensive review of clinical subtypes, risk factors, diagnosis, and prognosis. *Scientific World Journal.* 2014;2014:742826.
45. Mauskar M. Erosive Lichen Planus. *Obstet Gynecol Clin North Am.* 2017;44:407–420.
46. Bradford J, Fischer G. Management of vulvovaginal lichen planus: a new approach. *J Low Genit Tract Dis.* 2013;17:28–32.
47. Simpson RC, Littlewood SM, Cooper SM, et al. Real-life experience of managing vulval erosive lichen planus: a case-based review and U.K. multicentre case note audit. *Br J Dermatol.* 2012;167:85–91.
48. Moyal-Barracco M, Edwards L. Diagnosis and therapy of anogenital lichen planus. *Dermatol Ther.* 2004;17:38–46.
49. Cheng H, Oakley A, Rowan D, Lamont D. Diagnostic criteria in 72 women with erosive vulvovaginal lichen planus. *Australas J Dermatol.* 2016;57:284–287.
50. Byrd JA, Davis MD, Rogers RS. 3rd. Recalcitrant symptomatic vulvar lichen planus: response to topical tacrolimus. *Arch Dermatol.* 2004;140:715–720.
51. Jensen JT, Bird M, Leclair CM. Patient satisfaction after the treatment of vulvovaginal erosive lichen planus with topical clobetasol and tacrolimus: a survey study. *Am J Obstet Gynecol.* 2004;190:1759–1763 discussion 1763-1755.
52. Goldstein AT, Thaçi D, Luger T. Topical calcineurin inhibitors for the treatment of vulvar dermatoses. *Eur J Obstet Gynecol Reprod Biol.* 2009;146:22–29.
53. Simpson RC, Thomas KS, Leighton P, Murphy R. Diagnostic criteria for erosive lichen planus affecting the vulva: an international electronic-Delphi consensus exercise. *Br J Dermatol.* 2013;169:337–343.
54. Cooper SM, Wojnarowska F. Influence of treatment of erosive lichen planus of the vulva on its prognosis. *Arch Dermatol.* 2006;142:289–294.
55. Day T, Weigner J, Scurry J. Classic and Hypertrophic Vulvar Lichen Planus. *J Low Genit Tract Dis.* 2018;22:387–395.
56. Brown LMG, Singh N. *Pathology of the Vulva and Vagina.* New York: Springer; 2013.
57. Alomari A, McNiff JM. The significance of eosinophils in hypertrophic lichen planus. *J Cutan Pathol.* 2014;41:347–352.
58. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. *Curr Opin Allergy Clin Immunol.* 2009;9:316–321.
59. Fischer G. Vulvar fixed drug eruption. A report of 13 cases. *J Reprod Med.* 2007;52:81–86.
60. Zaouak A, Chabchoub I, Essid D, Ben Jennet S, Hammami H, Fenniche S. Genital Involvement in Bullous Fixed Drug Eruption. *Skinmed.* 2019;17:306–309.
61. Sehgal VH, Gangwani OP. Genital fixed drug eruptions. *Genitourin Med.* 1986;62:56–58.
62. Sharma VK, Dhar S, Gill AN. Drug related involvement of specific sites in fixed eruptions: a statistical evaluation. *J Dermatol.* 1996;23:530–534.
63. Wain EM, Neill S. Fixed drug eruption of the vulva secondary to fluconazole. *Clin Exp Dermatol.* 2008;33:784–785.
64. Korkij W, Soltani K. Fixed drug eruption. A brief review. *Arch Dermatol.* 1984;120:520–524.
65. Mizukawa Y, Shiohara T. Fixed drug eruption: a prototypic disorder mediated by effector memory T cells. *Curr Allergy Asthma Rep.* 2009;9:71–77.
66. Choi HJ, Ku JK, Kim MY, et al. Possible role of Fas/Fas ligand-mediated apoptosis in the pathogenesis of fixed drug eruption. *Br J Dermatol.* 2006;154:419–425.
67. Ozkaya E. Fixed drug eruption: state of the art. *J Dtsch Dermatol Ges.* 2008;6:181–188.
68. 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;20:461–464.
69. Suzuki S, Ho J, Rosenbaum M, Bhawan J. Neutrophilic fixed drug eruption: a mimic of neutrophilic dermatoses. *Clin Exp Dermatol.* 2019;44:236–238.
70. Ciavattini A, Clemente N. Female genital tract chronic graft-versus-host disease: review of the literature. *Anticancer Res.* 2015;35:13–17.
71. Stratton P, Turner ML, Childs R, et al. Vulvovaginal chronic graft-versus-host disease with allogeneic hematopoietic stem cell transplantation. *Obstet Gynecol.* 2007;110:1041–1049.
72. Cizek SM, El-Bietar J, Rubinstein J, et al. Pediatric and Young Adult Vulvovaginal Graft-versus-Host Disease. *Biol Blood Marrow Trans.* 2019;25:2408–2415.
73. Kornik RI, Rustagi AS. Vulvovaginal Graft-Versus-Host Disease. *Obstet Gynecol Clin North Am.* 2017;44:475–492.
74. Smith Knutsson E, Björk Y, Broman AK, et al. A prospective study of female genital chronic graft-versus-host disease symptoms, signs, diagnosis and treatment. *Acta Obstet Gynecol Scand.* 2018;97:1122–1129.
75. 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;20:806–811.
76. Sri T, Merideth MA, Pulanic TK, Childs R, Stratton P. Human papillomavirus reactivation following treatment of genital graft-versus-host disease. *Transpl Infect Dis.* 2013;15:E148–E151.
77. Lev-Sagie A, Adar-Walling E, Gumer A, Grisariu S, Avni B. Management and long-

term consequences of genital graft versus host disease following hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2020.
78. Shulman HM, Kleiner D, Lee SJ, et al. Histopathologic diagnosis of chronic graft-versus-host disease: national Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology Working Group Report. *Biol Blood Marrow Transplant.* 2006;12:31–47.
79. Sharon VR, Konia TH, Barr KL, Fung MA. 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;39:413–418.
80. Marra DE, McKee PH, Nghiem P. Tissue eosinophils and the perils of using skin biopsy specimens to distinguish between drug hypersensitivity and cutaneous graft-versus-host disease. *J Am Acad Dermatol.* 2004;51:543–546.
81. Abate MS, Battle LR, Emerson AN, Gardner JM, Shalin SC. Dermatologic Urgencies and Emergencies: what Every Pathologist Should Know. *Arch Pathol Lab Med.* 2019;143:919–942.
82. Li Q, Wu H, Liao W, et al. A comprehensive review of immune-mediated dermatopathology in systemic lupus erythematosus. *J Autoimmun.* 2018;93:1–15.
83. Méndez-Flores S, Hernández-Molina G, Enríquez AB, et al. Cytokines and Effector/Regulatory Cells Characterization in the Physiopathology of Cutaneous Lupus Erythematous: a Cross-Sectional Study. *Mediators Inflamm.* 2016;2016:7074829.
84. Burge SM, Frith PA, Juniper RP, Wojnarowska F. Mucosal involvement in systemic and chronic cutaneous lupus erythematosus. *Br J Dermatol.* 1989;121:727–741.
85. Garelli CJ, Refat MA, Nanaware PP, Ramirez-Ortiz ZG, Rashighi M, Richmond JM. Current Insights in Cutaneous Lupus Erythematosus Immunopathogenesis. *Front Immunol.* 2020;11:1353.
86. Del Alcázar-Viladomiu E, López-Pestaña A, Tuneu-Valls A. Lupus Erythematosus Affecting the Genitalia: an Unusual Site. *Actas Dermosifiliogr.* 2018;109:78–80.
87. Kahlenberg JM. Rethinking the Pathogenesis of Cutaneous Lupus. *J Invest Dermatol.* 2020.
88. Chen KL, Krain RL, Werth VP. Advancing understanding, diagnosis, and therapies for cutaneous lupus erythematosus within the broader context of systemic lupus erythematosus. *F1000Res.* 2019;8.
89. Prenner J, Kelley K, Elkeeb D, Onajin O. Hypertrophic Discoid Lupus Erythematosus of the Vulva Mimicking Lichen Simplex Chronicus: a Case Report and Review of the Literature. *Am J Dermatopathol.* 2020;42:191–195.
90. Jolly M, Patel P. Looking beyond the ordinary: genital lupus. *Arthritis Rheum.* 2006;55:821–822.
91. Bilenchi R, Pisani C, Poggiali S, Andreassi A, de Padova LA, di Perrit T. Discoid lupus erythematosus of the vulva. *Lupus.* 2004;13:815–816.
92. Walsh NM, Lai J, Hanly JG, et al. Plasmacytoid dendritic cells in hypertrophic discoid lupus erythematosus: an objective evaluation of their diagnostic value. *J Cutan Pathol.* 2015;42:32–38.
93. Cardinali C, Caproni M, Fabbri P. The composition of the lupus band test (LBT) on the sun-protected non-lesional (SPNL) skin in patients with cutaneous lupus erythematosus (CLE). *Lupus.* 1999;8:755–760.
94. Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol.* 1993;128:542–545.
95. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. *Int J Dermatol.* 2012;51:889–902.
96. Patterson JW. *Weedon's Skin Pathology.* 4th ed Churchill LivingstoneElsevier Limited; 2016.
97. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol.* 1997;24:726–729.
98. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993;129:92–96.
99. Nolen L. How Medical Education Is Missing the Bull's-eye. *N Engl J Med.* 2020;382:2489–2491.
100. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau JC. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol.* 2002;138:1019–1024.
101. Paquet P, Piérard GE. Erythema multiforme and toxic epidermal necrolysis: a comparative study. *Am J Dermatopathol.* 1997;19:127–132.
102. Rzany B, Hering O, Mockenhaupt M, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol.* 1996;135:6–11.
103. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *Clin Rev Allergy Immunol.* 2018;54:147–176.
104. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: an Update. *Am J Clin Dermatol.* 2015;16:475–493.
105. Paul C, Wolkenstein P, Adle H, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. *Br J Dermatol.* 1996;134:710–714.
106. Paquet P, Pierard GE. Toxic epidermal necrolysis: revisiting the tentative link between early apoptosis and late necrosis (review). *Int J Mol Med.* 2007;19:3–10.
107. Schneider JA, Cohen PR. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: a Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures. *Adv Ther.* 2017;34:1235–1244.
108. Meneux E, Paniel BJ, Pouget F, Revuz J, Roujeau JC, Wolkenstein P. Vulvovaginal sequelae in toxic epidermal necrolysis. *J Reprod Med.* 1997;42:153–156.
109. Correia O, Delgado L, Ramos JP, Resende C, Torrinha JA. Cutaneous T-cell recruitment in toxic epidermal necrolysis. Further evidence of CD8+ lymphocyte involvement. *Arch Dermatol.* 1993;129:466–468.
110. Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens-Johnson syndrome during an 8-year period at Mayo Clinic. *Mayo Clin Proc.* 2010;85:131–138.
111. Canavan TN, Mathes EF, Frieden I, Shinkai K. Mycoplasma pneumoniae-induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: a systematic review. *J Am Acad Dermatol.* 2015;72:239–245.
112. Norton SA. Diagnosing Mycoplasma pneumoniae-induced rash and mucositis (MIRM) in the emergency room. *J Am Acad Dermatol.* 2015;73:e67.
113. Martínez-Pérez M, Imbernón-Moya A, Lobato-Berezo A, Churruca-Grijelmo M. Mycoplasma pneumoniae-Induced Mucocutaneous Rash: a New Syndrome Distinct from Erythema Multiforme? Report of a New Case and Review of the Literature. *Actas Dermosifiliogr.* 2016;107:e47–e51.
114. Kavanagh GM, Burton PA, Kennedy CT. Vulvitis chronica plasmacellularis (Zoon's vulvitis). *Br J Dermatol.* 1993;129:92–93.
115. Salopek TG, Siminoski K. Vulvitis circumscripta plasmacellularis (Zoon's vulvitis) associated with autoimmune polyglandular endocrine failure. *Br J Dermatol.* 1996;135:991–994.
116. Virgili A, Corazza M, Minghetti S, Borghi A. Symptoms in plasma cell vulvitis: first observational cohort study on type, frequency and severity. *Dermatology.* 2015;230:113–118.
117. Damiani L, Quadros M, Posser V, Minotto R, Boff AL. Zoon vulvitis. *An Bras Dermatol.* 2017;92:166–168.
118. Souteyrand P, Wong E, MacDonald DM. Zoon's balanitis (balanitis circumscripta plasmacellularis). *Br J Dermatol.* 1981;105:195–199.
119. Brix WK, Nassau SR, Patterson JW, Cousar JB, Wick MR. Idiopathic lymphoplasmacellular mucositis-dermatitis. *J Cutan Pathol.* 2010;37:426–431.
120. Virgili A, Levratti A, Marzola A, Corazza M. Retrospective histopathologic re-evaluation of 18 cases of plasma cell vulvitis. *J Reprod Med.* 2005;50:3–7.
121. Thomson MA, Carr RA, Ganesan R, Humphreys F. Extensive mucinous metaplasia of the vulva arising within Zoon's vulvitis. *Br J Dermatol.* 2007;156:750–752.
122. Santonja C, Suárez-Peñaranda JM, Carrasco L, Fariña MDC, Requena L. Mucinous Metaplasia of the Vulva in Zoon Vulvitis and Lichen Sclerosus et Atrophicus. Description of 3 Additional Cases of a Rarely Reported Histopathologic Finding. *Am J Dermatopathol.* 2019;41:e39–e42.
123. 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;30:572–576.
124. Botros SM, Dieterich M, Sand PK, Goldberg RP. Successful treatment of Zoon's vulvitis with high potency topical steroid. *Int Urogynecol J Pelvic Floor Dysfunct.* 2006;17:178–179.
125. Virgili A, Mantovani L, Lauriola MM, Marzola A, Corazza M. Tacrolimus 0.1% ointment: is it really effective in plasma cell vulvitis? Report of four cases. *Dermatology.* 2008;216:243–246.
126. Baba Y, Umegaki-Arao N, Kimura Y. Successful treatment of intractable vulvitis circumscripta plasmacellularis via combination therapy with topical tacrolimus and tetracycline. *J Dermatol.* 2017;44:1183–1185.
127. Frega A, Rech F, French D. Imiquimod treatment of vulvitis circumscripta plasmacellularis. *Int J Gynaecol Obstet.* 2006;95:161–162.
128. Ee HL, Yosipovitch G, Chan R, Ong BH. Resolution of vulvitis circumscripta plasmacellularis with topical imiquimod: two case reports. *Br J Dermatol.* 2003;149:638–641.
129. Jaimes Suarez J, Vidal Conde L, Collazos Robles R, et al. Zoon Vulvitis Treated Successfully With Platelet-Rich Plasma: first Case Reported. *J Low Genit Tract Dis.* 2017;21:e48–e51.
130. Tilakaratne W, Dissanayake M. Paraneoplastic pemphigus: a case report and review of literature. *Oral Dis.* 2005;11:326–329.
131. Didona D, Fania L, Didona B, Eming R, Hertl M, Di Zenzo G. Paraneoplastic Dermatoses: a Brief General Review and an Extensive Analysis of Paraneoplastic Pemphigus and Paraneoplastic Dermatomyositis. *Int J Mol Sci.* 2020:21.
132. Ohzono A, Sogame R, Li X, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. *Br J Dermatol.* 2015;173:1447–1452.
133. Kappius RH, Ufkes NA, Thiers BH. *Paraneoplastic Pemphigus. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2020.* StatPearls Publishing LLC; 2020.
134. Kokubu H, Nishikawa J, Kato T, et al. Paraneoplastic Pemphigus Mimicking Toxic Epidermal Necrolysis Associated with Follicular Lymphoma: possible Pathological Role of CD8 T Cells. *Acta Derm Venereol.* 2020;100:adv00204.
135. Okahashi K, Oiso N, Ishii N, et al. Paraneoplastic pemphigus presenting lichen planus-like lesions. *J Dermatol.* 2019;46:e140–e142.
136. Chen WS, Tetzlaff MT, Diwan H, et al. Suprabasal acantholytic dermatologic toxicities associated checkpoint inhibitor therapy: a spectrum of immune reactions from paraneoplastic pemphigus-like to Grover-like lesions. *J Cutan Pathol.* 2018;45:764–773.
137. Cervoni GE, By CC, Wesson SK. An atypical syphilis presentation. *Cutis.* 2017;100:E25–e28.
138. Flamm A, Alcocer VM, Kazlouskaya V, Kwon EJ, Elston D. Histopathologic features distinguishing secondary syphilis from its mimickers. *J Am Acad Dermatol.* 2020;82:156–160.
139. Abell E, Marks R, Jones EW. Secondary syphilis: a clinico-pathological review. *Br J Dermatol.* 1975;93:53–61.