Human Pathology (2019) **91**, 86–113

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Human PATHOLOGY

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Current topics

The interface reaction pattern in the skin: an integrated review of clinical and pathological features☆,☆☆

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Received 9 May 2019; revised 18 June 2019; accepted 20 June 2019

Keywords:
Interface;
Lichenoid;
Vacuolar;
Inflammatory dermatoses

Summary Not uncommonly, pathologists encounter biopsies displaying inflammation at the dermoepidermal junction and confronted with its numerous diagnostic possibilities. As with other inflammatory dermatoses, the correct diagnosis relies on careful integration of clinical, laboratory, and histopathological features. Knowledge of clinical aspects of these disorders is crucial, and at times, lack of training in clinical dermatology can make clinicopathological correlation challenging for the pathologist. This review is organized following the classical classification of cell-poor (vacuolar) and cell-rich (lichenoid) interface processes. The various entities are described based on their clinical presentation along their clinical differential diagnosis followed by their histopathological features and pathological differential diagnosis. Our aim is to provide an updated, clinically relevant review that integrates nuanced clinical and pathological features, with an emphasis on clues that may help differentiate entities in the differential diagnosis.

1. Introduction

The interface reaction pattern classically refers to a predominantly mononuclear infiltrate that is centered at the dermoepidermal junction and targets basal keratinocytes, its damage manifesting as apoptotic keratinocytes, vacuolar change, and pigment incontinence [1]. Ackerman distinguished 2 major types of lymphocytic interface reaction patterns based on the degree of cellularity of the infiltrate: vacuolar (cell-poor) or lichenoid (cell-rich) [2]. Although useful in providing an initial direction to orient the pathologist regarding the diagnostic possibilities, the degree of cellularity of the infiltrate can vary based on the age of the clinical lesion or from patient to patient. Entities that are classically described in the cell-poor category can occasionally present with more cellular infiltrates, and vice versa. One example of this is erythema multiforme (EM), which although classified by certain authors as vacuolar can present with more cellular infiltrates. Therefore, a thorough review of overall histopathological, other laboratorial, and clinical findings is required to arrive to a correct diagnosis. Tables 1 and 2 present the entities commonly associated with a vacuolar or lichenoid pattern of inflammation.

☆ Competing interests: The authors have no conflicts of interest to declare.
☆☆ Funding/Support: This study was supported by the Appignani Lichen Planus Research Award.
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https://doi.org/10.1016/j.humpath.2019.06.004
0046-8177/

Table 1 Diseases typically associated with a cell-poor (vacuolar) type interface inflammation

1. EM
2. SJS
3. TEN
4. Phototoxic dermatitis
5. Acute GVHD
6. TEC
7. Connective tissue disorders
8. Morbilliform drug and viral eruptions

2. Cell-poor or vacuolar interface reaction pattern

2.1. Erythema multiforme

EM is a self-limited, albeit sometimes recurrent, cutaneous or mucocutaneous disease characterized clinically by fixed targetoid lesions with preferential involvement of the extremities and face (Fig. 1A). EM is often precipitated by an infection (eg, herpes simplex virus, mycoplasma). Mucosal involvement and/or systemic symptoms are usually absent or minimal in EM minor but, when present, lead to classification as EM major. The diagnosis is established by clinicopathological correlation. In the appropriate clinical scenario, clinical differential diagnoses include Stevens-Johnson syndrome (SJS); generalized fixed drug eruption (FDE); hand, foot, and mouth disease; and paraneoplastic pemphigus (PNP).

Table 2 Diseases typically associated with a lichenoid type interface inflammation

1. The idiopathic lichenoid dermatoses:
   a. LP
   b. Lichen striatus
   c. Lichen nitidus
2. LDE
3. FDE
4. PNP/paraneoplastic autoimmune multiorgan syndrome
5. Lichenoid GVHD
6. Pityriasis lichenoides
7. Secondary syphilis
8. Lichenoid pigmented purpuric dermatosis
9. Early lichen sclerosus
10. MF
11. Miscellaneous:
    a. Benign lichenoid keratosis
    b. Lichenoid actinic keratosis
    c. Resolving melanocytic neoplasms, including atypical or malignant
    d. Lichenoid viral reactions
    e. Imiquimod reaction

2.2. Histopathology

Histopathologic features reflect the stage of the lesion sampled [3,4]. Common to all include an interface reaction pattern with varying degrees of necrotic keratinocytes, spongiosis, edema of the papillary dermis, and a predominantly superficial lymphohistiocytic infiltrate. In early lesions (red macules and patches), the predominant findings are in the dermis with prominent papillary dermal edema and a superficial perivascular lymphohistiocytic infiltrate (Fig. 1B). Closer inspection usually reveals few lymphocytes along with vacuolar alteration at the dermoepidermal junction and focal, solitary necrotic keratinocytes in an epidermis showing spongiosis and a preserved stratum corneum. As lesions evolve, the epidermal changes become more evident with increased intracellular and intercellular edema and increased numbers of necrotic keratinocytes. The inflammatory infiltrate at the interface can become more cellular (lichenoid). The accentuation of all these findings gives rise to the vesicles/bullae and dusky centers of the targetoid lesions where subepidermal or intraepidermal clefting along with full-thickness epidermal necrosis may occur. Eosinophils are usually not prominent [3,5], and when present, careful consideration should be given to other diagnostic possibilities, especially medication (including FDE), photoallergic reactions, and possibly immunobullous diseases such as PNP. Given the acute nature of these lesions, the epidermis is usually of normal thickness and has basket weave orthokeratosis [3,6]. Direct immunofluorescence is of value in ruling out immunobullous diseases that may enter into the differential diagnosis, such as PNP. Important histopathologic considerations that often enter into the clinical differential diagnosis include SJS and toxic epidermal necrolysis (TEN), a spectrum of diseases usually secondary to drugs (see below) from which EM cannot be reliably differentiated merely on histological grounds and require clinical distinction. Another clinically relevant differential diagnosis is generalized FDE, which is favored when the inflammatory infiltrate contains neutrophils and eosinophils.

3. SJS and TEN

These represent severe adverse drug cutaneous reactions that are characterized by epithelial detachment with frequent involvement of mucosal membranes. Their differentiation relies on the extent of epithelial detachment (<10% for SJS, 10%-30% for SJS-TEN, and >30% for TEN) [7]. The most commonly implicated drugs are allopurinol, sulfonamides, anticonvulsants, nevirapine, and oxicam nonsteroidal anti-inflammatory drugs, and it usually manifests within 1-3 weeks of initial drug introduction [8]. Clinically, tender, poorly defined dusky erythematous macules with occasional atypical targets appear. The lesions progress to confluence with formation of flaccid blisters with detachment (Fig. 2A) and frequent involvement of mucous membranes [9,10].

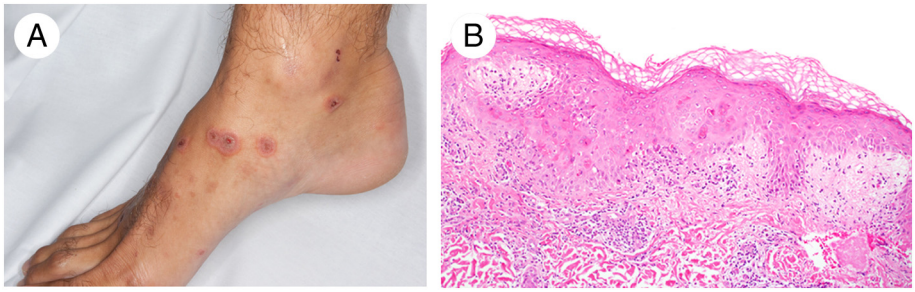

Figure 1 Erythema multiforme. A, Classical presentation with targetoid lesions on extremities. B, Interface dermatitis. The inflammatory infiltrate at the dermoepidermal junction in this case is scant but shows the hallmark changes of interface inflammation, with cytoid bodies, hydropic degeneration at the basal layer, and pigment incontinence. These changes are accompanied by a superficial perivascular infiltrate. Except for the presence of numerous dyskeratotic keratinocytes scattered at all levels, the epidermis appears essentially normal, with basket weave stratum corneum and appropriate keratinocyte maturation. Along with the presence of papillary dermal edema and the scant cellularity, this biopsy suggests sampling of an early lesion. hematoxylin and eosin (H&E), original magnification ×100.

The clinical differential diagnoses include EM from which it is differentiated mostly on clinical grounds, as there is considerable overlap on histopathology. Other considerations include staphylococcal scalded skin syndrome, generalized bullous FDEs, grade IV graft-versus-host disease (GVHD), PNP, and drug-induced linear immunoglobulin (Ig) A bullous dermatosis.

3.1. Histopathology

The characteristic microscopic change of an advanced lesion in TEN is a cell-poor subepidermal blister with necrosis of the entire epidermis (Fig. 2B). In clinical practice, a frozen section is frequently performed to confirm the clinical impression and rule out staphylococcal scalded syndrome, in which the level of the split is at the level of the stratum corneum [11]. The histopathologic features of SJS and TEN can be identical to those of EM, so clinicopathological correlation is required. Although EM usually displays more cellular infiltrates than SJS-TEN [12], this is not always the case, and TEN can display more cellular infiltrates [13]. A particularly challenging differential diagnosis occurs in the setting of hematopoietic and solid organ transplantation, where severe (grade IV) GVHD enters into the differential diagnosis. Unfortunately, these 2 scenarios cannot be differentiated by histopathology. Chimerism analysis may be helpful in the setting of solid organ transplantation [14,15]. Direct immunofluorescence can help to rule out an immunobullous disease that on occasion can have TEN-like presentations, such as linear IgA bullous dermatosis [16-19].

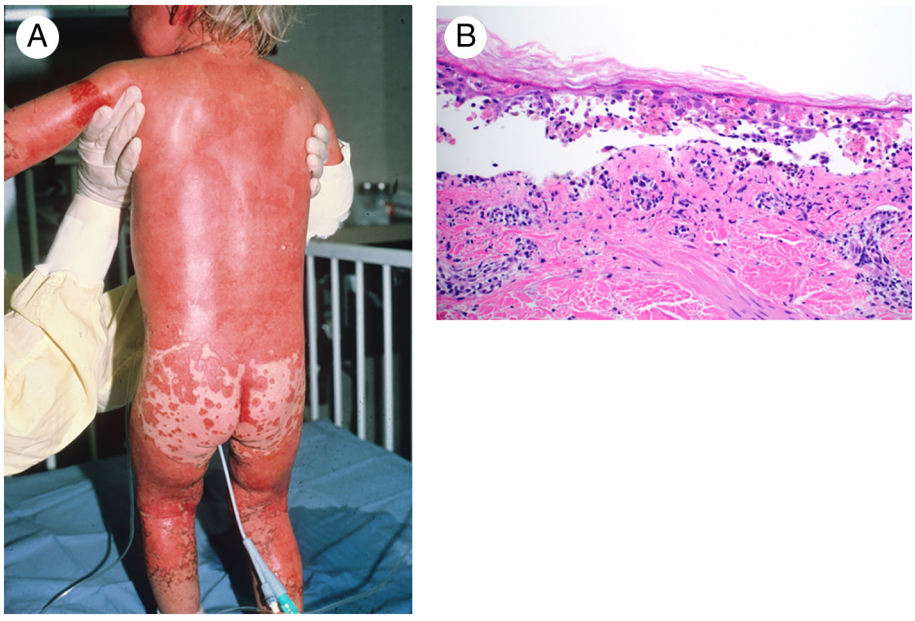

Figure 2 Toxic epidermal necrolysis. A, Erythematous, dusky macules coalescing into patches, with large areas of desquamation. B, Full-thickness epidermal necrosis and epithelial detachment from dermal papillae. H&E, ×200.

4. Phototoxic dermatitis

Phototoxic dermatitis is an immediate cutaneous reaction to an external chemical agent (systemic or topical) that by interacting with ultraviolet light radiation creates free radicals and reactive oxygen species. Clinically, it appears as exaggerated sunburn with clear delineation of areas that are sun protected [20,21]. Drugs commonly implicated include tetracycline, doxycycline, nalidixic acid, voriconazole, amiodarone, hydrochlorothiazide, naproxen, piroxicam, chlorpromazine, and thioridazine [22]. Although not always indicated in classic cases, biopsy may be helpful in evaluating for other photosensitive conditions such as porphyria cutanea tarda or connective tissue diseases.

4.1. Histopathology

There is vacuolar change along the dermoepidermal junction, along with intracellular edema of keratinocytes and necrotic keratinocytes (so-called sunburn cells), which are preferentially located in the upper portion of the epidermis, a hint pointing toward the external nature of the trigger (UV light) [2].

5. Graft-versus-host disease

GVHD is a systemic disease in which the donor graft's T cells attack host cells. Although most common after allogeneic hematopoietic cell transplantation (HCT), GVHD can also develop rarely after solid organ transplantation and the use of nonirradiated blood in an immunocompromised host. The incidence of GVHD depends on the several factors, mainly, the HLA mismatch, the source of hematopoietic stem cells (higher incidences when obtained by peripheral blood), the conditioning regimen used, and age, for example. Acute and chronic GVHD was originally classified based on the appearance of manifestations within 100 days of HCT. However, the increasing use of reduced intensity regimens is defying this classification, with late-onset acute GVHD and overlap syndromes [23].

The skin is the most common organ affected in GVHD (81% of patients) and usually the first organ affected. The gastrointestinal tract is affected in 54% and the liver in 50% [24].

The rash is maculopapular ("morbilliform") that tends to be folliculocentric and may coalesce. Preferential sites of involvement are dorsal hands and trunk. The concomitant involvement of face and palms/soles can be a clinical clue that favors GVHD over a drug hypersensitivity reaction [25] (Fig. 3A).

The diagnosis of GVHD can be particularly challenging because the clinicopathological features of GVHD can overlap with those of vacuolar interface drug and viral eruptions as well as with toxic erythema of chemotherapy (TEC).

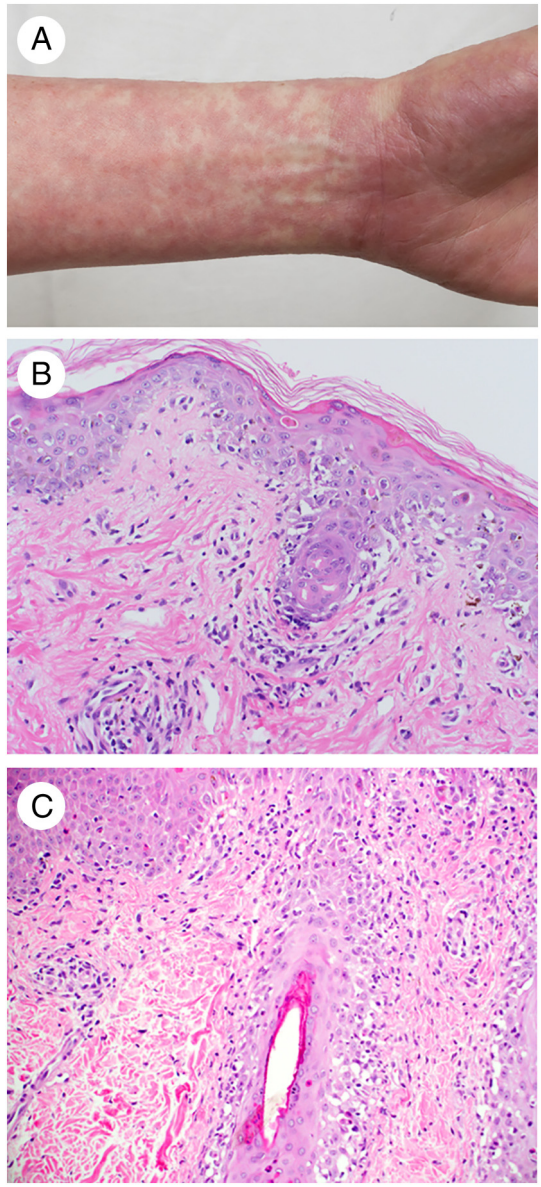

Figure 3 Acute graft-versus-host disease. A, Dull red to violaceous maculopapular eruption, with involvement of palms. B and C, Acute GVHD, histopathological grade 2, displaying basilar vacuolar change, scattered dyskeratotic keratinocytes at all levels of the epidermis, and frequent involvement of hair follicles. H&E, ×200.

5.1. Histopathology

Although the histopathology of acute GVHD is nonspecific and its clinical utility has been questioned given difficulty in differentiating it from the common clinical considerations (drug reaction or viral exanthem) [26,27], skin biopsies have value in this setting and are still widely performed in clinical practice. The classical grading system of acute GVHD was originally described by Lerner et al and then later modified to include inflammation as additional features (Table 3) [28]. This histological grading however does

Table 3 GVHD grading system [28]

Grade 0	No histopathologic abnormality
Grade 1	Basal vacuolar degeneration and mild superficial perivascular lymphocytic infiltrate
Grade 2	Basal vacuolar degeneration, focal or diffuse spongiosis, lymphocyte exocytosis, scattered dyskeratosis, dermal lymphocytic infiltrate
Grade 3	Increased basal vacuolar degeneration with DEJ cleft formation and increased numbers of dyskeratotic keratinocytes
Grade 4	Frank loss of epidermis

not always follows the clinical grading [29], and a histological grade 2 or above is necessary (albeit not sufficient) to establish the diagnosis [30]. The vacuolar interface inflammation involves the epidermis and hair follicle epithelium [28,31] (Fig. 3B and C). Satellite necrosis (tagging of a necrotic keratinocyte by a lymphocyte) can be seen, but this feature is neither sensitive nor specific [31]. An important confounding variable in the acute posttransplant scenario is the effect of chemotherapy and radiotherapy in the skin, as it can manifest with features suggestive of mild aGVHD (mild basilar vacuolar change, occasional dyskeratosis, and slight superficial dermal inflammation) [28,30,32]. This is usually accompanied by keratinocyte dysmaturation [32]. Because of these overlapping features, some authors suggest to avoid areas of chemotherapy effect [32]. Unfortunately, this is difficult in clinical practice, and the possibility of their coexistence cannot be excluded either.

The histopathological features mimic those of other entities in the differential diagnosis: drug reactions; viral exanthems; TEC; and, in severe cases, TEN. It is important to note that the presence of eosinophils does not exclude a diagnosis of GVHD [33] and cannot be used as a discriminating feature to favor drug hypersensitivity reactions. TEC is characterized by slight to nonexistent inflammation, and a very helpful feature when present is eccrine squamous metaplasia. Severe, fulminant cases of acute GVHD cannot be reliably distinguished from TEN by histopathology. Chimerism analysis along with the clinical features may help to discriminate in the setting of solid organ transplantation [14,15] but has limited role in post-HCT GVHD.

6. Toxic erythema of chemotherapy

TEC is a term that encompasses several previously described entities (hand-foot syndrome, acral erythema/dysesthesia, flexural erythematous eruption, chemotherapy-induced hidradenitis) seen in association with several chemotherapeutic agents, the most commonly implicated

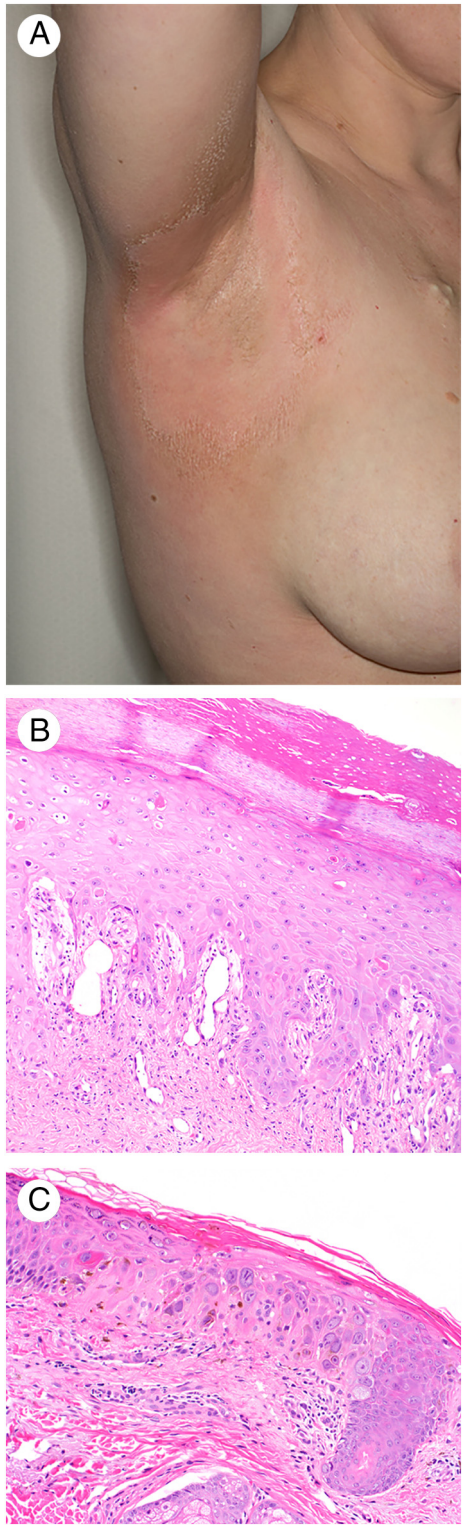

Figure 4 Toxic erythema of chemotherapy. A, Erythematous patch with peripheral desquamation involving the axilla. B, Minimal inflammatory infiltrate along with numerous scattered dyskeratotic keratinocytes and vascular ectasia. In this case, significant keratinocyte dysmaturation was absent, in contrast to another case illustrated in panel C, where dysmaturation was a prominent feature. H&E, ×200 and ×400, respectively.

Table 4 Direct immunofluorescence findings in different subtypes of cutaneous lupus [49-51,54]

DIF results	Acute cutaneous LE	Subacute cutaneous LE	Chronic LE
Positive lesional LBT	>95% [51]	60% [50]	>90% [49]
Positive, sun exposed, non-lesional LBT	75% [51,54]	44% [50]	0% [54]
Positive, non- sun exposed, non lesional LBT	50% [54]	26% [50]	0% [54]

being cytarabine [34]. Patients present with erythematous patches or edematous plaques with preferential involvement of palms, soles, ears, intertriginous areas, and elbows and knees (Fig. 4A). The lesions can evolve into bullae in areas of pressure and be associated with burning/pain sensations [34-36]. The eruption usually occurs 2-3 weeks after administration of the chemotherapeutic agent, a timeline which overlaps with a high risk to develop GVHD in patients who had received an HCT. Its distinction from the latter is therefore of major clinical relevance because TEC usually self-resolves.

6.1. Histopathology

Biopsies of TEC show a cell-poor vacuolar interface along with scattered necrotic keratinocytes (Fig. 4B). The epithelium can show keratinocyte dysmaturation that at times can be striking, especially with cyclophosphamide [37-39] (Fig. 4C). As keratinocyte dysmaturation is a common finding after the administration of chemotherapy and in the post-transplant period, care should be taken to not overinterpret this finding as being synonymous to TEC or GVHD [32,39,40]. Squamous metaplasia of the eccrine sweat ducts with or without associated necrosis can be a valuable finding when present, as it can help in distinguishing this entity from acute GVHD, its most important differential in the post-transplant patient [41-44]. In addition, the infiltrate in TEC is more scant or even nonexistent than that of acute GVHD [45]. Nevertheless, careful consideration of the clinical presentation is necessary to distinguish among these entities including the possibility of their coexistence.

The presence of a neutrophilic infiltrate around the eccrine glands (so-called neutrophilic eccrine hidradenitis) with epithelial degenerative changes with or without accompanying eccrine syringometaplasia can be another pattern seen [43,46]. When neutrophils are a predominant feature, it is important to exclude the neutrophilic dermatoses (such as Sweet syndrome) and infectious eccrine hidradenitis [47].

7. Autoimmune connective tissue disorders

Autoimmune connective tissue disorders are a diverse collection of conditions that have myriad clinical manifestations depending on the particular organs involved. Diagnosis requires careful correlation of clinical features, biopsy data, and serum antibody profiles, and patients are often best served by a multidisciplinary clinical team.

7.1. Lupus

Lupus erythematous is an autoimmune disease with a wide spectrum of clinical manifestations ranging from isolated skin involvement to a severe systemic disease. The dermatologist and dermatopathologist need to be able to recognize the cutaneous manifestations and investigate possible extracutaneous involvement.

Classically, cutaneous lupus has been subdivided in acute, subacute, and chronic forms [48-51], and these have varying degrees of associations with systemic lupus erythematous (SLE). This wide array of presentations seems to respond to different serologic profiles, host immune response, and HLA phenotypes [51]. Diagnosis of systemic lupus erythematosus is based on clinical and laboratorial criteria. Although the original lupus criteria established by the American College of Rheumatology were developed for the purpose of clinical trial inclusion criteria, they can be helpful in clinical practice [52]. These criteria include 4 dermatologic manifestations: the malar rash (flat or raised erythema over the malar eminences and sparing the nasolabial folds), discoid rash (a form of chronic cutaneous lupus erythematosus, characterized by erythematous plaques with adherent scale and follicular plugging with tendency to scar), photosensitivity, and oral/nasopharyngeal ulcers. However, several other dermatologic manifestations of lupus can be seen, such as nonscarring alopecia, panniculitis, papulosquamous or annular lesions (subacute cutaneous lupus), or dusky purple papules and plaques on acral surfaces (lupus pernio).

Histopathologically, the typical cutaneous manifestations of lupus are characterized by a vacuolar interface dermatitis accompanied by a perivascular lymphohistiocytic infiltrate and mucin deposition. The degree of cellularity and depth of the infiltrate, the presence of epidermal or follicular changes, hyperkeratosis, and basement membrane thickening [50] are variable and can be helpful features to differentiate the subtypes of cutaneous lupus (description below). Eosinophils are usually absent in lesions of cutaneous lupus. On direct immunofluorescence testing, a lupus band may be observed. A lupus band is the granular deposition of IgM, singly or in association with other immunoglobulins or complement at the dermoepidermal junction [53,54]. The deposition should be bright and regular [54] to be considered positive, as weak and irregular deposition of

immunoreactants (especially IgM) at the DEJ can be found in clinically normal skin of normal patients [55]. It is also important to note that a positive lupus band test result can be positive in other connective tissue disorders including mixed connective tissue disorder and progressive systemic sclerosis [56,57]. A negative DIF does not exclude a diagnosis of lupus, as the test has imperfect sensitivity. Another pattern that can be seen on direct immunofluorescence in lupus is a particulate staining of the keratinocyte with IgG which indicates the presence of an antibody to an extractable nuclear antigen, most commonly anti-Ro [58]. Table 4 summarizes the DIF findings in the different types of cutaneous lupus.

Although rare, another histopathological pattern that is gaining recognition is the "Kikuchi-like inflammatory pattern," where the lymphohistiocytic infiltrate is intermixed with nuclear debris thought to be derived from plasmacytoid dendritic cells. This may or may not be accompanied by an interface dermatitis and/or dermal mucin and can be seen in all subtypes of cutaneous lupus [59].

7.2. Chronic cutaneous lupus erythematous

The most frequent manifestation of chronic cutaneous lupus is discoid lupus erythematous (DLE), which is characterized by chronic erythematous papules or plaques with follicular plugging and adherent hyperkeratotic scale with marked preference for the head and neck region (Fig. 5A), particularly the conchal bowls, although it can also be generalized. Lesions of CCLE have a tendency to scar. This subset of patients usually does not develop extracutaneous disease, with only about 5%-10% of patients developing SLE. It is important to note, however, that in patients with SLE, about 15% of them manifest these lesions and the discoid rash constitutes 1 of the SLE 11 criteria [51,60]. Patients with solely chronic scarring cutaneous lupus erythematous without clinical manifestations of extracutaneous involvement are usually ANA seronegative [49]. Another variant of chronic cutaneous lupus is tumid lupus; this rare variant manifests with edematous erythematous plaques with absent or minimal surface change affecting sun-exposed areas. These lesions heal without scarring and have a tendency to recur [61,62].

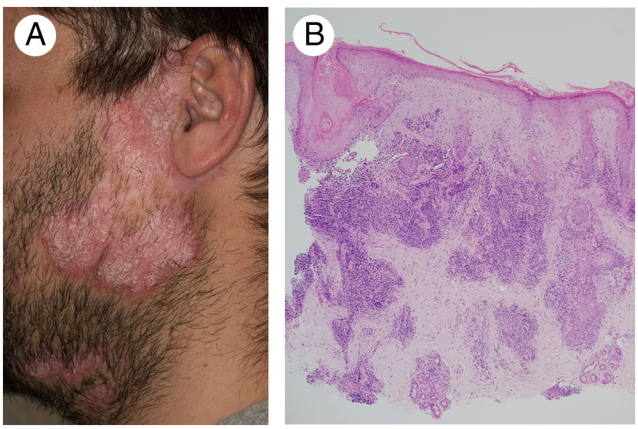

Figure 5 Chronic cutaneous lupus, discoid variant. A, Erythematous, polycyclic plaques with thick adherent scale and alopecia. B, Superficial, deep, and periappendageal lymphohistiocytic infiltrate along with follicular hyperkeratosis. The epidermis displays vacuolar interface changes and atrophy. H&E, ×40.

7.3. Histopathology

Classic histopathology of DLE is characterized by vacuolar alteration at the dermoepidermal and dermofollicular junction accompanied by a variably dense lymphohistiocytic infiltrate that sometimes can be lichenoid. The inflammatory infiltrate also involves the superficial and deep vascular plexus and adnexae. Hyperkeratosis; epidermal atrophy; or, less frequently, acanthosis can be seen. These changes when involving the follicles creates widened follicular infundibula plugged by hyperkeratosis (follicular plugs) (Fig. 5B). The basement membrane becomes thickened, and sometimes, a similar eosinophilic, homogenous material surrounds the blood vessels. Varying amounts of dermal mucin can be seen among the collagen bundles [2,63,64]. These features can be better highlighted by the use of PAS and colloidal iron stains, respectively. By DIF, a lesional lupus band can be seen in about 50%-90% of cases, with false-negative studies probably reflecting early lesions or chronic inactive lesions [49].

Lupus erythematous tumidus, similarly to DLE, shows a superficial and deep perivascular and periadnexal lymphohistiocytic infiltrate; however, epidermal changes (including vacuolar alteration) are minimal to absent, and mucin deposition tends to be more abundant. Direct immunofluorescence studies are usually negative. There is considerable histopathologic and clinical overlap between lupus erythematous tumidus and Jessner lymphocytic infiltration of the skin, favoring these entities to represent a spectrum of the same disease entity [65].

Polymorphous light eruption can be differentiated microscopically from discoid lupus and tumid lupus/Jessner lymphocytic infiltration by the presence of papillary dermal edema, absence of vacuolar alteration and basement membrane thickening, as well as absence of plasmacytoid dendritic cells as highlighted by CD123 [2,66].

The lymphoid infiltrate of lesions of cutaneous lupus at times can be quite prominent and may bring cutaneous lymphomas to the list of differential diagnosis. These pseudolymphomatous infiltrates are usually nodular but more rarely can also show a band-like pattern reminiscent of mycosis fungoides (MF) and even an angiocentric pattern suggestive of cytotoxic lymphoma. Helpful histopathological clues that point toward cutaneous lupus include the presence of interface inflammation, presence of mucin, and clusters of plasmacytoid cells [67].

Although the epidermis in lesions of discoid lupus is usually atrophic, at times, it can display hyperplasia and be so prominent as to mimic a squamous cell carcinoma or keratoacanthoma (hypertrophic DLE) [68]. Changes indicative of

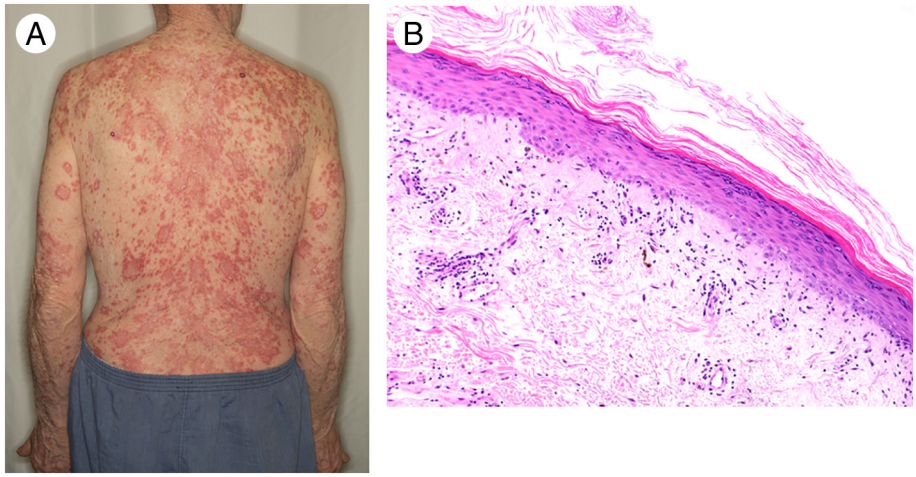

Figure 6 Subacute cutaneous lupus erythematous. A, Numerous erythematous, scaly annular plaques and papules involving the back and dorsal extremities. B, Subtle vacuolar interface dermatitis with epidermal atrophy and mild hyperkeratosis is seen. H&E, ×100.

DLE such as peripheral epidermal atrophy, interface changes, basement membrane thickening, perivascular and periadnexal inflammation, and dermal mucin should be sought carefully. At the same time, squamous cell carcinoma is a rare, known complication of long-standing DLE, and therefore, appropriate follow-up is necessary for these patients [69].

7.4. Subacute cutaneous lupus

Subacute cutaneous lupus is characterized by a superficial, nonscarring, annular, or papulosquamous rash with an exquisite photosensitive distribution (face, neck, upper back, chest, shoulders, and extensor areas of upper extremities) (Fig. 6A). Serologically, this subset usually has antibodies against extractable nuclear antigens (anti-Ro and anti-La) [70], although seropositivity for these antibodies is not pathognomonic for SCLE. Approximately 20%-50% of patients with subacute cutaneous lupus meet ARA SLE criteria [50,71]; however, development of significant renal or central nervous disease is rare, and the systemic manifestations that predominate are musculoskeletal (arthritis, arthralgias, myalgias) [50,51,71,72]. Drug-induced SCLE should always be excluded because it has identical clinical, histopathological, and serological features [73]. Medications most frequently implicated in drug-induced SCLE include antifungal and antihypertensive agents [73].

7.5. Histopathology

Skin biopsies of lesions of SCLE show vacuolar interface dermatitis along with a mild superficial perivascular infiltrate. The epidermis is classically atrophic [64] and surmounted by mild hyperkeratosis (Fig. 6B). The basement membrane thickening is usually minimal, and similarly to other types of cutaneous lupus, dermal mucin can be seen [64]. By DIF, SCLE has a positive lupus band in approximately 60% of cases along with a distinct staining pattern of particulate or granular IgG keratinocyte staining, which corresponds to seropositivity for extractable nuclear antigen antibodies [50,58].

7.6. Acute cutaneous lupus

Acute cutaneous lupus can present with the well-known, usually evanescent malar rash and less commonly with a widespread indurated erythema (Fig. 7A). The incidence of this acute cutaneous form in SLE is approximately 50%

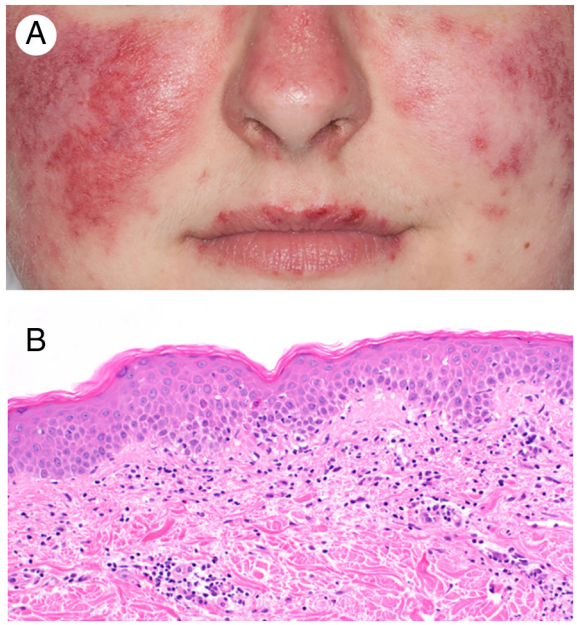

Figure 7 Acute cutaneous lupus. A, Erythematous patches in a butterfly distribution, with mucosal ulcerations. B, Subtle vacuolar interface changes affected the dermal-epidermal junction, which are associated with an epidermis that, aside from an occasional dyskeratotic keratinocyte, appears normal. H&E, ×100.

[51,60]. Patients with acute cutaneous lupus usually have multisystem disease, are ANA positive, and frequently have circulating dsDNA antibodies (60%-80%) [51].

7.6.1. Histopathology

Skin biopsies of this acute form are subtle with mild vacuolar degeneration of basal keratinocytes and a slight superficial perivascular lymphohistiocytic infiltrate along with telangiectasia and dermal mucin. The stratum corneum can be normal or show focal parakeratosis; the epidermis is usually of normal thickness but can show atrophy (Fig. 7B). The basement membrane is not thickened, and there is no follicular plugging [63]. Lesions of acute cutaneous lupus can mimic the histomorphology of dermatomyositis (DM); however, hypovascularity, vascular ectasia, and signs of vascular damage are features more characteristic of DM [74]. Immunofluorescence studies can also aid in this differential, with a positive lupus band test favoring the diagnosis of lupus and the deposition of the membrane attack complex (C5-C9) on the papillary dermal vessels and dermoepidermal junction by indirect immunofluorescence favoring the diagnosis of DM [74,75].

7.6.2. Mixed connective tissue disease

Mixed connective tissue disease was initially described in 1972 by Sharp et al as a distinct entity characterized clinically by overlapping features of systemic lupus, scleroderma. and myositis in association with high titers to anti-U1RNP [76]. Its cutaneous manifestations are protean and reflect the amalgam of overlapping conditions that characterize this condition. However, common cutaneous features, which also contribute to the diagnostic criteria, are swelling of hands with tapering of fingers (sausage digits) and/or Raynaud phenomenon [76-78]. Sclerodactyly, nonscarring alopecia, sclerodermatous skin changes with hypo- or hyperpigmentation, or lesions of cutaneous lupus including discoid, subacute, and, more rarely, acute forms (malar rash) can be occasionally seen [57,76,77].

About 10% of patients with MCTD evolve into another rheumatologic condition [79], and about one third of patients have a severe and progressive disease course, with the development of pulmonary hypertension being the major determinant of mortality [80].

The histopathology of mixed connective tissue disorder has not been studied extensively because it is heterogeneous and dependent on the type of lesion biopsied. Clinical lesions of cutaneous lupus (acute, subacute, and chronic forms) and sclerodermatous lesions will show their corresponding histopathologic features as previously described above. Magro et al noted in their case series of 8 patients that 5 had annular and/or papulosquamous lesions that were clinically and histopathologically similar to subacute cutaneous lupus with an interface reaction pattern that varied from a cell-poor vacuolar type to a more cellular lichenoid type with formation of colloid bodies. A reduction of the density of superficial vessels along with vascular ectasia and thrombogenic vasculopathy was the finding that the authors proposed to be helpful differentiating features that favor mixed connective tissue disorder over SCLE [57] . By DIF, there may a particulate or granular staining of IgG overlying the keratinocyte nuclei [57,77] denoting the presence of an antibody to a nuclear antigen (uRNP) that can be at times accompanied by a positive lupus band test result. By indirect immunofluorescence, deposition of C5b-9 around vessels and within the keratinocyte nuclei has also been described [57].

7.7. Dermatomyositis

DM is one of the idiopathic inflammatory myopathies. It was traditionally defined by the criteria of Bohan and Peter that required evidence of muscle involvement (proximal muscle weakness, elevated muscle enzymes, a triad of electromyographic findings, or positive muscle biopsy findings) along with classical cutaneous manifestations [81,82]. In patients with myositis, the cutaneous findings may precede the development of myositis, in which case it usually develops within 6 months. However, there is a subset of patients with the characteristic skin rash for prolonged periods of time (>6 months) that do not develop muscle weakness. These patients, on repeat longitudinal examination, may show subclinical evidence of myositis upon laboratory, electromyographic, and/or radiologic evaluation or have a repeated negative workup. Sontheimer et al referred to this subset of patients as having clinically amyopathic DM [83]. Both classical DM and clinically amyopathic DM are known to be associated with malignancy (especially in patients >40 years of age) and possible development of interstitial lung disease, which at times can be rapidly progressive.

The primary skin lesion in DM is macular violaceous erythema that usually has a characteristic distribution pattern (Fig. 8A). Secondary-types changes such as scaling, follicular hyperkeratosis, pigmentary alteration, bullous change, and ulceration can be observed. Lesions of DM, when chronic, can manifest as poikiloderma which is a lesion combining atrophy, pigmentary alteration, and telangiectasia. The classic pattern of distribution of the macular violaceous erythema involves the eyelids (heliotrope rash); the extensor surfaces of joints, especially the metacarpophalangeal and/or proximal interphalangeal joints and elbows (Gottron's sign and if papules or plaques: Gottron's papules); the neck and anterior chest (V-sign); the nape and posterior shoulders (shawl sign); the anterior hairline or scalp; face; and the lateral upper thighs and hips (Holster sign). Periungual telangiectasias with or without dystrophic cuticles can also be seen [84]. The "mechanic hands" are an important sign to recognize, as they have been shown to be associated with interstitial lung disease [85,86]. This is a symmetric, bilateral hyperkeratotic eruption with scaling and fissuring that predominantly affects the ulnar side of the thumb and radial aspect of the remaining fingers with possible extension to the palmar surface [87,88]. Similar eruption has also been

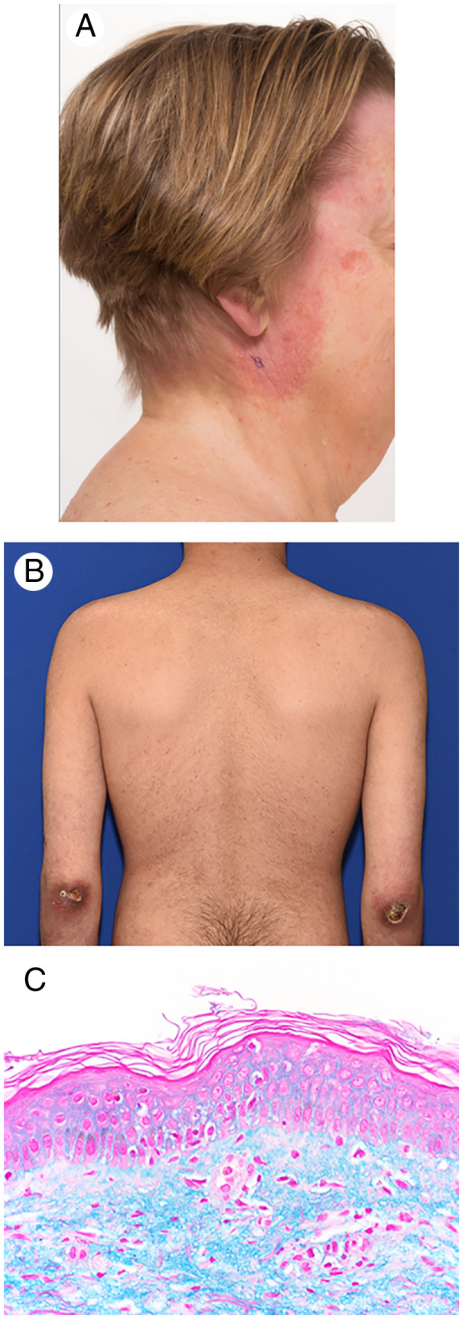

Figure 8 Dermatomyositis. A, Violaceous/pink macules and patches involving the hairline and periauricular areas. B, Punched out ulcers in bilateral elbows, suggestive of anti-MDA5 DM. C, Subtle vacuolar interface with prominent deposition of mucin, as highlighted by colloidal iron. Colloidal iron, ×200.

described in the feet (Hiker's feet) [89]. Ulceration of the Gottron's papules and/or lateral nailfolds and presence of palmar papules (inverse Gottron's papules) are also features that are associated with interstitial lung disease [90].

Rare presentations include an erythematous follicular hyperkeratotic rash that can become confluent accompanied or not with hyperkeratosis of palms and soles that resembles pityriasis rubra pilaris (Wong's-type DM). When this eruption extends to the dorsal hand and feet, it adopts a characteristic linear arrangement along the tendons and bony prominences [91].

Similarly to other connective tissue disorders, DM displays a considerable heterogeneity of signs, symptoms, and prognosis. Given the increased use of serological panels, better laboratorial techniques, and increasing knowledge in this area, associations of myositis antibodies and clinical findings are becoming better defined and are helping delineate more homogenous patient groups [92,93].

Examples of this include anti-Mi2–positive patients showing increased "V" and "shawl" signs and good response to therapy [92,94]; antisynthetase antibodies (among which anti Jo1 is the most prevalent) are associated with mechanic hands, arthritis, myositis, and interstitial lung disease: "the antisynthetase syndrome" [92,93], anti-MDA5 with characteristic ulceration of Gottron's papules (Fig. 8B) or lateral nailfolds, palmar papules, and interstitial lung disease [90,95]. Others have emphasized that features of the antisynthetase syndrome are also common in patients with anti-MDA5 [96].

7.8. Histopathology

The histopathology of DM is typically characterized collectively by an interface dermatitis and mucin deposition that can be histopathologically indistinguishable from lesions of acute cutaneous lupus [97,98] (Fig. 8C). The interface inflammation is usually cell poor, and the changes of the epidermis and stratum corneum are variable and depend on the clinical lesion biopsied [98]. Poikilodermatous lesions show, in addition, epidermal atrophy, vascular ectasia, and pigment incontinence [97,98]. Gottron's papules show hyperkeratosis, acanthosis, and variable basement membrane thickening [99]. Biopsies of mechanic hands can help rule out clinical entities that enter into the differential diagnosis such as eczema or acral psoriasis. In contrast to more typical lesions of DM, they usually do not display prominent vacuolization of the basal cell layer. However, the presence of colloid bodies and mucin, as well as the absence of changes more characteristic of entities in the differential diagnosis (such as intracorneal neutrophils for psoriasis or spongiosis for eczematous dermatitis), supports the diagnosis. Psoriasiform hyperplasia, hyperkeratosis, and focal parakeratosis accompany [100]. Wong's-type DM shows papillomatosis, follicular hyperkeratosis accompanied or not by vacuolar interface changes, and mucin deposition [91,101,102]. At times, myositis of the arrector pili muscles has been observed [103].

Crowson and colleagues noticed that lesions of DM show a greater degree of endothelial injury and have increased vascular ectasia and decreased density of the papillary vessels as compared to lesions of cutaneous lupus, suggesting microvascular injury as central in the pathogenesis of cutaneous lesions of DM [74]. Similarly, the palmar papules that are often seen in patients with anti-MDA5 antibodies also show signs

of pauci-inflammatory vasculopathy with fibrin deposition of vessel walls or thrombosis [90].

Plasmacytoid dendritic cells as ascertained by CD123 immunohistochemical stain are present in lesions of cutaneous lupus and DM. However, their pattern of distribution and quantity differ; lesions of DM show an epidermal pattern of distribution and are fewer as compared to lesions of cutaneous lupus where they are more abundant and predominate in the dermis [104].

Also, the combination of a negative lupus band test result and vascular deposition of C5b-C9 by indirect immunofluorescence has been reported to be predictive of DM [105].

7.9. Morbilliform drug and viral eruptions

Most drug eruptions are morbilliform and occur within 7-14 days of drug exposure; however, they may appear sooner on re-exposure. Lesions favor the trunk and extremities, and are erythematous macules and papules that may acquire a purpuric appearance on dependent areas. Low-grade fever and pruritus usually accompany the eruption. The most commonly implicated drugs are the aminopenicillins, sulfonamides, cephalosporins, and anticonvulsants. Morbilliform drug eruptions pose a significant diagnostic challenge in the posthematopoietic cell transplant period, where diagnostic considerations include GVHD as well as viral eruptions.

The value of histopathology in the setting of morbilliform drug eruption is debatable because these eruptions may present with variable histopathologic findings and can elicit all the inflammatory patterns described in the skin. The most common histologic pattern observed is that of a mild vacuolar type interface reaction with rare or few necrotic keratinocytes along with a sparse superficial and interstitial inflammatory infiltrate [106,107]. Eosinophils and neutrophils are estimated to be present in about 50%-60% and 30%-50% of cases, respectively [106,107], and their concomitant presence along with lymphocytes in the setting of a mild vacuolar interface favors a morbilliform drug eruption [106].

Likewise, the histopathology of morbilliform viral eruptions is usually nonspecific with spongiosis, lymphocyte exocytosis, a slight superficial perivascular lymphohistiocytic infiltrate, and mild vacuolar alteration. However, when present, the recognition of viral cytopathic effect is of extreme importance because it has the ability to impact patient outcomes especially in the immunocompromised patient. An example of this is the rare intranuclear inclusions within lymphocytes described in HHV-6 virus reactivation after stem cell transplantation [108].

8. Cell-rich or lichenoid interface reaction pattern

Lichenoid inflammation can be seen in a variety of conditions (Table 2) that require knowledge of the different clinical scenarios to be separated. Although there are histopathological features or clues that might help in their differentiation, the correct diagnosis is established through careful clinic pathologic correlation.

As a general rule, lichenoid inflammation is characterized clinically by the presence of dry, flat-topped papules or plaques with finer scale than that seen in the setting of psoriasis, for example. These skin lesions are not deeply indurated and often appear pink or violaceous in patients with light skin or brown and blue tones (slate-colored) in pigmented skin [109]. Histopathologically, a band-like infiltrate of inflammatory cells (characteristically lymphocytic or lymphohistiocytic) is the most striking feature. Varying numbers of apoptotic keratinocytes along the basal layers of the epithelium or papillary dermis, commonly known as *Civatte*, *colloid*, or *hyaline bodies* can be found. On direct immunofluorescence, these bodies can be positive for immunoglobulins and C3, and fibrinogen is deposited in a shaggy configuration along the basement membrane zone [110,111].

1. The idiopathic lichenoid dermatoses

A. Lichen planus

Lichen planus (LP), first described by Erasmus Wilson in 1869 [112], is an idiopathic inflammatory disorder of unknown etiology. LP is clinically characterized for violaceous, flat-topped papules and plaques with a distinct overlying reticulation (Wickham's striae) with preferential involvement of the wrists, ventral forearms, and dorsum of feet, although widespread involvement is also possible (Fig. 9A). The disease can also affect the scalp, nails, and mucosal membranes, where the oral and genital mucosae are the most frequent sites of involvement. However, esophageal, otic, and ocular involvements are also possible.

Although lacy, white streaks are common clinical presentations when involving the oral and vulvar mucosa, erosive disease is also quite common in these sites. The concomitant presence of gingival and vulvovaginal erosions is a phenomenon first observed by Pelisse and is termed the *vulvovaginal gingival syndrome* [113].

This syndrome is associated with increased morbidity because the lesions are extremely painful; are often difficult to treat; and, in the vulvovaginal area, can lead to synechiae and deformity [113,114]. In contrast to cutaneous LP, mucosal disease tends to have a more prolonged clinical course. The association of LP with squamous cell carcinoma, especially in the setting of oral LP, is still a matter of debate. However, most authors favor close follow-up of affected patients to monitor for malignant transformation.

LP can also involve the hair follicles (follicular LP or lichen planopilaris), in which case keratotic, acuminated papules develop. The process can involve the scalp or other hair-bearing regions, leading to alopecia [115-118], and might be accompanied by other manifestations of LP [115,117]. In the scalp, involvement can be patchy with

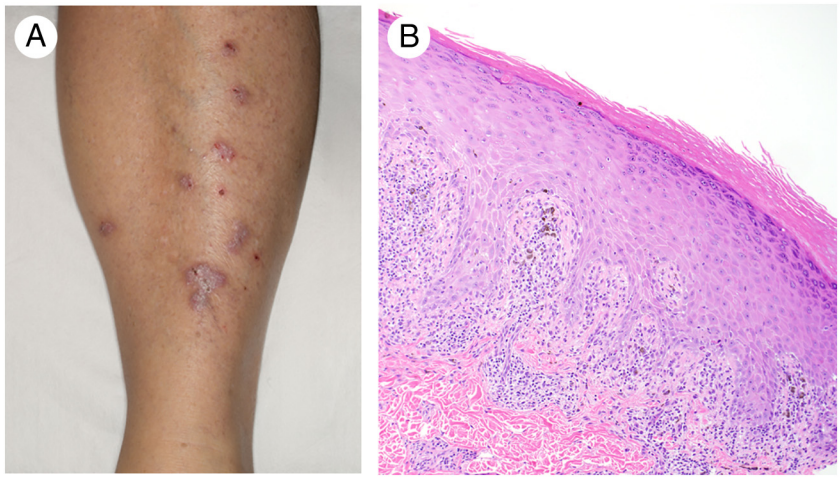

Figure 9 Lichen planus. A, Violaceous, flat-topped papules, some of them excoriated with overlying thin silver scales involving the shin. B, Band-like lymphohistiocytic infiltrate at the dermoepidermal junction, sawtooth rete ridges, and a squamatized epidermis with cytoplasmic eosinophilia, tightening of intercellular spaces, wedge-shaped hypergranulosis, and hyperkeratosis. Eosinophilic globular material can be seen in the papillary dermis and lower epidermis (colloid/Civatte bodies). H&E, ×100.

perifollicular erythema and keratotic acuminate plugs usually seen at the margin of the alopecic patch or have a distinct pattern of distribution with symmetric involvement of the frontal and temporal hairline, usually accompanied by loss of the eyebrows (frontal fibrosing alopecia) [119-122] (Fig. 10A). This latter variant is usually seen in postmenopausal women and might be accompanied by lichen planus pigmentosus (LPP), especially on individuals of darker skin complexion [123,124]. Occasionally, the scarring scalp alopecia of LPP is accompanied by nonscarring alopecia of the axillae and groin and follicular LP on the extremities and trunk, a triad known as *Graham-Little-Picardi-Lasseur syndrome*.

Although the etiology of LP is obscure, several associations have been described, among which the association with hepatitis C virus is the most notable and studied [125].

The variants of LP with a characteristic histopathology are presented on Table 5.

Lichenoid drug eruptions (LDEs) can present with identical clinical and histopathologic features, and therefore, a thorough evaluation of potential drug etiology should be sought in all patients with a new diagnosis of LP.

8.1.1. Histopathology

LP is characterized by a dense, band-like infiltrate of lymphocytes that obscures the dermoepidermal junction along with vacuolization of the basal layer. The epidermis undergoes premature terminal differentiation with the keratinocytes displaying increased cytoplasmic eosinophilia, tightening of their intercellular junctions, wedge-shaped hypergranulosis, and hyperorthokeratosis, a phenomenon also observed in wound-healing states [129,130]. The rete ridges become pointed, simulating the appearance of a saw tooth. Eosinophilic globular material is frequently seen in the papillary dermis (colloid bodies) and basal layers of the epidermis (Civatte bodies) (Fig. 9B). Melanophages are present within the papillary dermis. Eosinophils are rare, except in cases of hypertrophic LP. Mucosal LP, in contrast to cutaneous LP, can show parakeratosis. Hypergranulosis is often

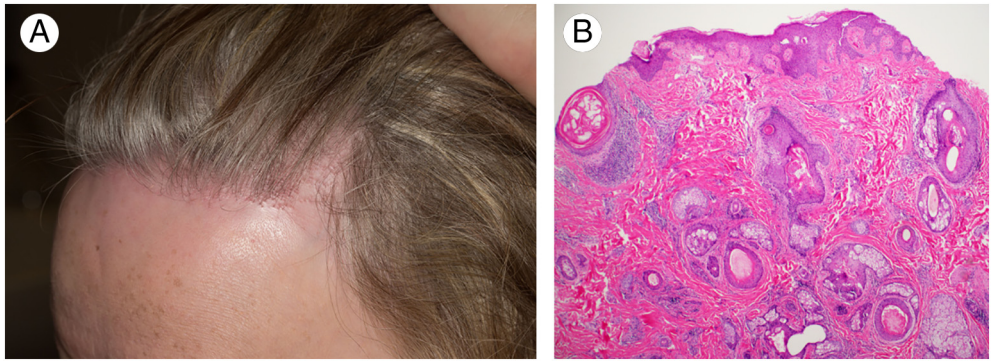

Figure 10 Lichen planopilaris. A, Frontal fibrosing alopecia variant. Keratotic acuminate papules, perifollicular erythema, and hair loss involving the frontotemporal area. B, Lichenoid interface inflammation at the level of the follicular infundibulum and isthmus with occasional follicular plugging. H&E, ×40.

Table 5 LP variants with their respective distinct histopathology

LP variant	Clinical presentation	Histopathological features
Hypertrophic	Pruritic, thick plaques with adherent scale, especially on bilateral shins.	Lichenoid interface + pseudoepitheliomatous hyperplasia, at times so prominent as to simulate SCC. Eosinophils are often present.
Atrophic	Atrophic plaques that may be reminiscent of lichen sclerosus, can adopt an annular configuration, preferential involvement of lower extremities.	Lichenoid inflammation is often less dense, epidermis is atrophic with loss of retiform pattern.
Pigmentosus	Pruritic dark-brown macules on flexures and sun-exposed skin of dark-skinned patients	Extensive pigment incontinence manifested as numerous dermal melanophages
Ulcerative	Painful ulcers involving soles, toes ± nail loss [126]. Painful ulcers usually rimmed by Wickham's striae in oral and or vulvar mucosa.	Ulceration and classic changes of LP on periphery. Plasma cells can be seen in mucosal LP.
LP pemphigoides	Simultaneous occurrence of LP lesions and tense blisters arising on them and/or normal skin with preferential involvement of trunk, extremities and oral mucosa [127].	Subepidermal blister + lichenoid inflammation + DIF positive for linear C3 and/or IgG along the BMZ. IIF positive for IgG against the basement membrane. Bullous pemphigoid antigens (especially BPAG2) usually positive [127].
Lichen planopilaris (follicular LP)	Keratotic follicular papules that lead to irreversible, scarring alopecia in scalp or other hair-bearing sites. When involving the scalp, LPP presents with perifollicular erythema and acuminate keratotic plugs at the margins of the alopecic patches [115,128]. Distribution can be patchy involving the entire scalp [128] or have a distinct pattern with frontotemporal recession and eyebrow loss usually in postmenopausal women (frontal fibrosing alopecia) [119] (Figure 10A).	Lichenoid interface inflammation at the level of the follicular infundibulum and isthmus. (Figure 10B). Interfollicular epithelium is affected in about one third of patients. Hypergranulosis and hyperkeratosis with follicular plugging can be seen. Ultimately, hair follicles are replaced by fibrous tracts [128]

less prominent, and plasma cells and eosinophils are often found within the inflammatory infiltrate [131].

By direct immunofluorescence, the colloid bodies are positive for immunoglobulins and C3, and shaggy deposition of fibrinogen is observed at the DEJ. This adjunct diagnostic modality is especially helpful in the setting of erosive disease, when it is important to exclude autoimmune bullous dermatoses, such as pemphigoid and pemphigus.

Although LDEs can present with identical histopathological features, this diagnosis can be favored when parakeratosis, disruption of the granular layer, dyskeratotic cells are in the cornified and granular layers, and eosinophils are present [6,132,133]. Another histopathological mimic is benign lichenoid keratosis. This is often a single lesion located usually on the trunk that gets often biopsied with the clinical impression of a basal cell carcinoma. At times, changes of seborrheic keratosis or lentigo can be seen on the periphery. Rarely, a melanocytic neoplasm may be concealed by the lichenoid inflammation [134].

B. Lichen striatus

Lichen striatus usually affects children and manifests as flat-topped (lichenoid) pink to skin-colored papules in a linear or curved array following Blaschko's lines, with preferential involvement of extremities and trunk (Fig. 11A). Lesions tend to be unilateral, resolve spontaneously, and heal with hypopigmentation [135,136]. The eruption is believed to reflect cutaneous mosaicism and can follow viral, bacterial, or fungal infections [137,138] and vaccinations [139,140] .

A similar eruption occurring predominantly in adults, "Blaschkitis" is characterized by recurrent papulovesicles along multiple bands usually affecting the trunk [141]. Although there is controversy surrounding this entity, as some authors believe that it is indistinguishable from lichen striatus [142], others support the notion of it being a distinct entity within a disease spectrum [143].

Lichen striatus can be confused clinically with linear LP, linear psoriasis, and inflammatory linear verrucous epidermal nevus.

8.1.2. Histopathology

Lichen striatus displays features of interface and spongiotic dermatitis (Fig. 11B), along with a periappendegeal and superficial and deep perivascular inflammation. The interface inflammation is usually manifested as a lichenoid process with lymphocytes and histiocytes along the DEJ and scattered dyskeratosis that can be seen at all levels of the epidermis. The epidermis usually shows mild spongiosis; lymphocyte exocytosis; and, at times, Langerhans cell

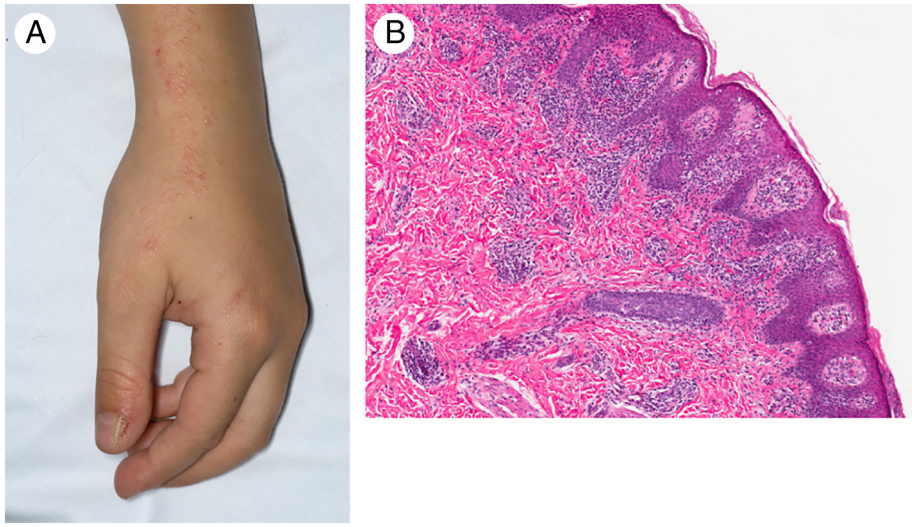

Figure 11 Lichen striatus. A, Pink, flat-topped papules in a linear array associated with nail dystrophy. B, The biopsy combines changes of a lichenoid and spongiotic dermatitis. H&E, ×100.

microabscesses. Focal parakeratosis usually surmounts the spongiotic foci. The inflammation characteristically surrounds hair follicles and eccrine glands and represents a key feature that helps to distinguish this entity from others in the differential diagnosis, such as LP, lichen nitidus, and blaschkitis [144,145]. Blaschkitis tends to be categorized more as a spongiotic dermatosis. However, in some cases, a lichenoid component can also be seen [141,143] .

C. Lichen nitidus

This is a rare entity where asymptomatic, small (usually pinpoint), monomorphic, skin-colored papules with a distinct histopathology appear in groups. The extremities, genitalia, and trunk are most commonly affected (Fig. 12A). However, generalized involvement may also occur [146,147]. As with lichen striatus, this entity is more common in children and young adults than in adults.

Generalized lichen nitidus has also been seen in the setting of immunotherapy (interferon-α and more recently with anti-CCR4, -CTL4, and -PD1 inhibitors) [148-150]. An association with the other idiopathic lichenoid dermatoses (LP and lichen striatus) is suggested by reports of patients where these coexist [151–153].

8.1.3. Histopathology

Lichen nitidus has a characteristic histomorphology that is frequently known as the *ball-and-claw* or *ball-in-clutch*, where the dermal papillae are expanded by an interstitial aggregate of lymphocytes, histiocytes, and sometimes epithelioid and giant cell histiocytes. This infiltrate can cause the adjacent rete ridges to curve toward the expanded dermal papillae, partially encircling it [146] (Fig. 12B). The proportion of lymphocytes and histiocytes is variable and is thought to be dependent on the lesional age, with older lesions having a more granulomatous appearance [2]. The epidermis

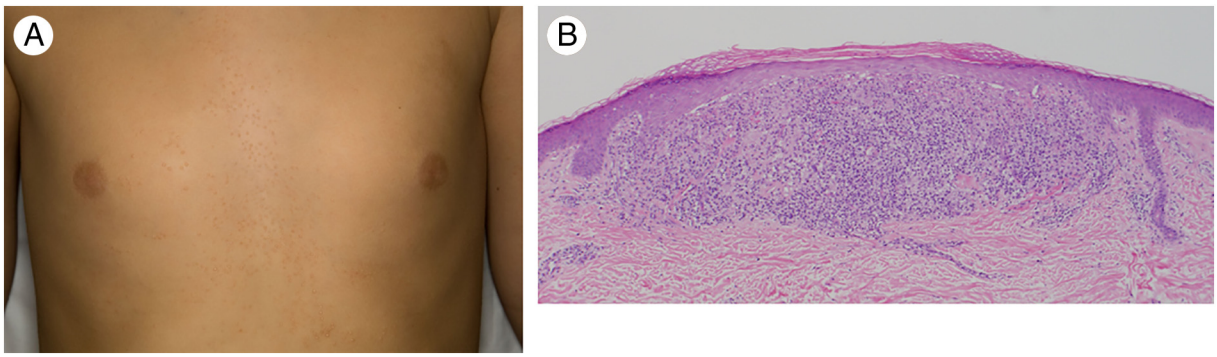

Figure 12 Lichen nitidus. A, Numerous skin-colored, pinpoint papules over the chest of an infant. B, "Ball-and-claw" pattern where an aggregate of lymphocytes and histiocytes expands the dermal papillae and is partially encircled by curved adjacent rete ridges. H&E, ×40.

Table 6 List of agents commonly implicated in LDEs

Therapeutic class	Agents
Antimalarials	Quinine, quinidine
Diuretics	Thiazides, furosemide
Anthypertensives	β-Blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers
Hypoglycemic agents	Sulfonylureas
Antituberculosis drugs	Isoniazid, ethambutol
Miscellaneous	Gold salts

overlying the nodular infiltrate becomes thinned and is surmounted by parakeratosis. Basilar vacuolar change with occasional clefting and dermal melanophages can also be seen [146].

9. Lichenoid drug eruption

LDEs are adverse cutaneous reactions to an ever-growing list of medications. The clinical presentation can be identical to that of idiopathic LP or present with more atypical features such as lesional photodistribution (in case of photosensitizers such as thiazides, furosemide, and quinine), and have a nonspecific morphology or an eczematous appearance [132,133,154,155]. Mucosal membrane involvement is possible, albeit observed less frequently than in cases of idiopathic LP.

A nonexhaustive list of medications commonly implicated in this type of reaction is presented in Table 6. LDEs are also now being recognized in the setting of newer therapies such as TNF-α inhibitors or immunotherapy (anti-PD1 and anti CTLA-4) [156,157]

Histopathologically, LDE can also mimic idiopathic LP. However, the following features when present point to a drug etiology: parakeratosis, granular layer disruption, dyskeratotic cells present in the cornified or granular layers, and an infiltrate with eosinophils that may also involve the deep vascular plexus [6,132,133,154].

10. Fixed drug eruption

FDE is a distinct drug-induced dermatosis that characteristically recurs at the same site with the reintroduction of the culprit medication [158] . The lesions appear as well-demarcated round to oval macules and patches that progress to edematous plaques that may have a vesicular or bullous component (Fig. 13A). The lesions tend to heal leaving hyperpigmented patches and most commonly present as a solitary lesion with predilection for lips and genitalia [158,159]. However, multiple lesions or even generalized involvement is also possible [160]. Generalized bullous FDEs may simulate EM, SJS, and TEN [161,162]. The medications most commonly implicated in this type of reaction are listed on Table 7. Patch testing performed on sites of previous FDE can be a helpful adjunct for diagnosis [163,164].

10.1. Histopathology

When biopsied in the acute stage, lesions of FDE are characterized by vacuolization of the basal layer of the epidermis along

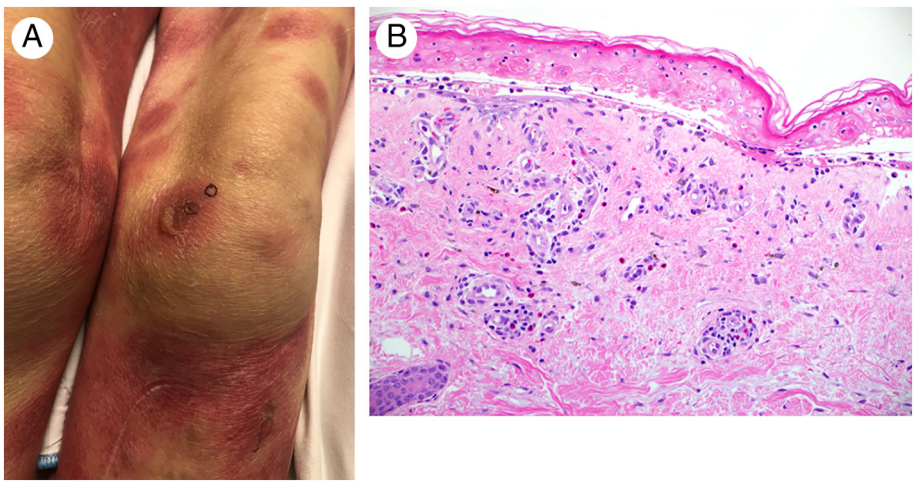

Figure 13 Bullous fixed drug eruption. A, Numerous oval dusky erythematous patches, one of them with a central bulla. B, Full-thickness epithelial necrosis, epithelial detachment, a perivascular infiltrate containing numerous eosinophils and few melanophages in the papillary dermis. H&E, ×200.

Table 7 Drugs commonly implicated in FDE

Therapeutic class	Agents
Anti-inflammatory, analgesics, antipyretics	Nonsteroidal anti-inflammatory drugs
Analgesic, antipyretic	Acetaminophen
Antibiotics	Sulfonamides, tetracyclines, B-lactams, metronidazole, fluoroquinolones
Antifungals	Griseofulvin, azoles, terbinafine
Antiepileptics, sedative hypnotics	Barbiturates

with a moderately dense inflammatory infiltrate that obscures the dermoepidermal junction. A variable number of necrotic keratinocytes at all levels of the epidermis and, at times, full-thickness epidermal necrosis can be observed (Fig. 13B). Intraepidermal and subepidermal vesiculation may also be seen as result of intercellular and papillary dermal edema. The inflammatory infiltrate in FDE is characteristically mixed with neutrophils, eosinophils, lymphocytes, and histiocytes (Fig. 13B) and surrounds both superficial and deep vascular plexus [2,165]. Abundant neutrophils might be present early on, and as the lesion evolves, pigment incontinence becomes more pronounced [165,166]. Biopsy of a late lesion may only show a thickened papillary dermis along a slight lymphohistiocytic infiltrate and numerous melanophages.

The major histopathological entity in the differential diagnosis is EM. In contrast to EM where the inflammatory infiltrate is exclusively mononuclear and superficial, FDEs have a mixed infiltrate with neutrophils and eosinophils and affect both the superficial and deep vascular plexus [2]

11. PNP/paraneoplastic autoimmune multiorgan syndrome

An autoimmune mucocutaneous blistering disorder in the setting of neoplasia, most commonly non-Hodgkin lymphomas, PNP can present with lichenoid lesions. Patients classically present with an extensive erosive gingivostomatitis (Fig. 14A) that often extends beyond the vermillion border along with polymorphic skin lesions that may be targetoid, bullous, or lichenoid [167]. The disease can involve other mucosal membranes including the conjunctiva [168] and the gastrointestinal [169] and bronchial mucosa [170], the latter of which is one of the major determinants of mortality. The term *paraneoplastic autoimmune multiorgan syndrome* has been proposed so as to highlight the potential for involvement of visceral organs. Given the polymorphic nature of the cutaneous lesions along with stomatitis, cases might bear resemblance to LP [171-174], EM [167], SJS [167], TEN [175,176], and pemphigus vulgaris [177]. The diagnosis is supported by histopathology, the detection of serum antibodies against periplakin and envoplakin, direct immunofluorescence, and especially indirect immunofluorescence studies using rat bladder as substrate [178].

11.1. Histopathology

The classical histomorphology of PNP combines suprabasilar acantholysis and interface dermatitis that tends to be lichenoid, with dyskeratotic cells scattered at all levels of the epidermis [179] (Fig. 14B and C). The infiltrate is mostly

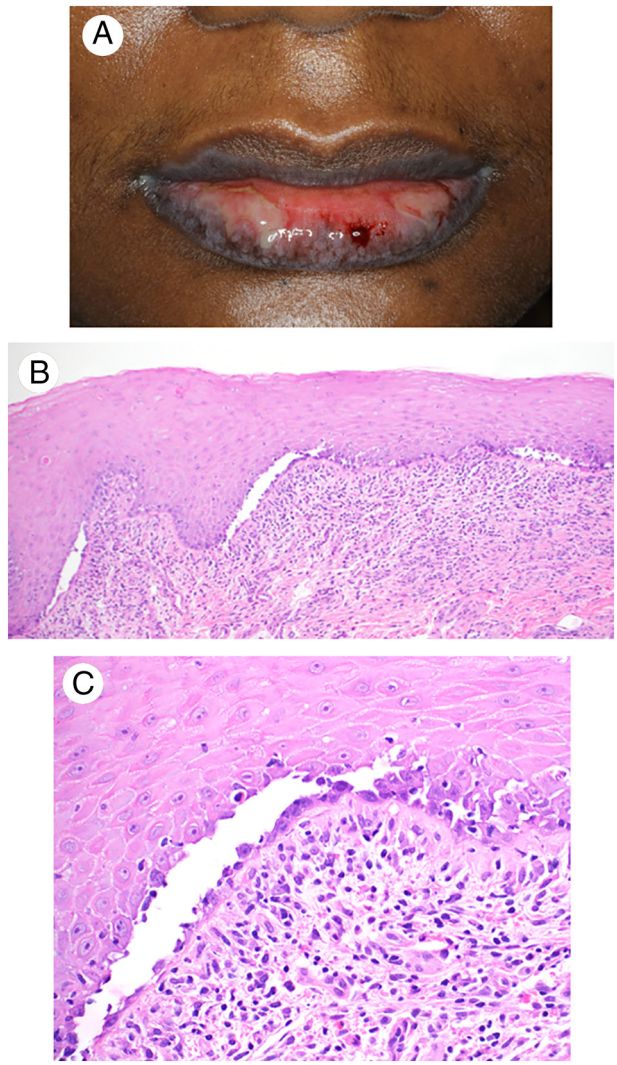

Figure 14 Paraneoplastic pemphigus. A, Erosive stomatitis. B and C, Lichenoid inflammation with scattered dyskeratotic keratinocytes and suprabasilar clefting. H&E, ×100 and ×200, respectively.

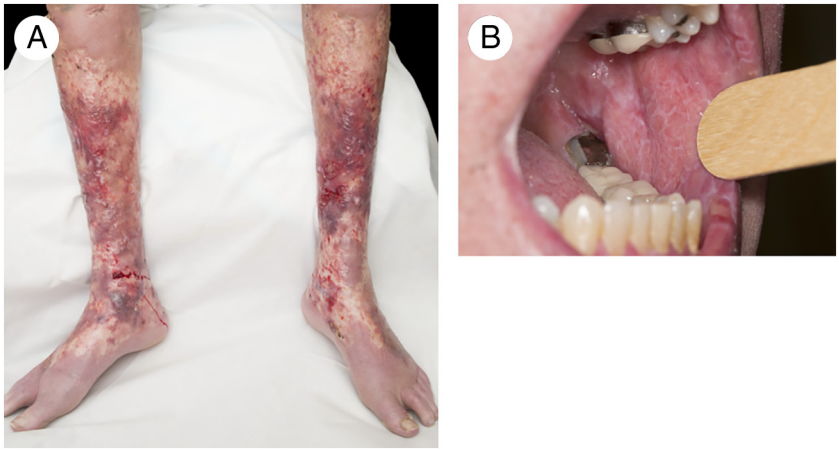

Figure 15 Chronic graft-versus-host disease. A, Sclerodermatous variant with ivory, indurated atrophic plaques with bullae, ulcers, and hemorrhage involving bilateral lower extremities. B, Reticulated white patches involving the buccal mucosa. The changes are reminiscent of idiopathic scleroderma (A) and LP (B) and their histopathology, likewise concordant.

mononuclear, but cases with considerable number of eosinophils have also been reported [179,180]. The changes can also extend to the follicular epithelium [179]. At times, the suprabasilar acantholysis is not seen, and then the findings are exclusively that of interface dermatitis. The infiltrate is most often band-like but can be of variable cellularity, with cases resembling EM, SJS, TEN, or LP [176,178,179]. Conversely, changes of isolated suprabasilar acantholysis resembling pemphigus vulgaris can also be seen, although less frequently [178]. Therefore, additional studies are indicated. Direct immunofluorescence usually reveals the deposition of intercellular and basement membrane IgG and/or C3 [178,179]. However the most sensitive and specific test is the deposition of intercellular IgG with indirect immunofluorescence using rat bladder as substrate [178].

12. Chronic GVHD

Chronic GVHD is a major contributor to increased morbidity and mortality in patients following hematopoietic cell transplantation. With the increasing use of peripheral blood as source of stem cells, use of unmatched transplants, and older age of recipients, the incidence of this complication is on the rise.

Although chronic GVHD was historically defined by the appearance of characteristic signs and symptoms after 100 days posttransplant [181], the current consensus is that the constellation of clinical features and not how many days after transplantation these occur is the discriminating factor between the acute and chronic forms [182,183].

As with the acute form of GVHD, chronic GVHD most commonly involves the skin and may appear as a continuation of the acute form after its resolution or may appear de novo. Cutaneous manifestations of chronic GVHD classically include an LP-like eruption [184,185] (Figure 15B) with frequent involvement of the oral mucosa and/or scleroderma [186,187] (Fig. 15A). Papulosquamous lesions and depigmentation are also distinctive features, albeit not diagnostic per se. Diagnosis requires confirmation with either a skin biopsy or evidence of other organ involvement [182].

12.1. Histopathology

Most authors agree on the value of skin biopsy in the evaluation of a rash where chronic GVHD is in the differential diagnosis [188].

Mirroring the clinical expression of chronic GVHD, the histopathology of chronic GVHD may be lichenoid or sclerosing and may overlap with features of the acute GVHD [188,189]. The lichenoid form is characterized by prominent epidermal changes of hyperkeratosis, hypergranulosis, acanthosis, and a moderately dense band-like infiltrate along the dermoepidermal junction accompanied by basilar vacuolar change and dyskeratosis involving the basal and lower spinous layers. Satellitosis, or the presence of a lymphocyte directly juxtaposed to an apoptotic keratinocyte, may be observed, although this feature is not entirely specific. The inflammatory infiltrate may host a few eosinophils, and pigment incontinence can also be seen in the papillary dermis. These changes can also affect the adnexae [188,189]. The histopathological picture can be identical to that of LP or LDE and is distinguished by the clinical context.

13. Pityriasis lichenoides

This is an inflammatory dermatosis characterized by recurrent crops of self-regressing papules. The acute form (pityriasis lichenoides et varioliformis acuta [PLEVA]) and

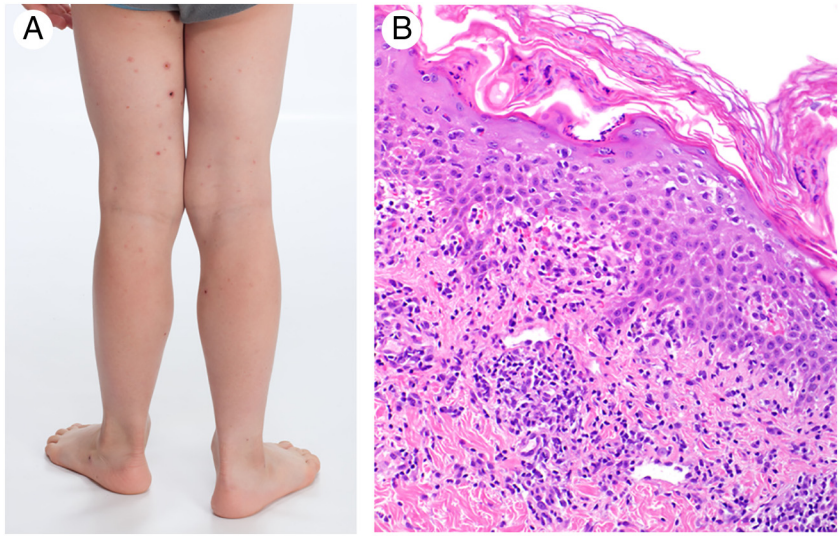

Figure 16 Pityriasis lichenoides et varioliformis acuta. A, Scattered, polymorphic papules, some of them with hemorrhagic crusts involving the posterior lower extremities of a child. B, Lichenoid inflammatory infiltrate with lymphocyte exocytosis, spongiosis, red blood cell extravasation, and a perivascular mononuclear infiltrate. Parakeratosis with neutrophilic debris is also seen. H&E, ×200.

chronic forms (pityriasis lichenoides chronica [PLC]) are considered to represent the ends of a single disease spectrum. The disease is more common in children and young adults, and its incidence is highest in winter and fall [190]. A viral association has been noted in several reports, and recently, a varicella zoster virus glycoprotein antigen was shown in the endothelial and eccrine epithelium in 5 of 6 patients with PLEVA, suggesting varicella zoster virus as possible trigger for the development of PLEVA [191].

In PLEVA, the eruption is usually polymorphic, reflecting different stages with lesions usually starting as erythematous macules that progress to lichenoid papules and then to ulceration with hemorrhagic crusts (Fig. 16A). Finally, lesions heal leaving a varioliform scar. A rare variant of the acute form, the febrile ulceronecrotic Mucha-Haberman disease, presents with high fever along with numerous ulcerated papules and plaques and has a mortality rate of about 25%. PLC has a more monomorphic appearance with scaly papules that heal leaving hyper- or hypopigmented macules. Occasionally, patients can present with mixed features [190,192,193].

The clinical differential diagnosis for PLEVA include lymphomatoid papulosis; the rare papular variant of MF [194]; EM; primary or disseminated recurrent varicella; and, in cases of febrile ulceronecrotic Mucha-Haberman disease, an aggressive cytotoxic lymphoma. The scaly papules of PLC bring primarily pityriasis rosea and guttate psoriasis into the diagnostic possibilities.

13.1. Histopathology

Lesions of pityriasis lichenoides are characterized by interface dermatitis, spongiosis, parakeratosis, red blood cell extravasation in epidermis and/or dermis, and a perivascular infiltrate. Eosinophils are extremely rare [195]. The intensity of changes varies within the spectrum of PLEVA-PLC.

In PLEVA, there is usually a dense lymphohistiocytic infiltrate that is disposed along the DEJ and around the superficial and deep vascular plexus in a wedge-shaped fashion with the point toward the deep dermis. The epidermis usually displays spongiosis, with the occasional presence of spongiotic vesicles, exocytosis of lymphocytes, and dyskeratotic keratinocytes that at times can be confluent. A confluent band of parakeratosis with neutrophilic debris is usually seen. Red blood cell extravasation can be observed in the dermis or epidermis and in conjunction with the interface changes can be clues to the diagnosis (Fig. 16B). In PLC, these changes are present to a lesser extent, and the infiltrate tends to be less dense and spares the deep vascular plexus. The lymphocytes in both conditions tend to be small to medium sized, with a predominance of a CD8-positive T cells in PLEVA and CD4 in PLC [196,197]. CD30-positive cells are usually absent to rare, and this feature, along with the lack of cytologic atypia, is helpful in its distinction from lymphomatoid papulosis [196,198]. It is important to point out that T-cell receptor rearrangement studies should be interpreted with caution, as studies have shown monoclonal populations in both PLEVA and PLC and therefore is not helpful in their differentiation from cutaneous lymphoma [199-201]. The use of an immunohistochemical panel in the evaluation of pityriasis lichenoides is suggested by some authors as evidence of a T-cell phenotypic aberrancy (loss or expression of both CD4 and CD8 or loss of a pan-T cell antigen: CD2, CD3, or CD5, expression of CD56 or TCR-γ). These findings should prompt careful follow-up, as evolution to MF has been reported in this group [201]. Another diagnostic consideration for the acute presentation (PLEVA) is EM; however the

infiltrate tends to be more cellular and also involves the deep dermal vessels in the former.

14. Secondary syphilis

Similarly to other sexually transmitted diseases, the rates of infection with *Treponema pallidum* continue to steadily rise. In addition, the dermatologic signs of syphilis are varied and may mimic those of other inflammatory entities. Therefore, awareness of the different cutaneous manifestations of syphilis is of paramount importance. The primary stage of infection is typically characterized by a single, painless ulcer (chancre) appearing at the site of inoculation. Thereafter, the organisms disseminate via hematogenous and lymphatic routes in secondary syphilis. It is this stage of disease in which the signs and symptoms may mimic a variety of disorders, explaining the designation of syphilis as the great imitator; this is especially true regarding the mucocutaneous manifestations.

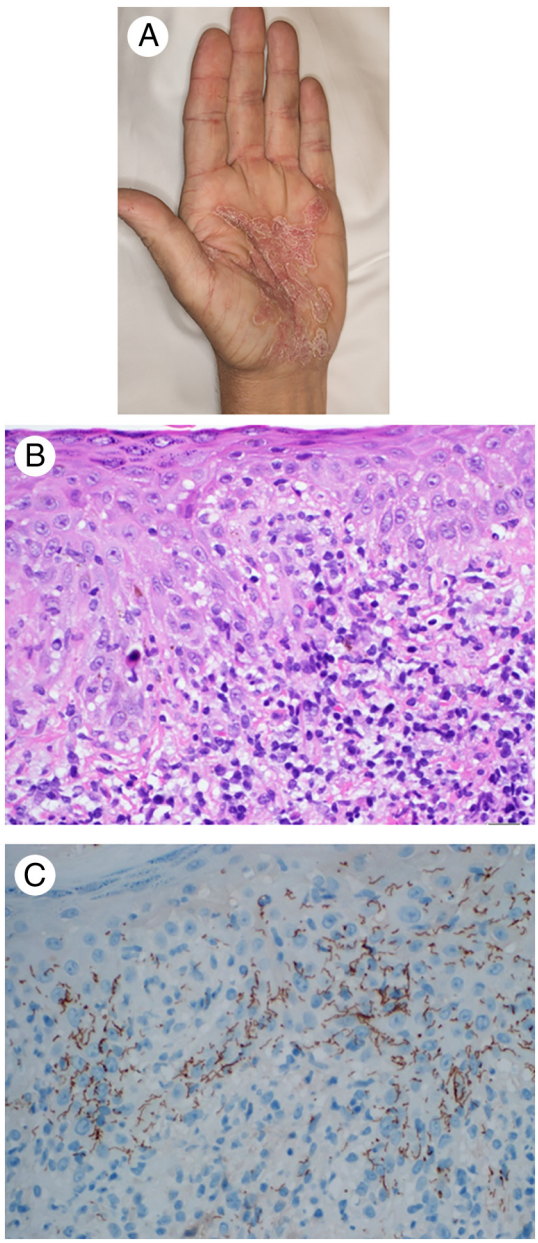

Figure 17 Secondary syphilis. A, Confluent annular plaques with peripheral scale (Biett's collarete) involving the palm. B, The dermoepidermal junction is obscured by a lichenoid infiltrate containing numerous plasma cells. C, An abundance of spirochetes at the lower epidermis and papillary dermis is revealed by the *T pallidum* immunohistochemistry. H&E, ×200; *T pallidum* immunohistochemistry, ×200.

The most common clinical presentation of secondary syphilis is a generalized maculopapular, macular, or papulosquamous eruption with frequent involvement of soles, trunk, arms and legs, palms, genitals, and face [202,203]. Less frequently, lesions can be confined to a single anatomic location, and when this occurs, it is usually on the soles and/or palms [202]. At this location, a helpful diagnostic clue is the presence of a peripheral scale overlying the papules and plaques (Biett's collarete) (Fig. 17A). Infrequently, the lesions may surround a larger papule (corymbiform arrangement) [203,204]; adopt an annular, arcuate, or gyrate configuration [203,205]; and even ulcerate [206]. The so-called malignant or rupioid syphilis, characterized by a pleomorphic appearance with papulopustules and ulcers of varying depth, at times surmounted by a lamellate brown and black scale resembling an oyster shell [207], is more common in cases of concomitant HIV infection [206]. Mucosal lesions in secondary syphilis are not infrequent and include vegetating plaques in anogenital areas (condyloma lata) and oral and pharyngeal ulcerations. A patchy nonscarring alopecia (often referred to as showing a moth-eaten appearance) can also be seen [202]. Systemic symptoms are more common and can be quite pronounced in cases of "malignant syphilis." Lymphadenopathy often accompanies these mucocutaneous manifestations [202].

As stated above, papulosquamous lesions are common presentations of secondary syphilis and bring other papulosquamous disorders in the clinical differential diagnosis, such as LP, pityriasis rosea, pityriasis lichenoides, psoriasis, and drug eruption.

14.1. Histopathology

Similar to the wide array of clinical presentations, the spectrum of histomorphological changes seen in secondary syphilis is also broad.

A commonly observed histopathologic pattern in secondary syphilis in lesions showing papulosquamous and papular clinical morphologies is that of a lichenoid interface infiltrate [208,209]. Usually, this is accompanied by irregular or regular epidermal hyperplasia and a perivascular infiltrate containing lymphocytes; histiocytes; and, classically, varying numbers of plasma cells [208] (Fig. 17B). Most often, both the superficial plexus and deep vascular plexus are involved,

but it can also be restricted to the superficial capillaries. Inspection of the vessels usually reveals endothelial cell swelling and, at times, vessel wall thickening.

Other features less commonly seen include focal parakeratosis that at times can harbor neutrophils. It is important to point out that plasma cells are absent in about 25%-30% of cases, and rarely, a few eosinophils may be present in the infiltrate [205,208]. The concomitant presence of dermal granulomatous inflammation may also be a clue for secondary syphilis.

The spirochete can be usually identified in the lower epidermis or dermis (particularly in the perivascular region) by the use of silver stain (eg, Warthin-Starry) or immunohistochemistry for *T pallidum* (Fig. 17C). This latter method is superior to the former because it has higher sensitivity (approximately 70%-90% versus 40%-60%) and specificity, as the high staining background of the silver stain is avoided [210-212]. Serological testing with both treponemal and nontreponemal assays usually has a positive result in the secondary stage and remains the gold standard for the diagnosis. However, cases of seronegative secondary syphilis are a possibility especially in cases with HIV coinfection possibly due to phenomena such as prozone or inability to produce a proper antibody response [213,214]. The limitations of serologic testing highlight the important role that the histopathologist may have in the diagnosis and therefore correct management of the patient.

LP is the major histopathological differential diagnosis in this pattern [208,209,215,216], and when present, the presence of plasma cells, involvement of the deep vascular plexus, and endothelial cell swelling suggest the diagnosis of secondary syphilis. These features and/or the pertinent clinical characteristics should prompt the evaluation with *T pallidum* immunohistochemistry or, when not available, Warthin-Starry stain.

15. Lichenoid pigmented purpuric dermatosis

The pigmented purpuric dermatoses are a group of closely related entities characterized clinically by purpuric and/or brown to red macules, papules, and plaques with preferential involvement of the bilateral lower extremities. The lesions form as result of petechial dermal hemorrhage that may result from vascular damage secondary to cell-mediated immunity [217,218] . Contributing factors may include increased hydrostatic pressure on vessels due to venous incompetence, prolonged standing, or excessive activity [219]. The different variants described, Schamberg's or progressive pigmentary purpura, purpura annularis telangiectodes of Majocchi, lichenoid pigmentary purpura of Gougerot-Blum, lichen aureus, and eczematous purpura of Doucas and Kapetanakis, are designated based on the morphology of the lesions. The 2 variants that histopathologically present with a lichenoid infiltrate are the lichenoid pigmentary purpura of Gougerot-Blum and lichen aureus.

Lichenoid pigmentary purpura of Gougerot-Blum manifests with lichenoid red-to-brown papules that may coalesce to form plaques. The lesions tend to be bilateral and restricted to the lower extremities. However, more rarely, lesions may involve also the trunk and upper extremities. Lichen aureus, in contrast, usually presents with a solitary rust-to-golden brown patch on the lower extremity.

Clinically, these lesions should be differentiated from small vessel vasculitis; hemorrhage in the setting of stasis; allergic contact dermatitis; and, more rarely, the purpuric variant of MF, especially if involvement is widespread.

15.1. Histopathology

The key elements in the pigmented purpuric dermatoses group are a perivascular lymphocytic infiltrate, red blood cell extravasation, and hemosiderin-laden macrophages (siderophages), which can be highlighted by an iron stain such as Perls Prussian blue stain. The siderophages might not be present in early lesions. In the lichenoid variants, a band-like infiltrate of lymphocytes and histiocytes is present along the above-described features. The epidermis is often hyperplastic with elongation of rete ridges in the Gougerout-Blum variant and shows flattening of the rete ridges in cases of lichen aureus. The papillary dermis usually shows dermal fibrosis with "wiry collagen" [220,221] and, at times, edema [221]. Exocytosis of lymphocytes is often observed and is usually restricted to the lower epidermal layers [220,221]. Careful inspection of the lymphocytes reveals absent or minimal nuclear irregularities [221].

Purpuric MF is a rare variant of MF that is an important differential diagnosis to consider, as there are some important similarities such as the presence of wiry collagen in the papillary dermis, a lichenoid infiltrate of lymphocytes that frequently ascend to the epidermis along with minimal spongiosis [220-222]. Significant cytologic atypia among lymphocytes, lymphocytes in the upper portion of the epidermis, or lymphocytes forming large intraepidermal groups are features that favor MF [221]. Monoclonal rearrangement of the gamma genes has been observed in both Gougerot-Blum purpura and lichen aureus, and so, results of this test should be interpreted with caution [221,222] .

16. Early lichen sclerosus et atrophicus

Lichen sclerosus is a chronic inflammatory disorder characterized by sclerosis that often involves the anogenital region. Extragenital involvement can also occur but is less common. This disorder is most common in postmenopausal women and prepubertal girls and manifests as pruriginous ivory, atrophic plaques that in the anogenital usually surround the anus and vulva adopting a "figure-of-eight"

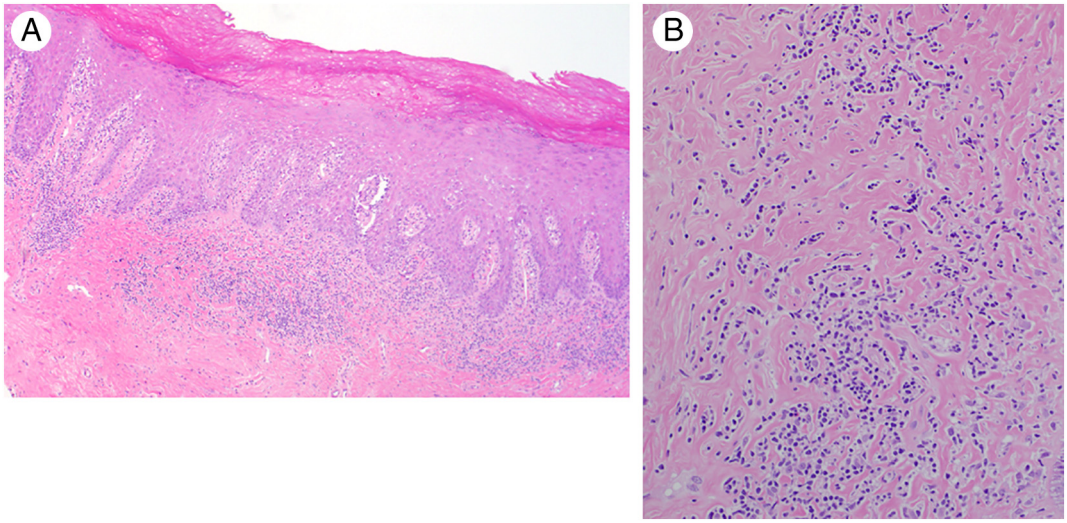

Figure 18 Early lichen sclerosus. A, Lichenoid infiltrate associated with psoriasiform epidermal hyperplasia. The dyskeratotic keratinocytes extend to the thickened stratum corneum. B, Rows of lymphocytes entrapped between thickened and sclerotic collagen fibers can be a diagnostic clue. H&E, ×40 and ×200, respectively.

configuration. These plaques are prone to erosions, fissures, and purpura (including hemorrhagic blisters due to shearing of the epithelium from the underlying sclerotic subepithelial tissue) and may lead to prominent scarring with obliteration of the clitoris, labial fusion, and vaginal stenosis in women or phimosis in men. When involving hirsute areas, follicular plugging may be seen [223,224]. Patients with longstanding vulvar lichen sclerosus have an increased risk of developing vulvar squamous cell carcinoma [225] and therefore warrant increased clinical surveillance. Vulvar lichen sclerosus should be differentiated from several entities including LP, lichen simplex chronicus, mucous membrane pemphigoid, inverse psoriasis, irritant contact dermatitis, and neoplastic processes such as vulvar intraepithelial neoplasia, squamous cell carcinoma, and extramammary Paget disease.

Vulvar lichen sclerosus rarely affects the vagina, in contrast to vulvar LP where vaginal involvement is common [224,226,227]. Although erosive disease is the most common presentation of vulvar LP, careful inspection of the areas may reveal Wickham's striae [224]. Also, involvement of other sites (most commonly the oral mucosa) favors the diagnosis of LP or even mucous membrane pemphigoid.

16.1. Histopathology

The histopathologic diagnosis of lichen sclerosus can be one of the most straightforward diagnoses for the pathologist to make provided that the distinct band of sclerosis is present. However, not infrequently, biopsies may show a lichenoid

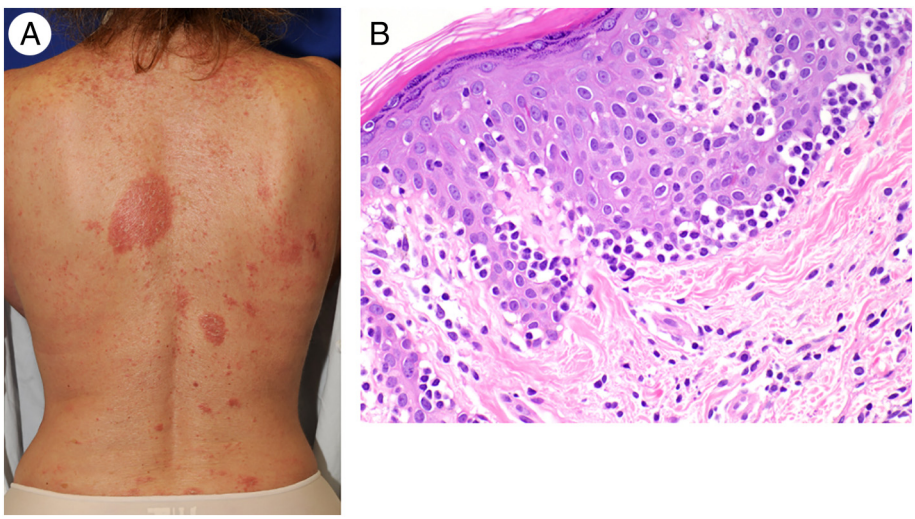

Figure 19 Mycosis fungoides. A, Asymmetric scaly papules and large scaly plaques involving the back. B, Small lymphocytes with nuclear irregularities can be seen at the basal epidermis, along with papillary dermal fibrosis. H&E, ×400.

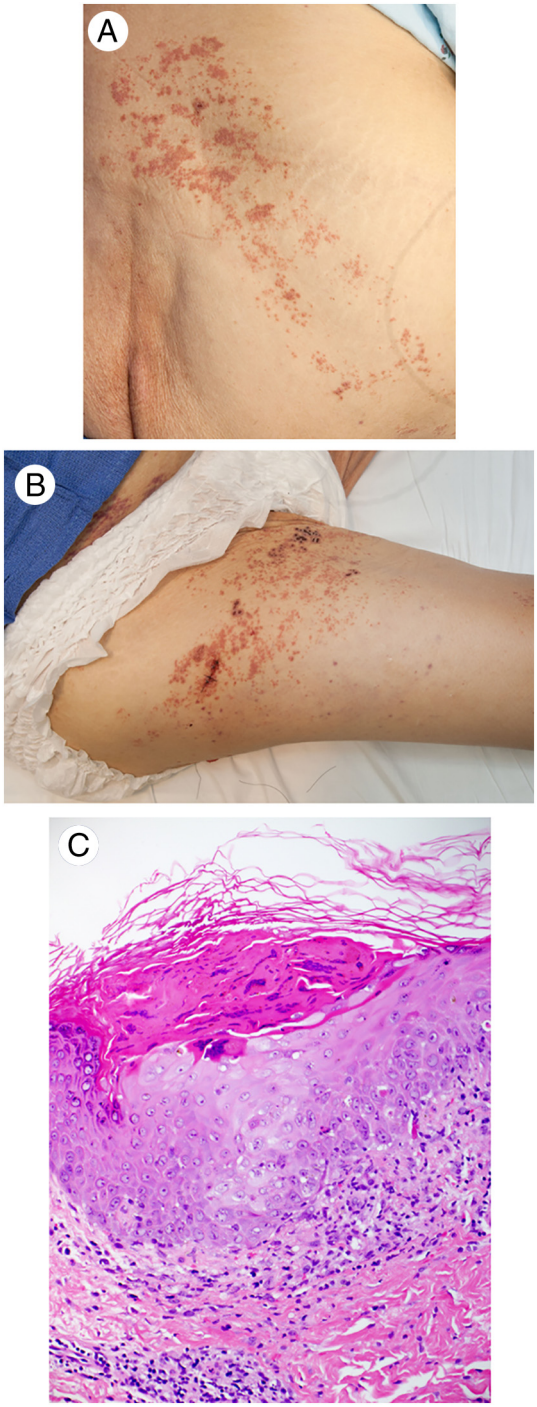

Figure 20 Lichenoid herpes zoster. A and B, Numerous small, flat-topped papules following the L2 dermatomal distribution. C, Lichenoid interface dermatitis with 2 giant cells in the stratum corneum showing multinucleation, molding, and chromatin margination. H&E, ×200.

infiltrate along with absent or minimal sclerosis that is thought to represent the inflammatory/early phase of lichen sclerosus [228]. As vulvar LP is usually in the clinical differential diagnosis, this usually poses a particular diagnostic challenge.

In these cases of absent sclerosis, the usual pattern seen is that of lichenoid psoriasiform dermatitis [228-230]. In contrast to well-established lesions of lichen sclerosus where epidermal atrophy is common, the epidermis in this inflammatory phase is usually hyperplastic with regular, elongated, and broad rete ridges and dermal papillae [228,230] (Fig. 18A). The inflammatory infiltrate can be scarce or abundant, and a helpful feature is the lymphocytes aligned in rows between thickened collagen fibers [230](Fig. 18B). In contrast to LP, colloid bodies are usually not found in the papillary dermis [228], and dyskeratotic cells can be seen scattered at all levels of the epidermis [230]. Thickening of the basement membrane, although uncommon, favors the diagnosis of lichen sclerosus over LP [228-230]. Lichen sclerosus also often involves the follicles and manifests as luminal hyperkeratosis, follicular hypergranulosis, and perifollicular basement membrane thickening [230]. Finally, a distinct pattern of compact parakeratosis overlying an epidermis with diminution of the granular layer and dykeratotic cells reminiscent of a cornoid lamella have been described as a helpful feature in cases of hypertrophic lichen sclerosus where sclerosis is absent. These columns of parakeratosis also contain dyskeratotic cells and are situated above the elongated dermal papillae [230].

As differentiated vulvar intraepithelial neoplasia commonly arises in the background of vulvar lichen sclerosus, cytologic atypia, abnormal mitoses, and architectural distortion should not be overlooked [231].

17. Mycosis fungoides

MF, the most common cutaneous T-cell lymphoma, can display interface changes in a small percentage of cases [232,233]. Although vacuolar and lichenoid variants have been described, the lichenoid pattern is the most common [232]. Knowledge of the clinical presentation in this particular scenario is of utmost importance because it might be one of the most helpful clues to suggest the diagnosis. Most of the cases of MF presenting with a lichenoid infiltrate had extensive, asymmetrical, slightly scaly, itchy patches and plaques involving the trunk, buttocks, groin, axillae, and extremities, a presentation typical of MF (Fig. 19A). The histopathology, in contrast, may show resemblance to other lichenoid dermatoses including LP [233]. Features that should be carefully sought for the diagnosis of MF are lymphocytes aligned in rows at the basal epidermis accompanied by no or very slight spongiosis (Fig. 19B), wiry collagen in the papillary dermis, and an infiltrate that in addition to lymphocytes has both eosinophils and plasma cells. Lymphocytic atypia is usually minimal, and the identification of groups of atypical lymphocytes within the epidermis (Pautrier's microabscesses) is helpful when present; unfortunately, these are not commonly present [232-234].

18. Miscellaneous

A lichenoid infiltrate can be found in the setting of a preexisting neoplasm and is thought to represent an attempt to its resolution. Lichenoid actinic keratosis, LP-like keratosis (LPLK), and regressing melanocytic lesions are examples of this phenomenon. LP-like keratosis presents usually as a solitary pink slightly scaly papule with preferential involvement of trunk and extremities of middle-aged adults [235-237]. These are commonly biopsied with the clinical concern for a superficial basal cell carcinoma [236]. Histopathologically, these lesions can be indistinguishable from LP, although patchy parakeratosis and the presence of plasma cells and eosinophils, when present, can be helpful histopathological clues that favor the diagnosis of LPLK [236,237]. About 27% of cases of LPLK display evidence of an adjacent seborrheic keratosis or solar lentigo [236]. Rarely, lesions that appear as LPLK may reveal an atypical melanocytic proliferation on deeper sectioning, and therefore, caution should be taken when interpreting these seemingly benign lesions [134].

Also, a lichenoid infiltrate can rarely be seen in cases of active varicella zoster virus infection [238] (Fig. 20A-C) and should be distinguished from zosteriform LP [239,240], a phenomenon which is thought to represent an isotopic phenomenon where lesions appear in healed, previously affected areas of herpesvirus infections [241].

Imiquimod, a Toll-like receptor 7 agonist that triggers an immune response against neoplastic and infectious diseases, is often used in dermatology for the topical treatment of superficial basal cell carcinoma, actinic keratoses, and condylomas. Clinically, the treated area develops a sequential change of erythema, edema, erosion, and crusting with eventual resolution. As expected, these lesions are rarely biopsied in clinical practice but may be sampled if the use of imiquimod is unbeknownst. The reaction can present with interface inflammation that is usually cell rich [242]. However, an atrophic vacuolar type of interface that might be mistaken for cutaneous lupus has also been reported [243]. Interestingly, reactivation or de novo development of other interface dermatoses such as LP [244-246], lichen sclerosus [246], and EM [247,248] has been reported after imiquimod use, highlighting shared pathways and the important role of the Th1 response in these disorders [242].

19. Conclusion

Inflammation at the interface may represent a considerable number of disease entities, including inflammatory dermatoses, infectious diseases, and even neoplasia. Although imperfect, its classification into lichenoid or vacuolar variants represents a practical way for the pathologist to approach the diagnostic possibilities. Recognition of other histopathologic features, as well as a keen awareness of other diagnostic considerations pertinent to the specific clinical scenario, will allow increased precision in diagnosis.

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