Epidermotropic Reactions

5

Uma N. Sundram

Atopic Dermatitis

Introduction and Clinical Features

Atopic dermatitis is an inflammatory disease of the skin which occurs in individuals with a personal or family history of atopy (Weedon 2010). It is a common disorder, and the diagnosis is made on the basis of a constellation of clinical features. The major criteria for its diagnosis include the presence of pruritus, chronicity, and a history of atopy (Williams et al. 1994). In young children, there is an erythematous papulovesicular rash with erosions involving the face, arms, and legs (Heskel and Lobitz 1983). Adults often have lichenified lesions involving the flexures (Ozkaya 2005).

Histopathology and Immunophenotype

The histopathology of atopic dermatitis falls into the category of spongiotic dermatitis. One can see acute, subacute, and chronic forms of this disease (White 1983). There can be significant overlap between the findings of atopic dermatitis and other entities within the category of spongiotic dermatitis. In acute lesions, there is spongiosis within the epidermis, accompanied in some cases by vesiculation. Exocytosis of lymphocytes is present, and when significant spongiosis is also present, the diagnosis of mycosis fungoides can be excluded. Langerhans' cells microabscesses are present in acute lesions. In subacute lesions, there is acanthosis of the epidermis with irregular psoriasiform hyperplasia. These findings are more pronounced in chronic atopic dermatitis, in which there can be significant psoriasiform hyperplasia with only mild spongiosis. In both the subacute and chronic forms, there can be overlying lichen simplex chronicus, which leads to hypergranulosis, hyperkeratosis, and papillary dermal fibrosis. Since spongiosis is decreased in subacute and chronic forms, hence in such cases, the presence of exocytosis can sometimes be mistaken for the epidermotropism of mycosis fungoides. In addition, Langerhans cell "microabscesses" or microvesicles can mimic Pautrier's microabscesses, particularly on low power examination. The presence of eosinophils is a useful clue pointing to the diagnosis of atopic dermatitis, as significant numbers of eosinophils are not present in mycosis fungoides (Dalton et al. 2012). In addition, Langerhans cells are larger than cerebriform cells, show grooved vesicular pale ovoid histiocytic nuclei, and with thin nuclear membrane and moderate amount of cytoplasm. The lymphocytes

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H.D. Cualing et al. (eds.), *Cutaneous Hematopathology*,
DOI 10.1007/978-1-4939-0950-6_5,

of atopic dermatitis are primarily T cells that express CD3 and CD4; this is also the immunophenotype of mycosis fungoides and other CD4-expressing cutaneous T-cell lymphoma, but one difference is that the collection of Langerhans cells expresses S100, CD1a, and Langerin, which are not true of cells of mycosis fungoides.

Interestingly, expression of adhesion molecules has been shown to be important in demonstrating the exocytosis/epidermotropism features of atopic dermatitis (Jung et al. 1997). In a study by Jung et al., α6 integrin was shown to be dramatically upregulated on endothelial cells and in the epidermis after exposure to atopic antigens. The authors speculate that α6 integrin may play a crucial role in the exocytosis of T cells in atopic dermatitis.

Genetics and Molecular Findings

Genetics probably plays a role in the pathogenesis of atopic dermatitis, given the usual presence of a family history of atopy and high twin concordance (Cookson 2001). Allelic associations have been described with chromosomes 11q13, 13q12-q14, and 5q31-q33 (Coleman et al. 1997; Beyer et al. 2000). Genes encoding GATA3, IL-4R, CTLA4, eotaxin, filaggrin, and portions of the receptors for IgE have all been implicated (Weedon 2010).

Prognosis and Clinical Course

The course of atopic dermatitis is one of remissions and exacerbations, and as the patient ages, there are increased symptom-free periods (Weedon 2010). The mainstay of treatment has been a combination of emollients and topical corticosteroids. Topical calcineurin inhibitors can also be used as second-line therapy for head and neck disease (Rustin 2007).

Differential Diagnosis

As noted above, atopic dermatitis shares nearly identical histologic features with other members of the "spongiotic dermatitis family," including contact dermatitis, id reaction, drug hypersensitivity reactions, nummular dermatitis, and arthropod hypersensitivity reactions. Cutaneous dermatophytosis can give similar findings, so a periodic acid-Schiff stain with diastase (PASD) or other fungal stain should always be done in these cases to exclude a fungal infection. Fungal infections can also give rise to a "mycosis fungoides"-like histologic picture. Careful correlation with clinical findings is important in arriving at the correct diagnosis (Table 5.1).

Table 5.1 Clinical and morphologic comparisons between atopic dermatitis and mycosis fungoides

	Atopic dermatitis	Mycosis fungoides
Common in children	Yes	No
Involvement of flexures	Yes	No
Spongiosis is present	Yes	No
Microabscesses	Langerhans cell	Pautrier's (tumor cells)
Cytologic atypia within T cells	No	Yes
Phenotype of T cells	CD4	CD4

Lymphomatoid Contact Dermatitis

Introduction and Clinical Features

Allergic contact dermatitis is an inflammatory condition caused by contact exposure to an allergen (Weedon 2010). Importantly, contact dermatitis is often seen in the context of an occupation, such as hairdressing or veterinary medicine (Sajjachareonpong 2002; Bulcke and Devos 2007). Clinically there may be papules, small vesicles, or plaques, which are pruritic. The lesions develop 12–48 h after exposure to the antigen. In 1976, Orbaneja et al. described four patients with skin lesions clinically and histologically compatible with mycosis fungoides (Orbaneja et al. 1976). The lesions first appeared on the anterior thighs before appearing on the face and arms and were accompanied by intense burning and pruritus. Interestingly, these patients gave a positive patch test with the striker part of a matchbox which was often stored in the trouser

Table 5.2 Clinical and morphologic comparisons between lymphomatoid contact dermatitis and mycosis fungoides

	Lymphomatoid contact dermatitis	Mycosis fungoides
Distribution	Extremities, face	Usually sun-protected areas (bathing trunk distribution)
Association with occupation	Yes	No
Pruritus is present	Yes, extensive	Sometimes
Temporal association with contactant	Yes	No
Spongiosis is present	Yes	No
Eosinophils are present	Yes, sometimes extensive	Yes, limited
Cytologic atypia within T cells	Yes	Yes
Phenotype of T cells	CD4	CD4
Positive clonality assays	No	Yes

pockets; a standard patch test was negative. The lesions resolved completely when contact with the substance (phosphorus sesquisulfide) was removed. Such lesions have also been described by Ackerman et al. as a stimulant of mycosis fungoides (Ackerman et al. 1974) and have been described in association with a variety of agents (Table 5.2).

Histopathology and Immunophenotype

On histology, these lesions demonstrate a band-like infiltrate of T cells with epidermotropism. In the study of lymphomatoid contact dermatitis by Gomez-Orbaneja et al., the band-like infiltrate contains histiocytes and eosinophils, as well as lymphocytes (Orbaneja et al. 1976). In chronic lesions, the epidermis may be acanthotic. Some epidermal spongiosis may be present, which can help to distinguish these lesions from mycosis fungoides. In most cases, however, it can be quite difficult to differentiate the intraepidermal collections of mononuclear cells in lymphomatoid contact dermatitis from the Pautrier's microabscesses of mycosis fungoides (Orbaneja et al. 1976; Ayala 1987). In addition, the cells on high power may show nuclear hyperchromasia, similar to mycosis fungoides. Detailed immunohistochemical studies have not been performed on these rare cases; however, it is known from the limited published immunohistochemical findings that the infiltrate in lymphomatoid contact dermatitis is composed of T cells that express CD4 (Smolle et al. 1990).

Prognosis and Clinical Course

In most cases described in the literature, these lesions have resolved when the offending agent is removed. This differs from lesions of mycosis fungoides, which do not demonstrate association with an offending agent. Interestingly, in at least one case, the patient developed T-cell prolymphocytic leukemia with involvement of the skin by malignant infiltrates after being initially diagnosed with lymphomatoid contact dermatitis (Braun et al. 2000; Abraham et al. 2006). It is the authors' supposition that the initial biopsy and diagnosis probably represented very early involvement of the skin by T-cell leukemia and emphasizes the necessity in these cases for careful long-term follow-up to ensure that the appropriate diagnosis has been made initially.

Differential Diagnosis

Similar to atopic dermatitis, contact dermatitis belongs to the "spongiotic dermatitis" family, and therefore the differential diagnosis includes atopic dermatitis, id reaction, drug hypersensitivity reactions, arthropod hypersensitivity reactions, and nummular dermatitis. If the patients have a more generalized eruption, and the eruption does not clear with avoidance of offending agents, one could also consider chronic photosensitivity dermatitis or actinic reticuloid within the differential (Ecker and Winkelmann et al. 1981). The presence of atypical T cells within the epidermis necessitates inclusion of mycosis

Table 5.3 Agents that cause lymphomatoid contact dermatitis

Agent	Reference
Para tertiary butyl phenol formaldehyde resin	Evans et al. (2003)
p-Phenylenediamine	Calzavara-Pinton et al. (2002)
Ethylenediamine dihydrochloride	Wall (1982)
Nickel	Danese and Bertazzoni (1995), Houck et al. (1997)
Cobalt naphthenate	Schena et al. (1995)
Gold	Conde-Taboada et al. (2007)
Isopropyldiphenylenediamine	Marlière et al. (1998), Martínez-Morán et al. (2009)

fungoides within the differential (Table 5.3), but a careful search for offending agents may help confirm the diagnosis of contact dermatitis.

Lymphomatoid Lichenoid Keratosis

Introduction and Clinical Features

Lichenoid keratosis is a common clinical entity with a differential diagnosis that includes basal cell or squamous cell carcinoma, actinic keratosis, verruca, and atypical nevi. Lymphomatoid lichenoid keratosis was originally proposed in 1997 to describe an entity which was clinically similar (a solitary erythematous patch) but showed the histologic features of mycosis fungoides (Al Hoqail and Crawford 2002; Arai et al. 2007; Kossard 1997; Evans et al. 1997; Choi et al. 2010; Morgan et al. 2005; Cerroni et al. 1999). The main differential diagnosis for this entity was unilesional mycosis fungoides, and indeed, on many occasions such a lesion has been misdiagnosed as mycosis fungoides (Kossard 1997). Al Hoqail and Crawford described a series of 15 patients who had solitary lesions, usually on the upper trunk, with a mean lesional size of around 0.6 cm (Al Hoqail and Crawford 2002). The lesions were biopsied or excised because of a clinical concern for cutaneous cancer, with basal cell carcinoma being the most common concern. Similarly, Arai and coworkers studied six cases which they defined narrowly as patients presenting with a solitary scaly plaque which demonstrated the histologic features of mycosis fungoides on microscopic examination (Arai et al. 2007). The patients were adults, the lesions were usually around 0.8 cm in size and demonstrated a predilection for the face. Clinically the lesions were thought to be either large actinic keratoses or seborrheic keratoses. None of these cases (in either study) were thought to clinically be mycosis fungoides.

Histopathology

On histology, the lesions demonstrate a striking resemblance to mycosis fungoides (Al Hoqail and Crawford 2002; Arai et al. 2007; Evans et al. 1997; Choi et al. 2010; Morgan et al. 2005) (Fig. 5.1). Al Hoqail and Crawford looked specifically for different specific findings of mycosis fungoides and found them to be represented in different percentages in these lesions. For example, Pautrier's microabscesses were present in 93 % of cases, epidermotropism in 80 %, basal alignment of lymphocytes in 93 %, atypical cytologic features in lymphocytes in 47 % (Figs. 5.2 and 5.3), and papillary dermal fibrosis in 40 % (Al Hoqail and Crawford 2002). Plasma cells were present in 60 % of cases, but no eosinophils were found. In the study of Arai et al., all cases demonstrated a band-like infiltrate of lymphocytes, epidermal involvement of lymphocytes out of proportion to accompanying spongiosis, basilar lymphocytes, and formation of Pautrier's microabscesses (Arai et al. 2007). No atypical keratinocytes or atypical lymphocytes were observed in this study, and lesions demonstrating the typical features of lichenoid keratosis were not studied. Within the lesions, there were plasma cells, eosinophils, and melanophages. Al Hoqail and Crawford documented the presence of typical findings of lichenoid keratosis such as hypergranulosis (53 % of cases), necrotic keratinocytes (73 % of cases), solar lentigo and seborrheic keratosis adjacent to the lesion

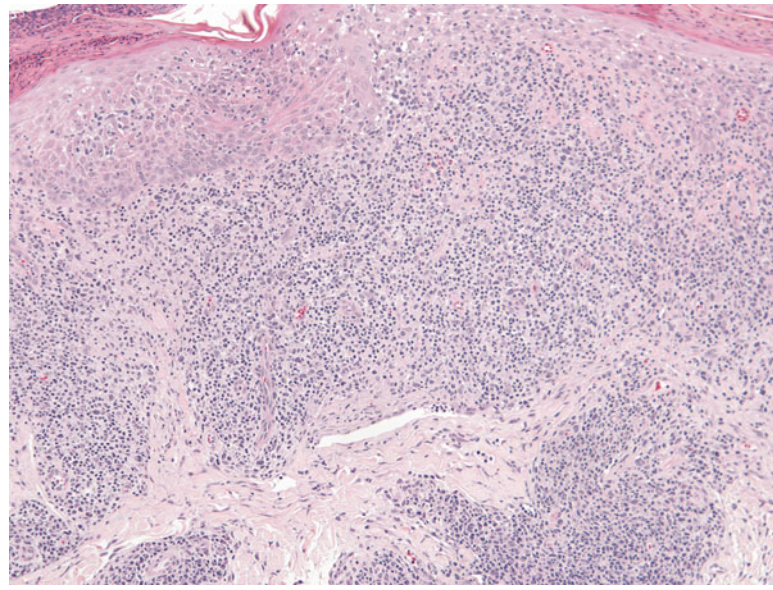

Fig. 5.1 Lymphomatoid lichenoid keratosis. There is a dense band-like infiltrate of small and large lymphocytes within the dermis with epidermal involvement (H + E, 10×)

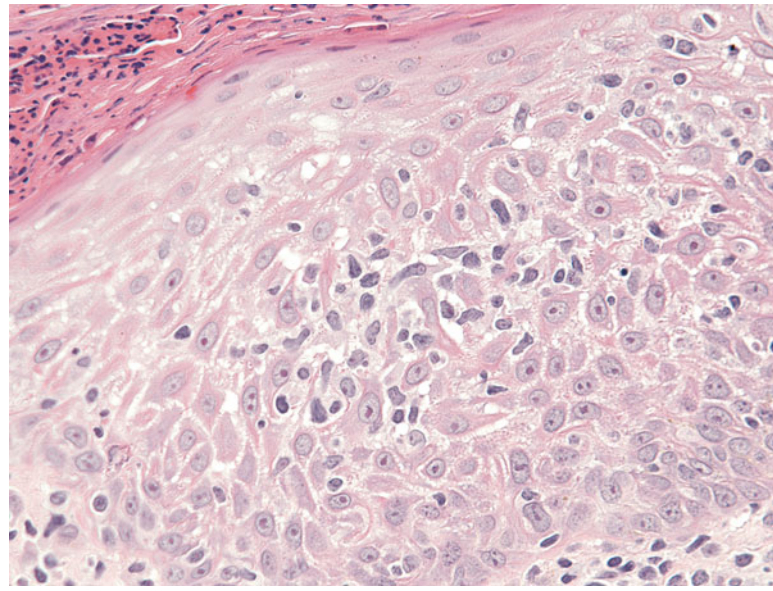

Fig. 5.2 Lymphomatoid lichenoid keratosis. Large atypical lymphocytes populate the lower half of the epidermis, and there are angulated forms (H + E, 20×)

(60 % of cases), and pointed contours of rete ridges (73 % of cases) (Al Hoqail and Crawford 2002). While the cases of Arai et al. were more narrowly defined, they still found parakeratosis and acanthosis, which are more typical findings of lichenoid keratosis (Arai et al. 2007). Both studies noted the presence of hypergranulosis and plasma cells, which are unusual findings in mycosis fungoides. However, it is important to note that in both studies, many if not all of the cases lacked characteristic findings of lichenoid keratosis, which would make the distinction from mycosis fungoides on morphologic grounds difficult (Arai et al. 2007).

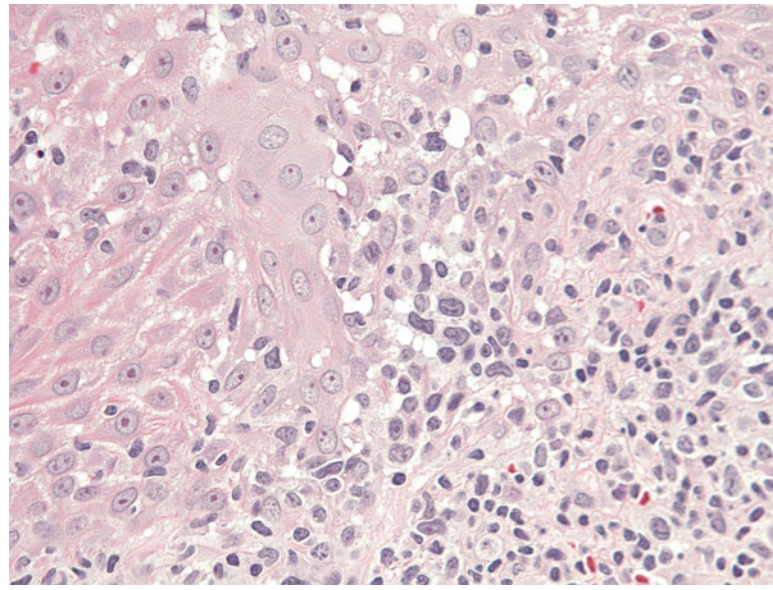

Fig. 5.3 Lymphomatoid lichenoid keratosis. Basal vacuolar alteration accompanies the infiltrate (H + E, 20×)

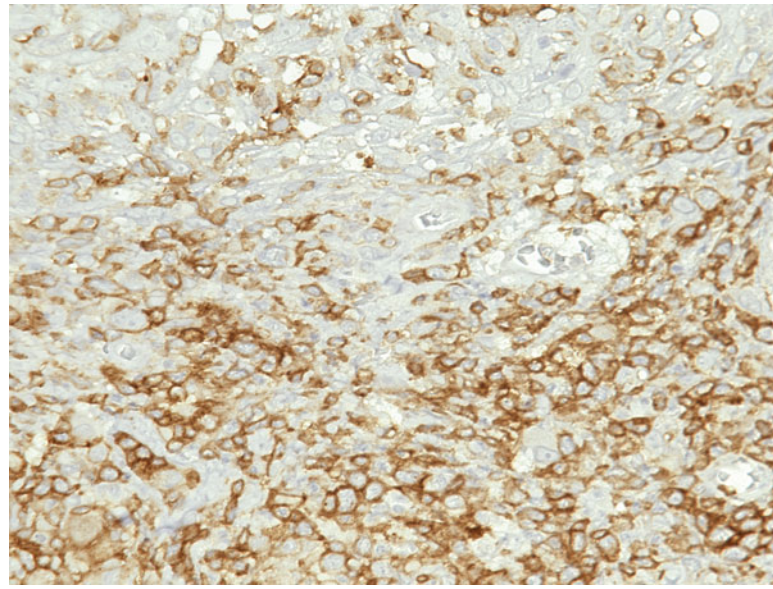

Fig. 5.4 Lymphomatoid lichenoid keratosis. The infiltrate is composed primarily of CD4-expressing T cells (20×)

Immunophenotype

Interestingly, in the study of Arai et al., numerous B cells were admixed with T cells within the infiltrate, and in some cases, B cells formed Pautrier's microabscesses (Arai et al. 2007). CD4-expressing T cells predominated over CD8-expressing T cells, and epidermotropism of CD3-expressing cells was seen (Fig. 5.4). Interdigitating and Langerhans cells were present within the epidermis and expressed S100 and CD1a, respectively. The presence of B-cell-predominant Pautrier's microabscesses and CD1a and S100 expressing cells within the epidermis are both thought to be unusual findings in mycosis fungoides (Igisu et al. 1983).

Table 5.4 Clinical and morphologic comparisons between lymphomatoid lichenoid keratosis and mycosis fungoides

	Lymphomatoid lichenoid keratosis	Mycosis fungoides (unilesional)	Mycosis fungoides (classic)
Solitary lesion	Yes	Yes	No
Distribution	Truncal and face	Truncal (Cerroni et al. 1999)	Buttocks, trunk, inner arms, upper thighs
Clinical suspicion for mycosis fungoides	Low	Intermediate to high (Arai et al. 2007)	High
Presence of parakeratosis, hypergranulosis, acanthosis, and plasma cells	Yes	No	No
Presence of saw tooth rete ridges	Yes (Al Hoqail and Crawford 2002)	No	No
Adjacent typical solar lentigo or seborrheic keratosis	Yes (Al Hoqail and Crawford 2002)	No	No
Cytologic atypia within T cells	Yes	Yes	Yes
Phenotype of T cells	CD4	CD4	CD4
Phenotype of epidermotropic cells	Admixed CD20+ B cells (Arai et al. 2007)	CD4+ T cells only	CD4+ T cells only

Genetics and Molecular Findings

T-cell receptor gene rearrangement and IgH clonality assays were both performed in the cases of Arai et al. (2007). IgH clonality assays were negative in all cases, but in two cases, T-cell receptor gene rearrangements were seen. Interestingly, T-cell receptor (TCR) gamma and TCR beta chains were both rearranged in one case.

Prognosis and Clinical Course

Complete excisions are curative in these cases. Although follow-up is limited, no patient to date has developed widespread lesions of mycosis fungoides.

Differential Diagnosis

The major differential diagnostic considerations include unilesional mycosis fungoides, lichenoid actinic keratosis, and lichenoid lymphomatoid drug eruption. In classic mycosis fungoides, the lesions consist of erythematous patches in sun-protected sites (bathing trunk distribution). The buttocks, inner arms, and trunk are often affected. In cases of unilesional mycosis fungoides, there is a single lesion, often truncal, with a size range between 1 and 2 cm. This entity is thought to be distinct from pagetoid reticulosis (Cerroni et al. 1999; Jones and Chu 1981). The distinction between unilesional mycosis fungoides and lymphomatoid lichenoid keratosis (as defined by Arai et al.) can be very difficult (Arai et al. 2007; Cerroni et al. 1999; Oliver and Winkelmann 1989). Histologic and immunohistochemical features can sometimes be helpful in making this distinction (Table 5.4). Lymphomatoid drug eruptions have a temporal connection to offending medications and other agents.

Mycosis Fungoides-Like Lymphomatoid Drug Eruption

Introduction and Clinical Features

Lymphomatoid drug eruption (also known as lymphomatoid hypersensitivity reaction (Gilliam and Wood 2000)) is a rash caused by certain medications (Navarro et al. 2011; Choi et al. 2003; Miranda-Romero et al. 2001; Fitzpatrick 1992; Welykyj et al. 1990). Lymphomatoid drug eruptions that mimic mycosis fungoides will be discussed in this section and are primarily caused by anticonvulsants (such as carbamazepine), but other drugs can cause this condition as well (Ploysangam et al.

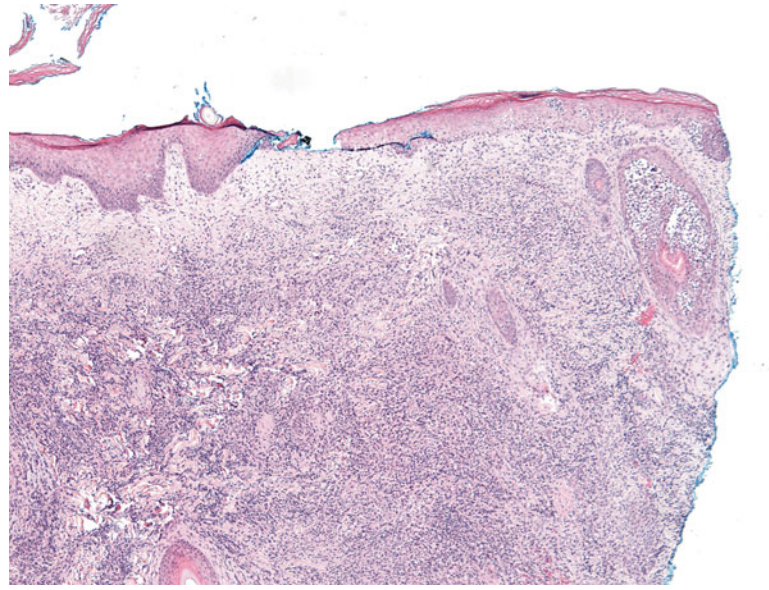

Fig. 5.5 Lymphomatoid drug eruption. There is a dense deep and diffuse infiltrate of atypical lymphocytes with involvement of the epidermis and hair follicle (H + E, 4×)

1998). Phenytoin- and carbamazepine-induced hypersensitivity is associated with a classic triad of fever, rash, and lymphadenopathy, as well as peripheral blood abnormalities, and these findings resolve after the agent is discontinued (Ploysangam et al. 1998). The syndrome can occur shortly after the drug is ingested, and skin lesions can be single or multiple and generalized. Rarely, a Sézary syndrome-like erythrodermic eruption can take place (Ploysangam et al. 1998). Drugs other than anticonvulsants can also give rise to pseudolymphomas. These too are temporally connected to the offending agent and can give rise to single or multiple lesions or a Sézary syndrome-like erythroderma.

Histopathology and Immunophenotype

On histology, the findings can be identical to mycosis fungoides (Fig. 5.5) (Souteyrand and d'Incan 1990). There can be a band-like infiltrate of lymphocytes, many of them atypical. They can demonstrate epidermotropism with formation of Pautrier's-like microabscesses, and follicular mucinosis has been documented (Fig. 5.6) (Navarro et al. 2011). On immunophenotyping, the atypical cells are usually of T-cell origin (Miranda-Romero et al. 2001), and CD30 expression can be seen (Fig. 5.7a, b) (Pulitzer et al. 2013).

Genetics and Molecular Findings

In a study by Brady et al., the skin lesions of 14 patients with known lymphomatoid drug eruptions were tested via T-cell receptor gene rearrangement studies and IgH clonality assays for the presence of a clone (Brady et al. 1999). Two of 14 patients were found to have TCR clones, but none had IgH clones. Both the skin rash and monoclonal population of T cells resolved upon discontinuation of the drug.

Differential Diagnosis

The main differential diagnosis is with mycosis fungoides, which can be excluded on the basis of good clinical information and resolution of the rash and other systemic findings upon discontinuation of the drug (Table 5.5).

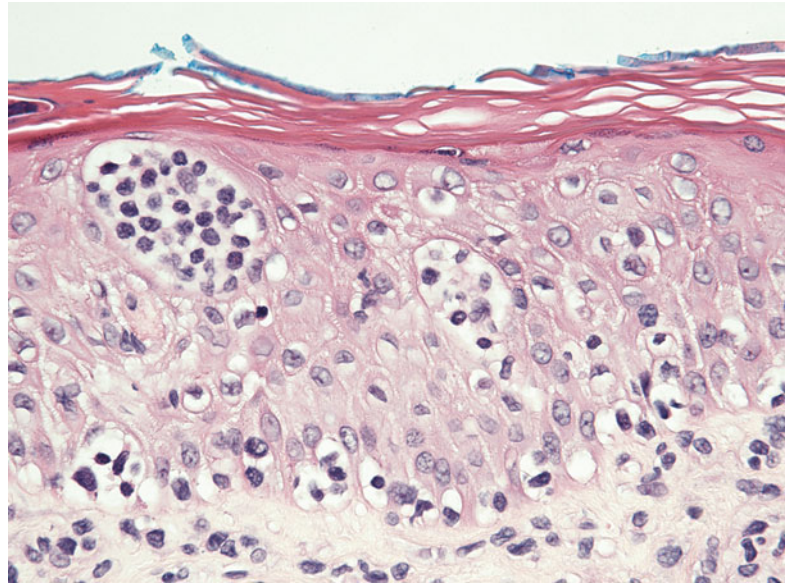

Fig. 5.6 Lymphomatoid drug eruption. Higher power view shows formation of Pautrier's-like microabscesses and basal lining by large atypical lymphocytes (H + E, 20×)

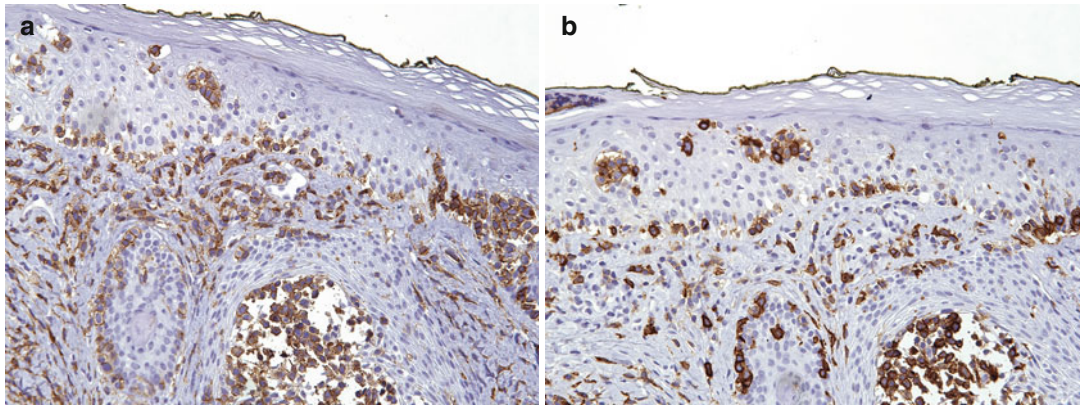

Fig. 5.7 Lymphomatoid drug eruption. The lymphocytes express both CD4 (**a**) and CD30 (**b**) (20× for both)

Table 5.5 Clinical and morphologic comparisons between mycosis fungoides-like lymphomatoid drug eruptions and mycosis fungoides

	Mycosis fungoides-like lymphomatoid drug eruption	Mycosis fungoides
Clinical findings	Widespread morbilliform eruption	Patches and plaques involving sun protected areas
Systemic symptoms	Yes, lymphadenopathy, fever, hepatosplenomegaly, eosinophilia	No
Resolution of lesions upon removal of offending agent	Yes	No
Microabscesses	Pautrier's like	Pautrier's (tumor cells)
Cytologic atypia within T cells	Yes	Yes
TCR clonality	Positive sometimes (Brady et al. 1999)	Usually positive

Table 5.6 Clinical and morphologic comparisons between lichenoid drug eruptions, lichen planus, and mycosis fungoides

	Lichenoid drug eruptions	Lichen planus	Lichenoid mycosis fungoides
Clinical distribution	Extremities, trunk, oral	Extremities (flexors), trunk, genitals, oral	No
Clinical appearance	Small flat-topped papules, pruritic	Small flat topped papules, pruritic	Erythematous patches, sun-protected areas
Resolution upon removal of drug	Yes	No	No
Eosinophils are present	Yes	Minor feature	Minor feature
Clusters of necrotic keratinocytes	Yes, high percentage	Yes, low percentage	Yes, very low percentage
Cytologic atypia within T cells	No	No	Yes

Lichenoid Drug Eruptions

Introduction and Clinical Features

Lichenoid drug eruptions clinically mimic lichen planus but are caused by a variety of medications, such as gold (Penneys 1979), methyldopa (Burry 1976), β-adrenergic blocking agents (Hawk 1980), penicillamine (Van Hecke et al. 1981), synthetic antimalarials (Bauer 1981), and ethambutol (Grossman et al. 1995). Newer drugs to cause this effect include imatinib (Kuraishi et al. 2010) and tumor necrosis factor-α antagonists (Asarch et al. 2009). The eruption clears when the offending agent is withdrawn (Weedon 1998). The lesions consist of flat-topped pruritic papules occurring on the limbs, chest, and back. More pronounced hyperpigmentation has been reported with lichenoid drug eruptions than with lichen planus. Oral lichen planus may also occur with ingestion of certain drugs and can take time to resolve even after the drug is removed (Weedon 1998).

Histopathology and Immunophenotype

On histopathology, there is hyperkeratosis, hypergranulosis, and acanthosis of the epidermis. A band-like infiltrate of lymphocytes is present and partially obscures the dermal epidermal junction; however, this infiltrate is thought to be less dense in lichenoid drug eruptions than in lichen planus and tends to involve the deeper reticular dermis. Necrotic keratinocytes, Civatte bodies, and Max Joseph spaces are seen, and there is usually more pigment dropout noted with lichenoid drug eruptions than with lichen planus (Weedon 1998). The presence of eosinophils is a good clue to the diagnosis (Lage et al. 2012).

Differential Diagnosis

The primary differential diagnosis is with lichen planus, and the distinction can be difficult as the clinical and histologic features of these two entities overlap significantly (Lage et al. 2012) (Table 5.6). A recent paper has suggested that the presence of clusters of apoptotic cells and eosinophils are both statistically significant findings in distinguishing between these two entities; lichenoid drug eruptions tend to have both findings more than lichen planus (Lage et al. 2012). Removal of any new drugs may shed light on the diagnosis, as idiopathic lichen planus is not associated with drug ingestion. Lichenoid mycosis fungoides is also a differential diagnostic consideration (Guitart et al. 1997). Rarely, a lichenoid drug eruption may mimic mycosis fungoides histologically, but the clinical presentation is usually that of a drug eruption (Wu et al. 2010). Other studies have demonstrated that paucity of intraepidermal Foxp3-positive T cells may be used to confirm the diagnosis of a lichenoid mycosis fungoides and argue against lichen planus or a lichenoid drug eruption (Wada et al. 2010). Molecular studies on lichenoid drug eruptions are very limited, but clonal reactive infiltrates in the skin have been documented (Zhang et al. 2010), and lesions

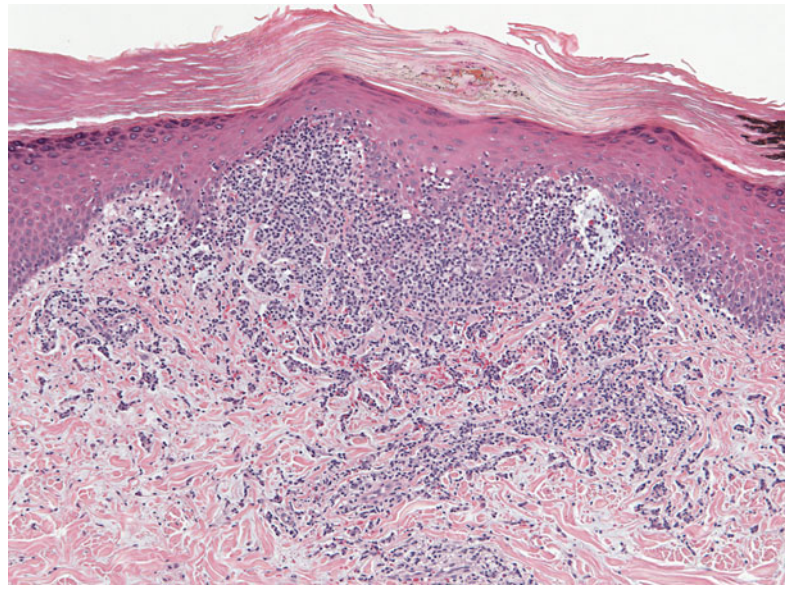

Fig. 5.8 Pigmented purpuric dermatosis. There is a dense band-like infiltrate of lymphocytes at the dermal epidermal junction with accompanying extravasation of erythrocytes. The infiltrate extends into the deeper reticular dermis in a wedge-shaped fashion (H + E, 10×)

of lichen planus are known to harbor clones (Holm et al. 2002). Removal of any new medication should first be initiated to determine if the agent is the cause of the eruption; this may be the most effective way of confirming that the eruption is related to a drug.

Pigmented Purpuric Dermatosis

Introduction and Clinical Features

Pigmented purpuric dermatosis (PPD) constitutes a group of diseases consisting of purpuric lesions, usually on the legs, with variable pigmentation due to extravasation of erythrocytes (Weedon 1998). The different clinical categories of PPD include Schamberg's disease, purpura annularis telangiectodes of Majocchi, pigmented purpuric lichenoid dermatosis of Gougerot and Blum, and lichen aureus. Schamberg's disease is the most common and is characterized by minute purpuric macules on the lower extremities which coalesce into patches. The lesions of purpura annularis telangiectodes of Majocchi are composed of annular patches with perifollicular punctate lesions and telangiectasias (Newton and Raimer 1985). The lesions of pigmented purpuric lichenoid dermatosis of Gougerot and Blum are composed of lichenoid papules which may coalesce to give plaque-like lesions, also primarily on the lower legs (Newton and Raimer 1985). The lesions of lichen aureus are a distinctive golden brown color and are usually annular. While they are often found on the lower legs, they can also involve the back and upper extremities. Some systemic diseases, such as lupus erythematosus and liver disease, have been associated with PPD, as well as numerous drugs, such as lipid-lowering drugs and angiotensin-converting enzyme (ACE) inhibitors (Sarantopoulous et al. 2013).

Histopathology and Immunophenotype

All entities in the category of PPD have similar histologic findings. They are composed of a mild to moderately dense infiltrate of lymphocytes at the dermal epidermal junction which extends to involve the superficial vascular plexus (Fig. 5.8). The lymphocytic infiltrate in Schamberg's disease may be mild, but it may be dense and band-like in lichen aureus (Weedon 1998). An overall lichenoid pattern has been described in the pigmented purpuric lichenoid dermatosis of Gougerot and

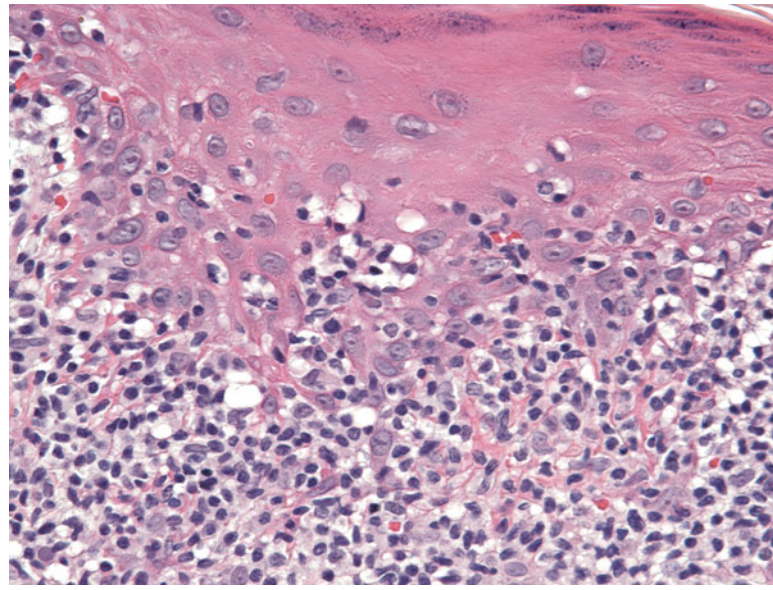

Fig. 5.9 Pigmented purpuric dermatosis. Sawtooth changes are noted within the rete pegs, and there is basal vacuolar change with intraepidermal extravasated erythrocytes (H + E, 40×)

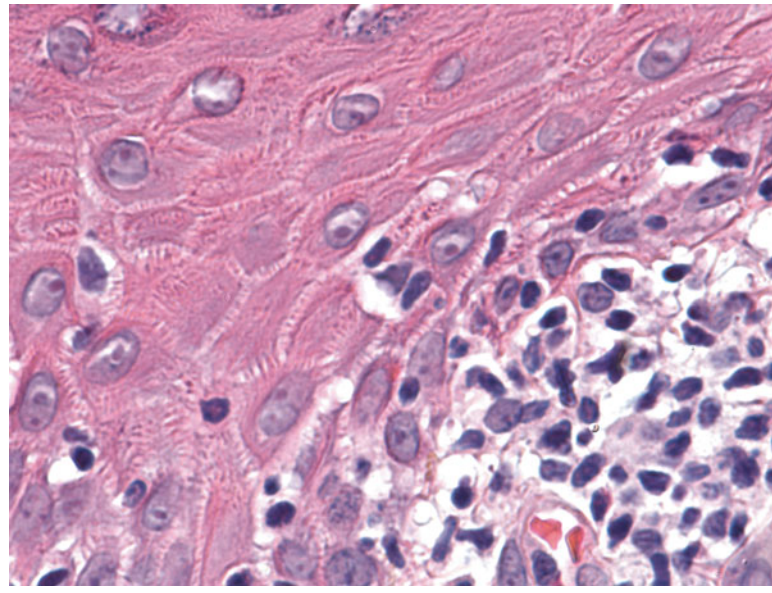

Fig. 5.10 Pigmented purpuric dermatosis. High power examination shows the presence of a small Pautrier's-like microabscess (H + E, 90×)

Blum, and in lichen aureus, there is usually a thin grenz zone (Sarantopoulous et al. 2013). The overlying epidermis may demonstrate orthokeratotic hyperkeratosis or demonstrate parakeratosis. The lymphocytes extend into the epidermis, and there is usually associated spongiosis. Sometimes basal vacuolar alteration and necrotic keratinocytes can be observed (Fig. 5.9). Extravasated erythrocytes are almost always present, and sometimes the erythrocytes are within the epidermis. Rarely one may see Pautrier's-like microabscesses (Fig. 5.10). In older lesions, hemosiderin deposition may be observed free in the dermis or within histiocytes, and these deposits are highlighted by a Prussian blue stain. Immunophenotyping of lesions of PPD shows these to be composed of T cells that express CD4 (Smoller and Kamel 1991; Harvell et al. 2003).

Table 5.7 Clinical and morphologic comparisons between pigmented purpuric dermatosis and pigmented purpuric dermatosis-like mycosis fungoides

	Pigmented purpuric dermatosis	Pigmented purpuric dermatosis-like mycosis fungoides
Purpuric lesions	Yes	Yes
Location of lymphocytic infiltrate	Mostly superficial dermis	Superficial and mid dermis
Extravasation of erythrocytes and hemosiderin deposition	Yes	Yes
Microabscesses	Pautrier's-like lymphocytic collections (Magro et al. 2007a, b)	Pautrier's (tumor cells)
Cytologic atypia within T cells	Yes, mild	Yes
Phenotype of T cells	Primarily CD4 (Sarantopoulos et al. 2013)	Primarily CD4
T-cell clonality assays	Sometimes positive	Usually positive

Genetics and Molecular Findings

PPD has been reported numerous times to harbor clones, and some authors consider this entity to be a precursor of mycosis fungoides (Sarantopoulous et al. 2013; Crowson et al. 1999; Toro et al. 1997; Magro et al. 2007b; Chen et al. 2004). Indeed, several reports exist documenting transformation of PPD into mycosis fungoides after several years (Georgala et al. 2001; Viseux et al. 2003).

Prognosis and Clinical Course

Although the condition is a benign one, in general, the course is chronic, with exacerbations and remissions of disease (Tristani Firouzi et al. 2001). Rarely, PPD may undergo spontaneous resolution. Treatment courses are generally ineffective, although topical corticosteroids, PUVA, and systemic steroids have been used.

Differential Diagnosis

Given the mild spongiosis accompanying this entity, one could also consider spongiotic dermatitis in the differential diagnosis, which would include atopic dermatitis, contact dermatitis, nummular dermatitis, drug hypersensitivity reactions, arthropod hypersensitivity reactions, and id reactions. This would be a particular problem if the clinical scenario is not well described and the biopsy does not show findings of extravasated erythrocytes or hemosiderin deposition. An eczematous lesion on the lower extremities would pose a particular problem if clinical descriptions of the lesions are not provided, as there is often a background of stasis changes. Other entities to consider include fixed drug eruption (which is usually not as extensive and has numerous well-formed necrotic keratinocytes) and a leukocytoclastic vasculitis (which would demonstrate a true vasculitis with neutrophils, leukocytoclasis, necrosis of vessel walls, and fibrin deposition) (Tristani Firouzi et al. 2001). There can also be significant overlap with the so-called pigmented purpuric dermatitis-like mycosis fungoides (PPD-like mycosis fungoides), a very rare variant of mycosis fungoides (Toro et al. 1997; Georgala et al. 2001; Lipsker 2003) (Table 5.7). These lesions clinically present similarly as those of PPD, but the lesions tend to be more extensive, with extension beyond the typical areas of involvement of PPD. Histologically they appear similar as well, but the lesions of PPD-like mycosis fungoides tend to have a much deeper infiltrate of lymphocytes (Reddy and Bhawan 2007). Both express CD4 (Magro et al. 2007a, b; Sardana et al. 2004), and both can demonstrate T-cell clonality (Zhang et al. 2010; Crowson et al. 1999; Toro et al. 1997; Magro et al. 2007a, b; Fink Puches et al. 2008; Thurber et al. 2007; Plaza et al. 2008). Close clinical follow-up is recommended of cases that seem suspicious for mycosis fungoides, as currently there are no good immunohistochemical or molecular

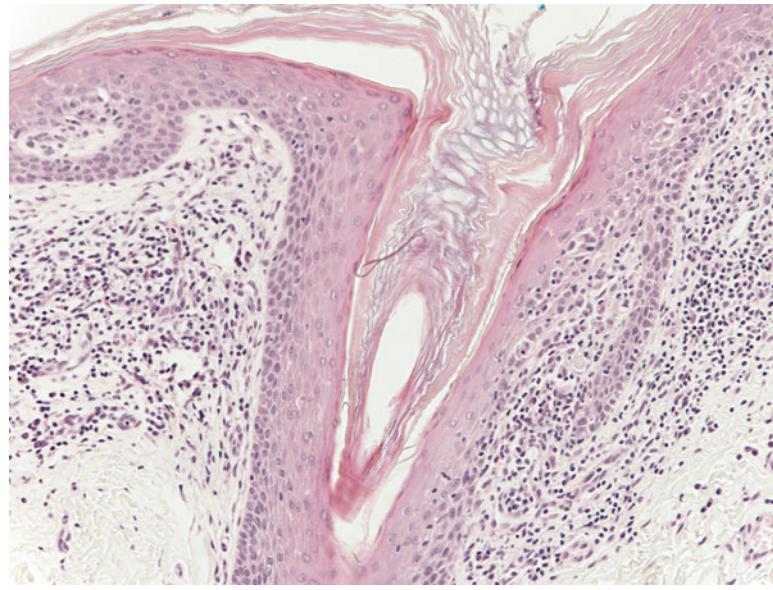

Fig. 5.11 Lichen sclerosus. There is a band-like infiltrate of lymphocytes with follicular plugging in an early inflammatory lesion. Focal involvement of the epidermis by lymphocytes is seen (H + E, 10×)

methods for differentiation between cases of very unusual PPD and PPD-like mycosis fungoides.

Lichen Sclerosus

Introduction and Clinical Features

Lichen sclerosus (previously known as lichen sclerosus et atrophicus) is a chronic condition that primarily affects postmenopausal women in the anogenital area, although premenopausal women and children can also be affected. Extragenital lesions of lichen sclerosus can occur and are often truncal or involve the upper extremities. Males are affected less commonly (known as balanitis xerotica obliterans), are usually children or young adults when affected, and the lesions in severe cases can result in phimosis (Weedon 1998). Clinically, these are ivory-colored papules that coalesce to form plaques. Follicular accentuation is often seen, and the lesions can undergo atrophy leading to a wrinkled and depressed scar ("cigarette paper atrophy"). The lesions in the genital area have a higher propensity to develop dysplasia and squamous cell carcinoma and should be carefully screened for malignancy.

Histopathology and Immunophenotype

On histology, the lesions demonstrate epidermal acanthosis, hyperkeratosis, and follicular plugging (Fig. 5.11). There can be superimposed hypergranulosis and fibrotic changes within the dermis which may be a result of superimposed scratching and lichenification. In early lesions, there is a band-like infiltrate of lymphocytes at the dermal epidermal junction, subtle basal vacuolar alteration, rare necrotic keratinocytes, and infiltration of the epidermis by lymphocytes. In later lesions, there are pale changes within the upper collagen (homogenization) that are bordered inferiorly by an infiltrate of lymphocytes. The overlying epidermis is flattened and atrophic with loss of rete pegs. Pigment dropout may be seen within the upper dermis. The upper vascular plexus is composed of dilated and ectatic vessels, and surrounding mild hemorrhage can be seen. Appendages appear normal and undisplaced, and there is no loss of perieccrine fat. Moderate cytologic atypia may be seen in some cases (Fig. 5.12), and Pautrier's-like microabscesses have been observed (Fig. 5.13). In some cases, there can be extensive colonization of the epidermis by lymphocytes

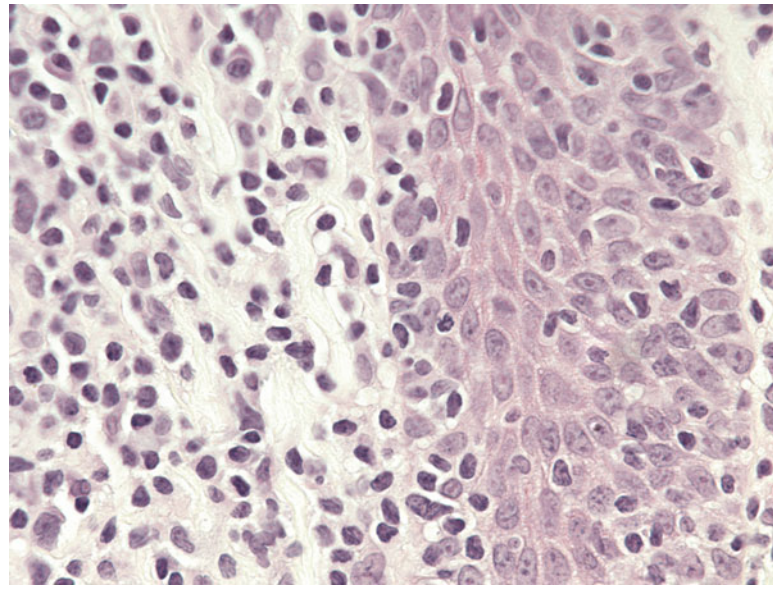

Fig. 5.12 Lichen sclerosus. Basilar lining by atypical lymphocytes is seen (H + E, 20×)

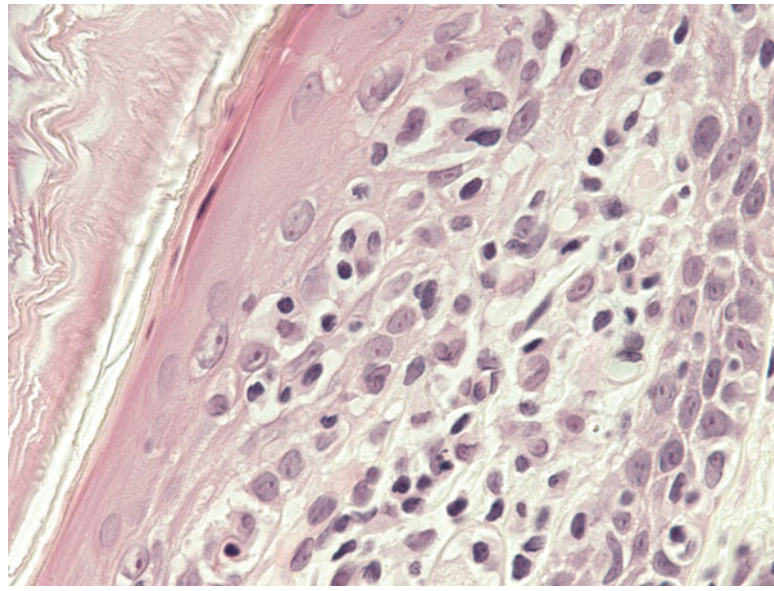

Fig. 5.13 Lichen sclerosus. High power view shows formation of a Pautrier's-like microabscess with moderately atypical lymphocytes (H + E, 20×)

without associated spongiosis (Fig. 5.14). On immunophenotyping, equivalent number of CD4- and CD8-expressing T cells are seen in the infiltrate; the number of B cells is much less (Smoller and Kamel 1991; Terlou et al. 2012; Regauer and Beham-Schmid 2006; Ben Hur et al. 2001; Gross et al. 2001; Carlson et al. 2000; Scrimin et al. 2000; Farrell et al. 1999; Hinchliffe et al. 1994).

Genetics and Molecular Findings

A correlation has been found between certain HLA subtypes and the development of lichen sclerosus, especially in children (Tilly et al. 2004), and lichen sclerosus has been described in twins (Meyrick Thomas and Kennedy 1986) and in sisters (Sahn et al. 1994), suggesting, at least in some cases, a genetic predisposition to the disease. In addition,

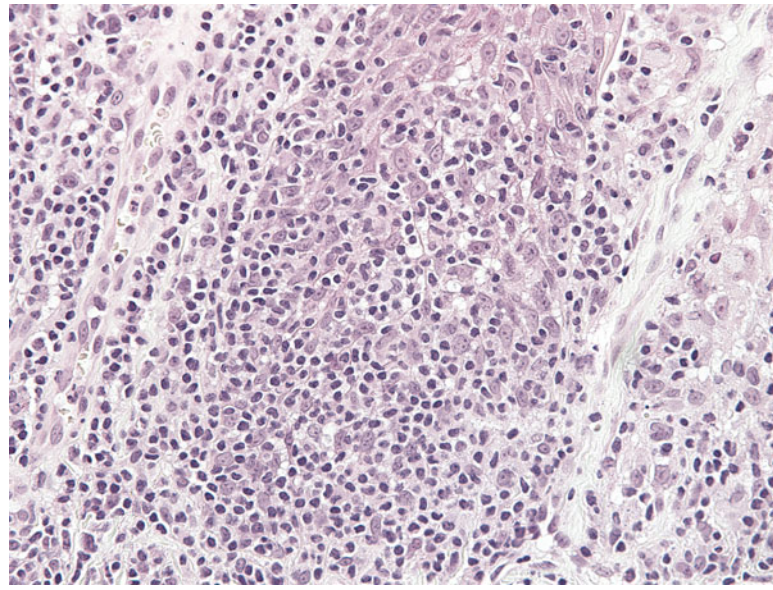

Fig. 5.14 Lichen sclerosus. In another case, extensive colonization of the overlying epidermis with lymphocytes is seen (H + E, 10×)

T-cell receptor clonality assays have been reported to show a monoclonal band in 50–60 % of cases of lichen sclerosus in some series (Regauer and Beham-Schmid 2006) and in a much smaller population of cases in others (Citarella et al. 2003).

Prognosis and Clinical Course

Unfortunately, hormonal interventions are largely ineffective, and the current treatment approaches usually involve the use of high-potency steroids on a scheduled basis to prevent steroid atrophy (Tilly et al. 2004). Surgical intervention may be necessary for treatment of highly advanced cases of phimosis or fused labial mucosae. There is a risk of development of squamous cell carcinoma, and the connection with the presence of high-risk subtypes of human papillomavirus is uncertain (McCluggage 2013). These cases are followed closely clinically to ensure that early lesions of dysplasia and carcinoma are adequately treated.

Differential Diagnosis

In early lesions, the differential diagnostic considerations include lichen planus, contact dermatitis, or atopic dermatitis, and many lesions of lichen sclerosus often have superimposed lichen simplex chronicus. Lichen planus and spongiotic entities do not usually demonstrate the characteristic changes of collagen seen in lichen sclerosus nor do they tend to have atrophic epidermal changes (unless there is coexisting steroid atrophy). Eosinophils are more common in atrophic and contact dermatitis than in either lichen planus or lichen sclerosus. The early lesions of lichen planus of the vulva and lichen sclerosus can be quite difficult to distinguish from each other. Early lesions of lichen sclerosus can also mimic mycosis fungoides (Citarella et al. 2003; Suchak et al. 2010) and can be clonal (Regauer and Beham-Schmid 2004) (Table 5.8). In such cases, it may be worthwhile to repeat the biopsy in a

Table 5.8 Clinical and morphologic comparisons between lichen sclerosus and mycosis fungoides

	Lichen sclerosus	Mycosis fungoides
Anogenital involvement	Yes	Yes
Ivory-colored coalescing papules with follicular accentuation	Yes	No, tend to be erythematous patches and plaques
Hyperkeratosis, follicular plugging, and epidermal atrophy	Yes, common	Yes, rare
Homogenization of collagen	Yes, but not in early lesions	No
Cytologic atypia within T cells	No	Yes
Phenotype of T cells	Mixture of CD4 and CD8	CD4
T-cell clonality	Positive sometimes	Usually positive

few months' time to determine if the lesions evolve to demonstrate the characteristic findings of lichen sclerosus (Suchak et al. 2010). Late lesions of lichen sclerosus, especially at extragenital sites, can mimic morphea. Clues that point to lichen sclerosus include the presence of pigment dropout, basal vacuolar alteration, necrotic keratinocytes, and preservation of appendages.

Annular Lichenoid Dermatitis of Youth

Introduction and Clinical Features

Annular lichenoid dermatitis of youth is a clinical entity which was first described by Annessi et al. in 2003 (Kleikamp et al. 2008; Tsoitis et al. 2009; Cesinaro et al. 2009; Leger et al. 2013; Huh and Kanitakis 2010). They observed 23 patients in whom they described red macules and annular lesions with central hypopigmentation. The lesions are bordered by lichenoid papules. These lesions are usually found on the flanks and groins of children (Tsoitis et al. 2009) and adolescents, but adults have been described with the condition (Cesinaro et al. 2009). Older lesions have hyperpigmented borders (Annessi et al. 2003).

Histopathology and Immunophenotype

On histology, a band-like infiltrate is noted at the dermal epidermal junction concentrated at the tips of rete pegs with associated necrotic keratinocytes (Kleikamp et al. 2008). In older lesions, there is flattening of the rete pegs with clusters of necrotic keratinocytes. Immunohistochemical analysis showed that the infiltrate was composed of a mixture of CD4- and CD8-positive T cells, with the intraepidermal T cells being primarily CD8 positive. The CD8-positive T cells co-expressed TIA-1 (Kleikamp et al. 2008).

Genetics and Molecular Findings

T-cell receptor gene rearrangements and IgH clonality assays are negative, as are polymerase chain reaction (PCR) testing for Borrelia DNA and parvovirus B19 DNA (Kleikamp et al. 2008).

Prognosis and Clinical Course

In the original report by Annessi et al., treatment with potent topical steroids cleared the lesions, but they recurred over a 5-year period with a

chronic clinical course (Annessi et al. 2003). Psoralen and ultraviolet A (PUVA) and systemic steroids have also been tried with similar results (Tsoitis et al. 2009). Interestingly, in the case report of Kleikamp et al., the patient's lesions resolve with topical tacrolimus without pigmentary changes, and there was no recurrence after a 2-year follow-up period (Kleikamp et al. 2008). Spontaneous resolutions of lesions have been described (Cesinaro et al. 2009).

Table 5.9 Clinical and morphologic comparisons between annular lichenoid dermatitis of youth and mycosis fungoides

	Annular lichenoid dermatitis of youth	Mycosis fungoides, hypopigmented variant
Primarily described in children	Yes	Yes
Involvement of sun-spared areas	Yes	Yes
Lichenoid infiltrate with colloid bodies	Yes	No, but present in lichenoid mycosis fungoides
Cytologic atypia within T cells	No	Yes
Phenotype of T cells	CD8	CD8
Positive T-cell clonality assays	No	Yes

Differential Diagnosis

The differential diagnosis includes pediatric annular erythema, inflammatory morphea, inflammatory vitiligo, and mycosis fungoides (and other CD8+ epidermotropic lymphomas) (Kleikamp et al. 2008) (Table 5.9). A lichenoid infiltrate would be unusual for both morphea and annular erythemas, and its presence would strongly argue against those diagnoses. The clinical distribution of vitiligo is different from annular lichenoid dermatitis of youth, and loss of melanocytes is seen (Cesinaro et al. 2009). The hypopigmented variant of mycosis fungoides poses a particular problem (Figs. 5.15 and 5.16) (Zackheim et al. 1982; Neuhaus et al. 2000). In general, mycosis fungoides is composed primarily of CD4-expressing T cells, whereas annular lichenoid dermatitis of youth shows a mixture of CD4- and CD8-expressing T cells in the dermis, and where intraepidermal lymphocytes are present, they express CD8 (Kleikamp et al. 2008). However, hypopigmented mycosis fungoides also expresses CD8 (Fig. 5.17) and is present in young people, similar to annular lichenoid dermatitis of youth. T-cell clonality assays can be useful, as they are usually positive in hypopigmented mycosis

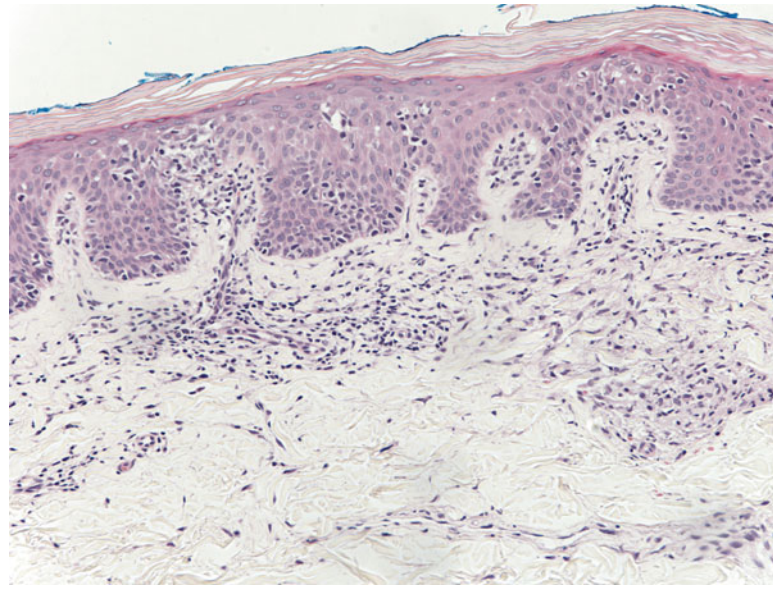

Fig. 5.15 Hypopigmented mycosis fungoides. A band-like infiltrate of highly atypical lymphocytes is noted at the dermal epidermal junction, and there is significant epidermotropism (H + E, 10×)

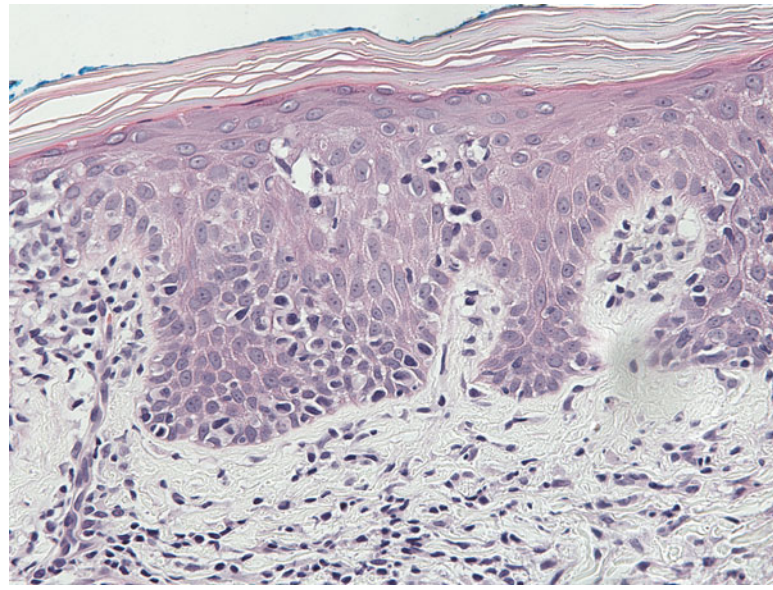

Fig. 5.16 Hypopigmented mycosis fungoides. There is lining of the basal layer by highly atypical lymphocytes and small Pautrier's microabscesses (H +E, 20×)

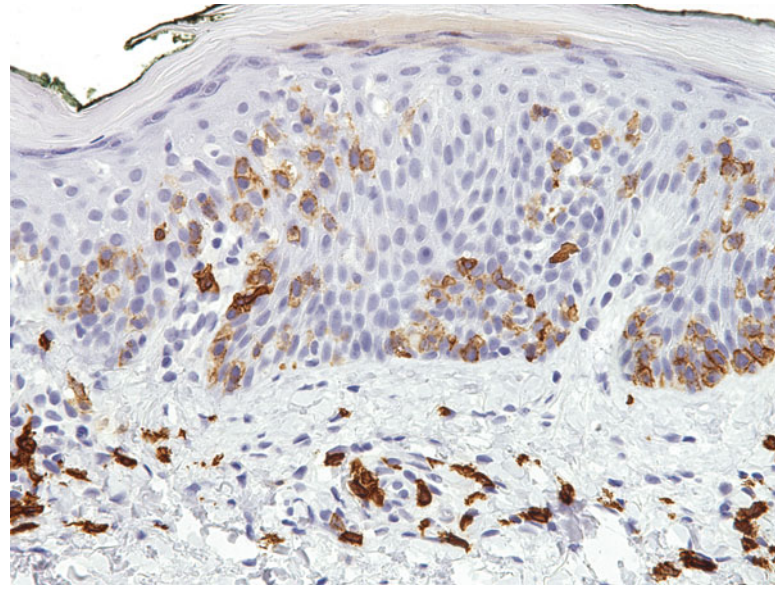

Fig. 5.17 Hypopigmented mycosis fungoides. The epidermotropic cells express CD8 (H + E, 20×)

fungoides but negative in annular lichenoid dermatitis of youth (Annessi et al. 2003; Kleikamp et al. 2008; Tsoitis et al. 2009). These findings do not overlap with CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, as those are highly aggressive nodular lymphoma lesions that do not usually occur in the pediatric population. Moreover, on histology, pronounced epidermotropism is seen. Similarly, while cutaneous gamma delta T-cell lymphoma can be CD8+ on occasion, and these are also rare, highly aggressive lymphomas that show pronounced epidermotropism and are uncommon in children.

Table 5.10 Clinical and morphologic comparisons between inflammatory vitiligo-like macules and hypopigmented mycosis fungoides

	Inflammatory vitiligo-like macules	Hypopigmented mycosis fungoides
Limited to the trunk	Yes	No
Dense lichenoid infiltrate	Yes	Yes, in lichenoid mycosis fungoides
Epidermotropism	Less common	More common (Koorse et al. 2012)
Cytologic atypia within T cells	No	Yes
Loss of melanocytes	Yes, complete	Yes, partial
Loss of pigment	Yes, total	Yes, partial
Wiry dermal collagen	No	Yes
Thickening of basement membrane	Yes	No
Phenotype of T cells	CD8	CD8
TCR clonality assays	Negative	Positive

Inflammatory Vitiligo Like Macules

Introduction and Clinical Features

In this condition, patients develop irregular symmetrical hypopigmented macules and patches on the trunk with no known antecedents, but the histopathologic findings resemble mycosis fungoides (Petit et al. 2003; El Darouti et al. 2006). The lesions contain an erythematous and papular border and can be quite large. Clinically they resemble vitiligo.

Histopathology and Immunophenotype

On histopathology, on a biopsy taken from an erythematous border, a dense band-like infiltrate is seen at the dermal epidermal junction with extensive involvement of the overlying epidermis (Petit et al. 2003). On immunohistochemistry, the lesional cells overwhelmingly express CD8, especially the intraepidermal lymphocytes. HMB-45 staining shows complete lack of melanocytes in the affected skin.

Genetics and Molecular Findings

PCR clonality assays using denaturing gradient gel electrophoresis performed on DNA isolated from the erythematous border of the lesion are negative (Petit et al. 2003).

Prognosis and Clinical Course

No changes were observed with the lesions when they were treated with PUVA; however, application of topical steroids stopped extension of the lesions and led to their diminution (Petit et al. 2003). Rebiopsy of the lesions poststeroid therapy showed regression of the infiltrate. Sun exposure did not repigment the lesions.

Differential Diagnosis

These lesions are thought to represent inflammatory vitiligo, given the loss of melanocytes and lack of preceding exposure to toxins or chemicals (Petit et al. 2003). The main differential diagnosis is hypopigmented mycosis fungoides (Tables 5.10 and 5.11) (El Darouti et al. 2006; Singh et al. 2006; Ranawaka et al. 2011; Koorse et al. 2012; Fink Puches et al. 2004). The presence of an erythematous, raised border surrounding the hypopigmented patches is an unusual finding for mycosis fungoides (Petit et al. 2003). In addition, while CD8+ T cells can be seen in both entities, T-cell clonality assays are negative in inflammatory vitiligo and positive in mycosis fungoides. Other features found to be helpful in distinguishing vitiligo from hypopigmented

Table 5.11 The differential diagnosis of hypopigmented patches in children and adolescents

	Pityriasis alba	Vitiligo	Lichen sclerosus	Hypopigmented mycosis fungoides
Common in children	Yes (Werner et al. 2005)	No	No	Yes
Distribution	Face primarily	Face, distal extremities	Primarily genitals, truncal	Sun-spared areas; in some cases, involvement of lower legs (Ngo et al. 2009)
Pigmentary status	Hypopigmented	Depigmented	Hypopigmented	Hypopigmented
Spongiosis is present	Yes, mild	Yes, mild	No, usually lichenoid	No
Cytologic atypia within T cells	No	No	No	Yes
TCR clonality assays	Negative	Negative	Positive, sometimes	Positive

mycosis fungoides include fibrosis of the papillary collagen, partial loss of pigment, and preservation of some melanocytes (all seen more commonly in mycosis fungoides). In vitiligo, complete loss of pigment, total loss of melanocytes, and thickening of the basement membrane are more common than in mycosis fungoides (El Darouti et al. 2006).

Human Immunodeficiency Virus (HIV)-Related CD8+ Atypical Skin Infiltrates

Introduction and Clinical Features

Patients with the human immunodeficiency virus (HIV) infection may suffer from a wide variety of immunologic disorders due to their profound immunosuppression (Guitart et al. 1999; Zhang et al. 1995; Weedon 1998). While many of them also develop aggressive lymphomas, a small percentage is thought to develop mycosis fungoides (Guitart et al. 1999). These have been reported to have a chronic course, similar to immunocompetent patients who develop mycosis fungoides (Burns and Cooper 1993). In addition, many develop cutaneous infiltrates that are CD8 + and mimic mycosis fungoides histologically (Zhang et al. 1995; Weedon 1998). These patients clinically can develop patches, plaques, and nodules, some of them in a photodistributed fashion, or erythroderma (Zhang et al. 1995; Weedon 1998). Bone marrow and lymph node involvement may be noted clinically (Zhang et al. 1995). Skin involvement may be widespread (Zhang et al. 1995).

Histopathology and Immunophenotype

On histology, there is a band-like infiltrate of lymphocytes at the dermal epidermal junction with epidermal involvement by lymphocytes (Fig. 5.18). In some cases, true interface activity can be seen as well as basilar lining by lymphocytes (Fig. 5.19). Follicular involvement by lymphocytes can also be seen, with focal follicular mucinosis. Some cases demonstrate syringeal involvement (Fig. 5.20). Eosinophils and dermal fibroplasia are also seen. Small Pautrier's-like microabscesses can be seen, and there is mild atypia within the lymphocytes (Fig. 5.21). The infiltrating cells were CD8 predominant in many of the cases tested, while a minority had a mixture of CD4- and CD8-expressing cells (Zhang et al. 1995; Weedon 1998). CD7 loss was seen in these cases, similar to mycosis fungoides.

Genetics and Molecular Findings

T-cell receptor gene rearrangement studies were performed in nine cases in two separate studies, and none were positive.

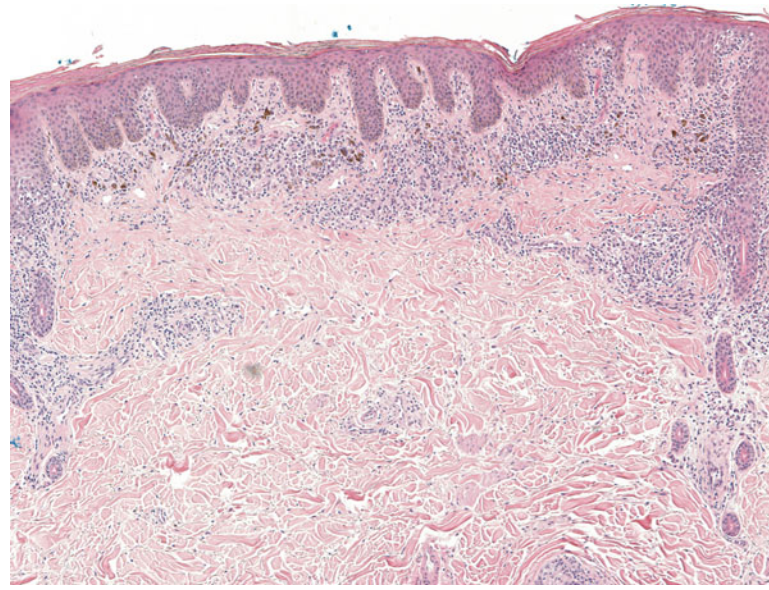

Fig. 5.18 HIV-related dermatitis. There is a band-like infiltrate of lymphocytes at the dermal epidermal junction with involvement of the overlying epidermis. There is mild hyperkeratosis of the stratum corneum (H + E, 4×)

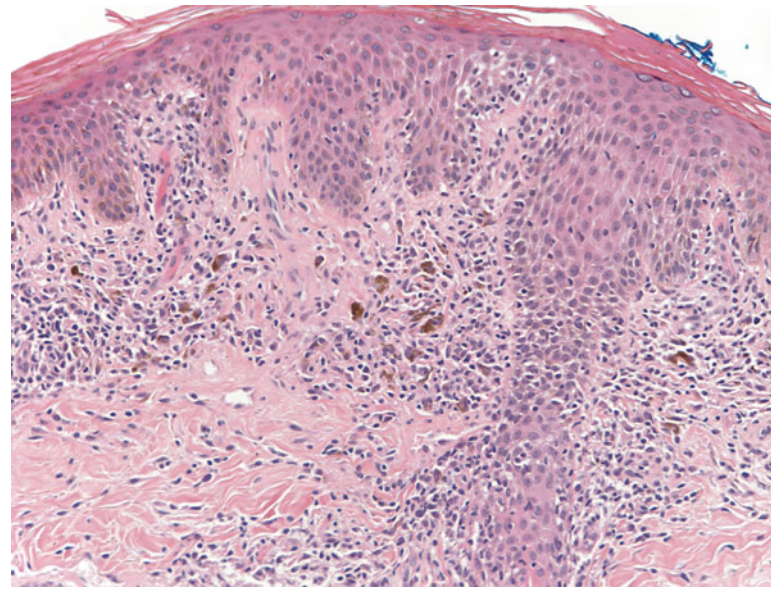

Fig. 5.19 HIV-related dermatitis. The papillary dermis is fibrotic and there is pigment dropout (H + E, 10×)

Prognosis and Clinical Course

In one well-documented study, eight of nine patients died, but this was primarily due to acquired immunodeficiency syndrome (AIDS) wasting syndrome or infection (Zhang et al. 1995). Their clinical lesions were treated with PUVA, chemotherapy, or topical steroids with partial to no response.

Differential Diagnosis

The primary differential diagnostic consideration in these cases is true mycosis fungoides, as this entity can mimic mycosis fungoides closely on histology (Table 5.12). Complicating the story is the fact that indolent mycosis fungoides can occur in patients with HIV (Guitart et al. 1999). These infiltrates differ from classic mycosis fungoides in

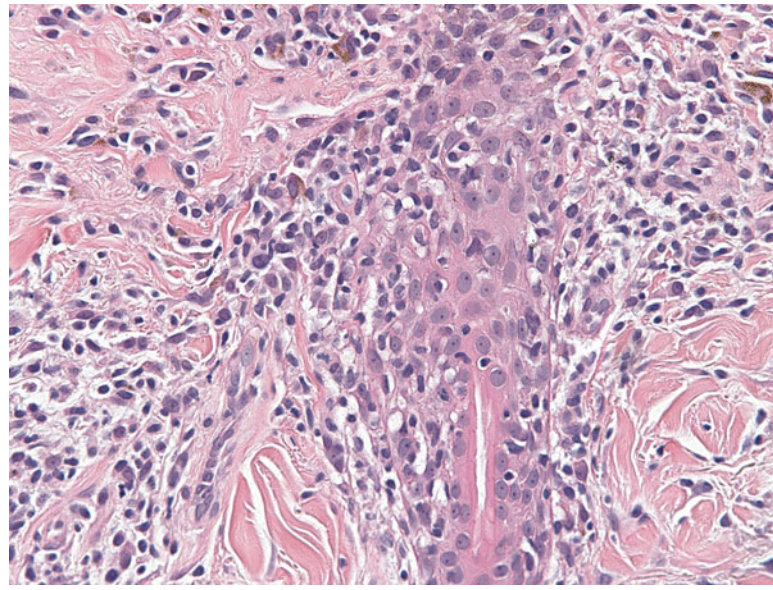

Fig. 5.20 HIV-related dermatitis. There is infiltration of the sweat duct by atypical lymphocytes (H + E, 20×)

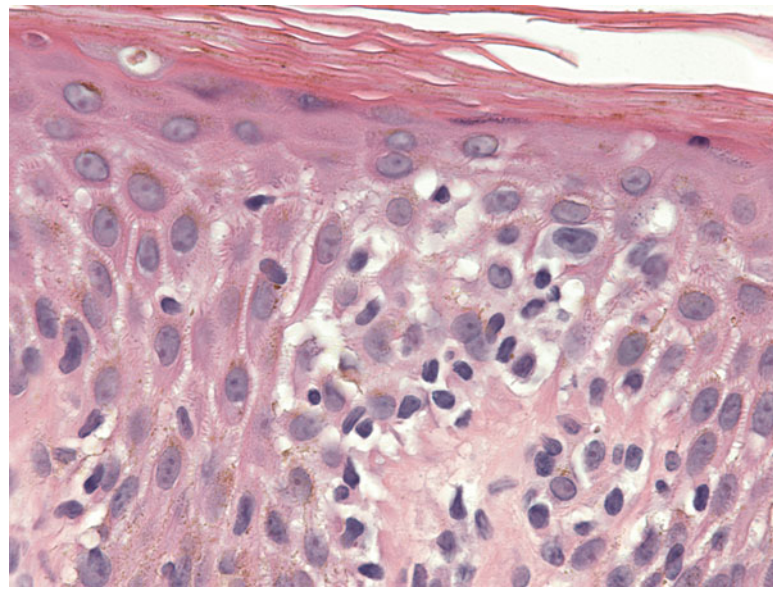

Fig. 5.21 HIV-related dermatitis. Higher power view of the lymphocytes shows nuclear hyperchromasia and small nuclear notches (H + E, 40×)

the fact that they express CD8 and do not demonstrate the presence of a T-cell clone. Another entity to consider in the differential diagnosis, given the photodistributed nature of the process in some cases, is chronic actinic dermatitis or actinic reticuloid, which is also predominantly of CD8 origin. In photodistributed cases, the distinction between HIV-related skin infiltrates and chronic actinic dermatitis may not be possible, and indeed they may represent the same entity.

Lichenoid Lupus Erythematosus

Introduction and Clinical Features

Cutaneous lupus erythematosus may be skin limited or linked to systemic lupus erythematosus (Weedon 1998). Typically, the lesions are photodistributed (head and neck, V of chest, arms), and the face is often involved (malar rash). The lesions can be large and are indurated,

Table 5.12 Clinical and morphologic comparisons between HIV-related CD8+ dermatitis and mycosis fungoides

	HIV-related CD8± dermatitis	Mycosis fungoides
Distribution	Erythroderma, extensive involvement by patches, plaques, and nodules	In advanced cases, erythroderma, extensive involvement by patches, plaques, and nodules
Photodistributed	Yes, sometimes	No
Interface dermatitis	Yes	Yes, in lichenoid mycosis fungoides
Microabscesses	Pautrier's like	Pautrier's (tumor cells)
Cytologic atypia within T cells	Yes, mild	Yes
Eosinophils	Yes	Rare
Phenotype of T cells	CD8	CD4 (except in cases of CD8-expressing MF)
T-cell receptor gene rearrangement	No	Yes

erythematous, scaly plaques. They can also present as subcutaneous nodules with little surface change (lupus panniculitis) as well as oral lesions. Serologic abnormalities can be present, and in systemic disease, the kidneys can be affected. The scalp can be affected, and a scarring alopecia can ensue. In lesions that show overlap with lichen planus (lichenoid lupus erythematosus), the lesions are large, atrophic plaques with a red to violet color, mild hyperpigmentation at the borders, and telangiectasias (Romero et al. 1977). No flat-topped papules are seen and follicular plugging is minimal. Photosensitivity is not usually seen. The lesions tend to involve the acral extremities with nail involvement being quite common.

Histopathology and Immunophenotype

On histopathology, there can be a variety of different patterns that can be present. Typically the lesions have a superficial and deep infiltrate of lymphocytes with periadnexal and perivascular accentuation. Interface activity is present and there is pigment dropout. In chronic lesions, the basement membrane is thickened and can be detected using a PASD stain. In the lichenoid variant, the infiltrate is quite dense with overlying compact hyperkeratosis, hypergranulosis, acanthosis, and necrotic keratinocytes. Necrotic keratinocytes are present within the dermis (Oliver et al. 1989), and dermal mucin is present. These areas comingled with areas that were lymphocyte poor with perivascular accentuation and little involvement of the epidermis (Romero et al. 1977; Oliver et al. 1989; Crowson and Magro 1999). Both eosinophils and plasma cells are seen. In oral lesions, the infiltrate is again band-like with numerous lymphocytes, and plasma cells are prominent. On immunohistochemistry, there is a mixture of CD4- and CD8-expressing T cells (Harvell et al. 2003). On direct immunofluorescence of involved skin, these cases tend to show both linear and granular deposition of antibody at the dermal epidermal junction of C3, IgG, IgM, and IgA.

Genetics, Molecular Findings, and Serologic Studies

While lichenoid lupus erythematosus has not been extensively studied via current molecular techniques, limited analysis of lupus erythematosus cases by T-cell receptor gene rearrangements using BIOMED 2 primers does not demonstrate a detectable clone (Zhang et al. 2010). On serology, in general, patients have a high titer of antinuclear antibodies (ANA), antibodies to DNA, and low to high titers of anti-Ro/SSA antibodies, even in skin-limited disease.

Prognosis and Clinical Course

This version of lupus erythematosus tends to be extremely long term with poor response to therapy, which includes topical and systemic

Table 5.13 The differential diagnosis of lichenoid lupus erythematosus

	Lichenoid lupus erythematosus	Chronic graft-versus-host disease	Lupus-like drug eruption	Mycosis fungoides
Acral and nail involvement	Yes	No	No	No
Necrotic keratinocytes within hair follicles	No	Yes	No	No
Dermal mucin	Yes	No	Yes	No
Microabscesses	Pautrier's like	No	No	Pautrier's (tumor cells)
Cytologic atypia within T cells	Yes	No	No	Yes
Phenotype of T cells	CD4	Mixture of CD4 and CD8	N/A	CD4
TCR clonality assays	Negative	Negative	N/A	Positive

corticosteroids, antimalarials, and immunosuppressive drugs (Romero et al. 1977).

Differential Diagnosis

The primary differential diagnosis includes lichen planus (Romero et al. 1977; Oliver et al. 1989), chronic graft-versus-host disease (Hu et al. 2012; Goiriz et al. 2008), drug eruptions (Crowson and Magro 1999), and lichenoid mycosis fungoides (Friss et al. 1995) (Table 5.13). In typical cases, lichen planus has an infiltrate limited to the dermal epidermal junction, with accompanying cytoid body formation and Max Joseph clefts. In contrast, in lupus erythematosus, the infiltrate tends to be more sparse with individual necrotic keratinocytes rather than cytoid body formation. No cleft formation is usually seen. However, there can be significant overlap between lichen planus and lichenoid lupus erythematosus in certain circumstances (Romero et al. 1977; Oliver et al. 1989), and careful clinical correlation with clinical follow-up may be the only way to distinguish between the two entities. Chronic graft-versus-host disease can have a lichenoid pattern and can rarely mimic lupus (Hu et al. 2012; Goiriz et al. 2008). The clinical setting can help distinguish between the two entities; in addition, dermal mucin deposition is not seen in lichenoid graft-versus-host disease (Goiriz et al. 2008). Drug eruptions resolve when an offending agent is removed, and this may be a good way to distinguish between a drug-related event and idiopathic lupus erythematosus (Crowson and Magro 1999). Finally, lichenoid mycosis fungoides remains within the differential. There are rare cases of cutaneous lupus pathologically mimicking mycosis fungoides reported in the literature. In these cases, atypical lymphocytes can involve the overlying epidermis with collections of Pautrier's-like microabscesses. Immunophenotypic analysis can show an overwhelming CD4 to CD8 ratio (20:1) (Friss et al. 1995). Direct immunofluorescence studies and serologic studies can help distinguish between these two entities, and TCR gene rearrangement studies should be negative in lupus and positive in mycosis fungoides (Weedon 1998).

Lichen Simplex Chronicus

Introduction and Clinical Features

Lichen simplex chronicus occurs in the context of chronic pruritus and usually overlies other inflammatory conditions such as atopic dermatitis and lichen sclerosus (Weedon 1998). Clinically, these are symmetric thick erythematous plaques with lichenification and are associated with other signs of pruritus (i.e., excoriations).

Histopathology and Immunophenotype

On histology, the epidermis is acanthotic with overlying hyperkeratosis and sometimes mild parakeratosis, usually patchy rather than diffuse. A very mild lymphocytic infiltrate usually infiltrates the epidermis, and there is underlying mild perivascular infiltrates of lymphocytes

with papillary dermal fibrosis. The collagen can demonstrate scar-like changes with vertically oriented collagen bundles and horizontally oriented vessels.

Prognosis and Clinical Course

The changes of lichenification can decrease if pruritus is controlled with emoliation and/or topical steroids.

Differential Diagnosis

The important differential diagnosis is with chronic spongiotic dermatitides, which include atopic dermatitis, contact dermatitis, id reaction, drug hypersensitivity reactions, nummular dermatitis, and arthropod hypersensitivity reactions. Cutaneous dermatophytosis can demonstrate similar findings (chronic tinea infection), and a PASD stain should be performed to exclude this possibility. Partially treated psoriasis may also show similar findings and may not demonstrate Munro's microabscesses or neutrophil transmigration; correlation with clinical findings may be necessary to exclude psoriasis. Rarely, partially treated mycosis fungoides may show overlap with lichen simplex chronicus; T-cell receptor PCR analysis, especially comparing analysis from more than one site, may help confirm the diagnosis of mycosis fungoides (Table 5.14). It is important to note that lichen simplex chronicus may be superimposed on all of the conditions listed in the differential diagnosis.

Table 5.14 Clinical and morphologic comparisons between lichen simplex chronicus and mycosis fungoides

	Lichen simplex chronicus	Mycosis fungoides
Lichenification	Present	Usually absent, unless lesions are extremely pruritic
Epidermal acanthosis	Yes	No, unless chronic, pruritic lesion
Spongiosis is present	Yes, mild	No
Cytologic atypia within T cells	No	Yes

Actinic Reticuloid

Introduction and Clinical Features

Actinic reticuloid is a chronic persistent photosensitive dermatosis that primarily affects older men and is part of the chronic actinic dermatosis group of disorders (Ploysangam et al. 1998; Ive et al. 1969; Frain-Bell and Johnson 1979; Johnson et al. 1979). It is thought to be caused by persistent exposure to sunlight, is extremely pruritic, and is often occupational in origin. The lesions are usually on the head and neck and other sun-exposed areas and are red purple, scaly, lichenoid infiltrative papules, plaques, and nodules (Ploysangam et al. 1998). Extension into areas of sun protection can be seen in severe cases. Chronic rubbing of the scalp can cause alopecia. Patients can develop lymphadenopathy, leonine facies, and erythroderma, and the findings may be difficult to distinguish from lymphoma (Neild et al. 1982; Thomsen 1977). There is evidence to suggest that actinic reticuloid may be in part due to contact allergy to plants and synthetic chemicals (Frain-Bell and Johnson 1979). Sensitivities have been demonstrated to UVB, UVA, fluorescent light, and visible light (Ploysangam et al. 1998).

Histopathology and Immunophenotype

On histology, there is psoriasiform hyperplasia and minimal spongiosis with involvement of the epidermis by lymphocytes (Ploysangam et al. 1998). On high power examination the lymphocytes are atypical with nuclear hyperchromasia and hyperconvolution, and Pautrier's-like microabscesses can be seen. The papillary dermal collagen is thickened, and there are vertically oriented collagen bundles and horizontally oriented blood vessels, similar to lichen simplex chronicus. The blood vessels have thickened

walls, and plump fibroblasts are present within the dermis. Immunophenotyping shows the infiltrate to be composed of CD8-expressing T cells (Bakels et al. 1998).

Genetics and Molecular Findings

Analysis of cases of actinic reticuloid and cases of Sézary syndrome showed that T-cell receptor clonality assays were positive in the skin and peripheral blood of patients with Sézary syndrome but not in patients with actinic reticuloid (Bakels et al. 1998).

Table 5.15 Clinical and morphologic comparisons between actinic reticuloid and mycosis fungoides

	Actinic reticuloid	Mycosis fungoides
Sun-exposed areas	Yes	No
Gender and age restricted	Yes, older males	No
Spongiosis is present	Yes, very mild	No
Microabscesses	Pautrier's microabscess-like collections	Pautrier's (tumor cells)
Cytologic atypia within T cells	Yes	Yes
Phenotype of T cells	CD8	CD4
TCR clonality assays	Negative	Positive

Prognosis and Clinical Course

In general, actinic reticuloid runs a chronic clinical course and does not respond to typical therapies of photosensitive disorders (Ploysangam et al. 1998). Strict photorestriction is paramount as is avoidance of all possible responsible contactants, and patients are encouraged to regularly apply topical sun protection or wear protective clothing and hats. Combinations of photochemotherapy, topical and systemic corticosteroids, azathioprine, and cyclosporine have been reported to be beneficial. Rarely patients with actinic reticuloid have developed lymphoma, and it is unclear whether these cases represent true lymphomas that were initially misdiagnosed as actinic reticuloid or actinic reticuloid undergoing malignant transformation (Neild et al. 1982; Thomsen 1977; De Silva et al. 2000). In one study of two patients, over a period of years after the initial diagnosis of actinic reticuloid, the patients developed what appeared to be erythroderma, patches and plaques consistent clinically with mycosis fungoides (De Silva et al. 2000). They also acquired a TCR clone in their skin biopsies, but peripheral blood remained negative for TCR clonality assays. The dermal infiltrates continued to be CD8+, however. Both patients developed lymphadenopathy which showed dermatopathic changes and had a negative clone. The authors speculate that these two cases may represent either extensive actinic reticuloid or so-called photosensitive mycosis fungoides.

Differential Diagnosis

The most important differential diagnostic consideration is with mycosis fungoides, and indeed, there is controversy in the literature regarding whether photosensitive mycosis fungoides exists or if it represents a clone positive version of actinic reticuloid (Table 5.15). The cases described in the literature of photosensitive mycosis fungoides arising in the context of actinic reticuloid are particularly interesting, as they are of CD8 origin, which is unlike 95 % of all cases of mycosis fungoides described (De Silva et al. 2000). Therefore, one could surmise that immunophenotyping and T-cell clonality assays may help distinguish actinic reticuloid from mycosis fungoides and Sézary syndrome in nearly all cases, as mycosis fungoides/Sézary syndrome should be of CD4 origin and harbor a T-cell clone, and actinic reticuloid should be of CD8 origin and be negative in a TCR clonality assay (Bakels et al. 1998). Very rare cases of actinic reticuloid that develop a widespread eruption may either be unusual clone positive versions of actinic reticuloid or true photosensitive mycosis fungoides, initially misdiagnosed as actinic reticuloid.

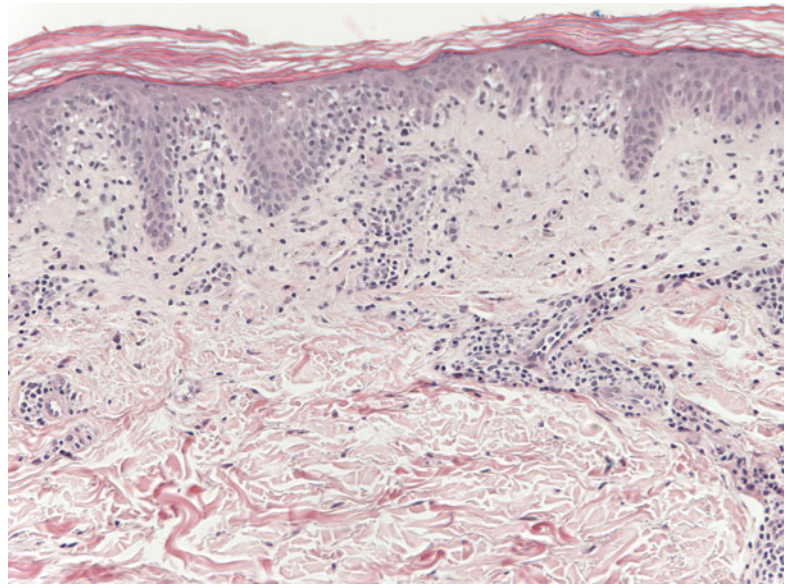

Fig. 5.22 Pityriasis lichenoides chronica. A patchy lymphocytic infiltrate is present in the papillary dermis with involvement of the overlying epidermis (H + E, 4×)

Pityriasis Lichenoides Chronica/ Pityriasis Lichenoides et Varioliformis Acuta

Introduction and Clinical Features

Pityriasis lichenoides chronica (PLC) shares a spectrum of findings with its acute clinical counterpart, pityriasis lichenoides et varioliformis acuta (PLEVA) (Weedon 1998). This papulosquamous eruption can affect all ages, involves the trunk and extremities, is primarily asymptomatic, and resolves without treatment, leaving behind an atrophic or varioliform scar (Magro et al. 2002). The crops of papules form continuously and last weeks to months before resolution. It is not unusual to see many lesions in different stages of evolution on the patient at one time. The lesions have a red-brown color upon initial formation and an adherent mica-like scale (Magro et al. 2002). The disease process itself may persist for years. PLEVA is more common in children, and the lesions are erythematous, variably purpuric papules with crusting and ulceration (Magro et al. 2002). In patients who eventually developed mycosis fungoides, a second clinical population of larger arcuate plaques was also present.

Histopathology and Immunophenotype

On histology, pityriasis lichenoides tends to show both a lichenoid and a spongiotic pattern (Sarantopoulos et al. 2013; Weedon 1998). The overlying stratum corneum shows mounds of parakeratosis, and there can be extensive lymphocyte involvement of the epidermis (Fig. 5.22). Extravasation of erythrocytes is often seen and can be present within the epidermis. There is basal vacuolar alteration and necrotic keratinocytes at the dermal epidermal junction, as well as intraepidermal collections of Langerhans cells as well as Pautrier's microabscess-like collections of lymphocytes (Fig. 5.23). A band-like infiltrate is present within the dermis. Lesions of PLEVA tend to have a deeper and dense infiltrate with ulceration. On immunophenotyping, the infiltrating lymphocytes have been reported to be predominantly CD4+ (Magro et al. 2002) and CD8+ (Fig. 5.24), in different series. In a series studied by Magro et al., small CD8+ T cells accompanied larger CD4+ intraepidermal T cells, and these smaller cells co-expressed CD56. Large atypical cells, often CD30+, can accompany the lesions of PLEVA.

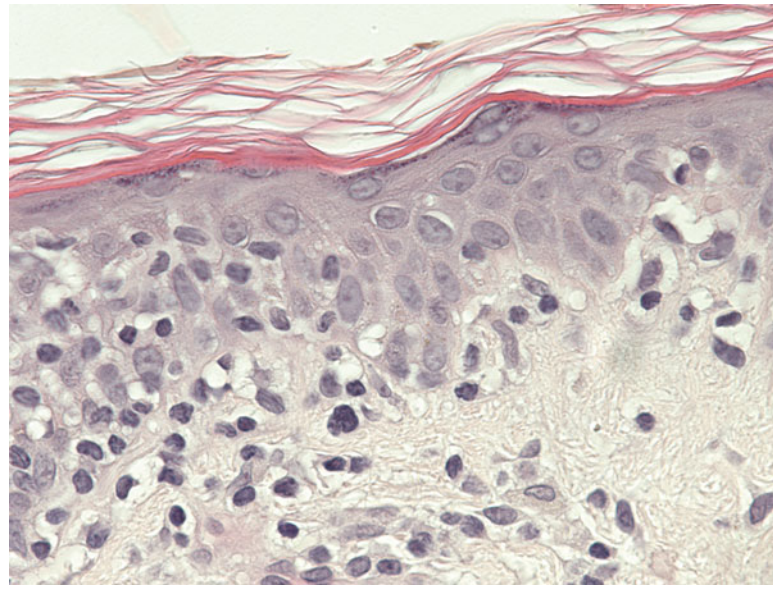

Fig. 5.23 Pityriasis lichenoides chronica. High power examination shows intraepidermal involvement by atypical lymphocytes with nuclear hyperchromasia, ovoid nuclei, and some notched nuclei (H + E, 40×)

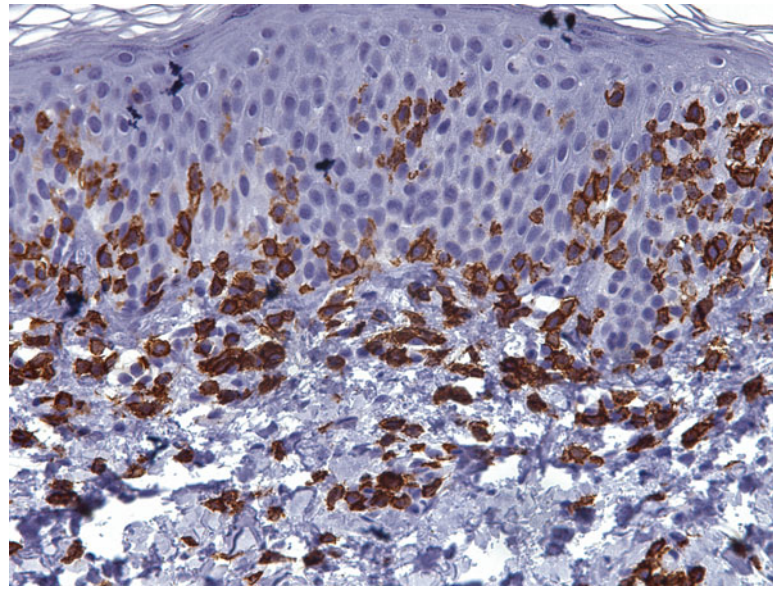

Fig. 5.24 Pityriasis lichenoides chronica. The infiltrate strongly expresses CD8 (H + E, 20×)

Genetics and Molecular Findings

Significant research has been done on the molecular characteristics of pityriasis lichenoides (Magro et al. 2002, 2007a, b; Panhans et al. 1996; Weiss et al. 1987; Dereure et al. 2000; Wang et al. 2007; Ko et al. 2000; Shieh et al. 2001; Weinberg et al. 2002). In the study of Magro et al., 25 of 27 cases of PLEVA and PLC in which amplifiable DNA could be found yielded a T-cell receptor clone. In addition, the authors detected the same clone in three different sites in at least one patient, which offers some evidence that PLC/PLEVA may (at least in some cases) represent a pre-lymphoma

state (Magro et al. 2002). These findings were subsequently duplicated in a follow-up prospective study which used current BIOMED 2 protocols for TCR β analysis (Magro et al. 2007a, b). In smaller studies of PLC in an adult and in three children, TCR clonality assays yielded a positive clone (Wang et al. 2007; Ko et al. 2000).

Prognosis and Clinical Course

By and large, the lesions of PLC and PLEVA have a chronic clinical course but remit over time. They show responsiveness to potent topical corticosteroids (Wang et al. 2007), PUVA (Ko et al. 2000) and chemotherapeutic agents such as methotrexate. In many studies of PLC and PLEVA, a proportion of patients have developed mycosis fungoides (Magro et al. 2002, 2007a, b; Ko et al. 2000; Boccara et al. 2012; Fortson et al. 1990). In some studies, there is some doubt as to whether the lesions studied are actually those of mycosis fungoides, since the lesions seem to have the clinical features of PLC but the histologic features of mycosis fungoides (Wang et al. 2007; Ko et al. 2000; Boccara et al. 2012). However, in the studies of Magro et al., the authors do have patients that develop the more characteristic patches of mycosis fungoides (Magro et al. 2002, 2007a, b). Therefore, it does seem prudent to follow all PLC/PLEVA patients over time, to ensure that they do not develop mycosis fungoides (Shieh et al. 2001; Pileri et al. 2012; Fraitag et al. 2012).

Differential Diagnosis

Given the lichenoid pattern of the infiltrate, entities within the lichenoid/interface differential diagnosis should also be considered, such as lichen planus, erythema multiforme, lichenoid/interface drug eruption, connective tissue disease, graft-versus-host disease, and fixed drug eruption. The clinical findings in lichen planus, erythema multiforme, fixed drug eruption, and connective tissue disease are quite distinctive and will serve to exclude these possibilities. In addition, the lack of preexisting transplantation and a careful search for offending drug agents should result in excluding graft-versus-host disease and drug eruptions, respectively. Spongiotic processes also enter into the differential, but can usually be excluded if extravasation of erythrocytes is prominent. Entities such as pityriasis rosea and pigmented purpuric dermatoses are harder to exclude, but their characteristic clinical findings should help place them further down on the differential. The distinction between lymphomatoid papulosis (Lyp) and PLEVA is particularly challenging, especially as both demonstrate expression of CD30 (Kempf et al. 2012). However, lesions of Lyp have a polymorphous population of cells, including neutrophils, eosinophils, and plasma cells, and lesions of PLEVA are often quite monomorphous and composed primarily of lymphocytes (Magro et al. 2002). Many lesions of PLC can closely mimic mycosis fungoides histologically, and T-cell receptor gene rearrangements can be positive, even on multiple biopsies (Table 5.16). The clinical setting would be very useful, as lesions of mycosis fungoides are usually patches, plaques, or tumors, and lesions of PLC tend to be regressing papules (an unusual presentation for mycosis fungoides). Also, intraepidermal lymphocytes in PLC tend to be a combination of CD4- and CD8-expressing T cells, whereas the intraepidermal lymphocytes in mycosis fungoides tend to be almost purely of CD4 origin. However, it is important to remember that at least in some cases, patients with PLC do develop mycosis fungoides, and as such, cases of PLC would benefit from long-term clinical follow-up.

Langerhans Cell Hyperplasia

Introduction and Clinical Features

Langerhans cells are important members of the skin immune system and are known to play a role during the induction phase of adaptive immune responses (Pigozzi et al. 2006). Langerhans cells and dermal dendritic cells are professional antigen-processing and antigen-presenting cells and express CD1a in high quantities. CD1-expressing cells primarily present lipid antigens for recognition by T cells

Table 5.16 Clinical and morphologic comparisons between pityriasis lichenoides chronica, pityriasis lichenoides et varioliformis acuta, and mycosis fungoides

	Pityriasis lichenoides chronica	Pityriasis lichenoides et varioliformis acuta	Mycosis fungoides
Common in children	No	Yes	No
Appearing and resolving in crops	Yes	Yes	No
Ulcerating, hemorrhagic lesions	No	Yes	No
Morphology of lesions	Papules, some plaques	Ulcerating hemorrhagic nodules	Patches, plaques, tumors
Lichenoid pattern	Yes	Yes	Yes, in lichenoid MF
Microabscesses	Pautrier's-like microabscesses, Langerhans' cell microabscesses	Pautrier's-like microabscesses, Langerhans' cell microabscesses	Pautrier's (tumor cells)
Lymphocytic involvement of epidermis	Yes, mild spongiosis	Yes, mild spongiosis	Yes, mild spongiosis
Extravasation of erythrocytes	Yes	Yes	Yes, in PPE-like MF
Cytologic atypia within T cells	Yes	Yes	Yes
Phenotype of T cells	Mixture of CD4 and CD8, in some cases CD8 predominates (Magro et al. 2002, 2007a, b)	Mixture of CD4 and CD8, in some cases CD8 predominates	CD4
Loss of CD5	Yes, subpopulation of cases (Magro et al. 2002)	Yes, subpopulation of cases	Yes
TCR clonality assays	Positive, especially in cases with atypical T cells	Positive, especially in cases with atypical T cells	Positive

and often populate infiltrates that are T-cell rich (McClain et al. 2004). Langerhans cell hyperplasia can be seen in many T-cell rich reactive entities, such as scabies (Bhattacharjee and Glusac 2007), contact dermatitis (Drut et al. 2010), lichen planus, psoriasis, atopic dermatitis, and pityriasis lichenoides chronica. It can also be seen in mycosis fungoides (Christie et al. 2006) and lymphomatoid papulosis (Jokinen et al. 2007).

Histopathology and Immunophenotype

On histology, numerous Langerhans cells are noted within the dermis and the epidermis. The Langerhans cells form microabscesses within the epidermis. Depending on the associated disorder, the epidermis can also show acanthosis, hyperkeratosis, and spongiosis. There can be a band-like infiltrate within the dermis, and the infiltrate can extend to involve the deeper reticular dermis. The infiltrate can be composed of lymphocytes, eosinophils, and plasma cells, as well as Langerhans cells and dermal dendritic cells. Scabetic mites may be identifiable in lesions of scabies.

Prognosis and Clinical Course

The prognosis and clinical course of the lesions depend on the underlying etiology. If treated appropriately, the lesions (such as those associated with scabies) resolve and do not persist, unlike lesions of mycosis fungoides. Lesions of lymphomatoid papulosis have a relapsing and remitting course but will respond to methotrexate.

Differential Diagnosis

The important differential diagnostic considerations include both Langerhans cell histiocytosis (LCH) and mycosis fungoides (Table 5.17). There

Table 5.17 Clinical and morphologic comparisons between Langerhans cell hyperplasia and mycosis fungoides

	Langerhans cell hyperplasia	Mycosis fungoides
Associated with scabies	Yes	No
Associated with CD1a + Langerhans cells	Yes	Yes, seldom
Spongiosis is present	Yes	No
Microabscesses	Langerhans cell	Pautrier's (tumor cells)
Cytologic atypia within T cells	No	Yes

is debate within the literature as to the benign or malignant nature of Langerhans cell histiocytosis, which renders more difficult our ability to distinguish between Langerhans cell hyperplasia seen in association with other entities and Langerhans cell histiocytosis (McClain et al. 2004; Murphy 1985). An underlying etiology should always be searched for histologically, including scabetic mites, the band-like infiltrate of lichen planus, Munro's microabscesses of psoriasis, significant epidermal spongiosis, and red blood cell extravasation. Careful clinical correlation is crucial to ensure that the lesion being treated is that of LCH and not a hyperplastic process. Children with LCH have a characteristic clinical setting: the lesions are composed of yellow-brown papules which appear on the face, trunk, and buttocks and can coalesce to form an eruption that resembles seborrheic dermatitis. Involvement of the bone and systemic symptoms can both be present. Histologically Langerhans cell hyperplasia can also resemble mycosis fungoides, especially when it is present in the context of lichen planus, psoriasis, and atopic dermatitis. Correlation with clinical findings and histologic examination of the cytology of the T cells can both be very helpful in excluding mycosis fungoides.

Reactive Erythroderma

Introduction and Clinical Features

Erythroderma (exfoliative dermatitis) is characterized by near complete erythema of the skin (over 90 %) accompanied by scaling (Sigurdsson et al. 1996; Yuan et al. 2010; Vonderheid 2006). The patients often have intractable pruritus and can sometimes have fever, lymphadenopathy, peripheral blood changes, alopecia, palmar hyperkeratosis, pitting edema, and nail changes. In one study of 82 patients, erythroderma was most often reactive in nature (95 %) and psoriasis was a common culprit (48 %) (Yuan et al. 2010; Vonderheid 2006). Reactive erythroderma can also be caused by seborrheic dermatitis (12 %), atopic dermatitis (22 %), contact dermatitis (9 %), id reaction, pityriasis rubra pilaris (4 %), drug eruptions (14 %), and photoreactions (such as chronic actinic dermatitis or actinic reticuloid (3 %). Less common reactive causes include dermatomyositis, sarcoidosis, hypereosinophilic syndrome, congenital ichthyosiform erythroderma, pemphigus foliaceus, and stasis dermatitis (Yuan et al. 2010; Vonderheid 2006). Erythroderma can also be paraneoplastic or caused by mycosis fungoides/Sézary syndrome or leukemia cutis (chronic lymphocytic leukemia). The patients are commonly men (Sigurdsson et al. 1996), and serum IgE levels were often elevated. In most instances, distinction between patients involved by reactive erythroderma and erythroderma caused by a malignancy was not possible by routine clinical examination, unless patients also have superimposed tumors and infiltrative plaques and leonine facies, which would favor lymphoma.

Histopathology and Immunophenotype

The histopathology can be very variable and reflect the underlying pathophysiology. For example, patients with erythrodermic psoriasis, seborrheic dermatitis, and pityriasis rubra pilaris often have psoriasiform epidermal hyperplasia, diffuse or alternating parakeratosis, and neutrophilic transmigration (in the case of psoriasis). Erythroderma due to contact or atopic dermatitis, drug hypersensitivity reaction, and id hypersensitivity reaction can also show psoriasiform changes but may have accompanying mild spongiosis and eosinophils. Erythroderma due to a paraneoplastic syndrome may have very nonspecific findings,

similar to that described above. While erythroderma due to advanced erythrodermic mycosis fungoides and Sézary syndrome may be easily diagnosed on histopathology due to the presence of atypical T cells, early lesions can be extremely difficult and show significant overlap histopathologically with reactive erythroderma (Vonderheid 2006). The histologic findings in chronic actinic dermatitis may show significant overlap with other entities in the reactive erythroderma group, and those of actinic reticuloid will show overlap with mycosis fungoides/Sézary syndrome. On immunophenotyping, T cells in many of the entities listed above (except actinic reticuloid) can show a CD4+ T-cell predominance, and cells of mycosis fungoides and Sézary syndrome will show an aberrant T-cell phenotype, such as loss of CD5 and CD2. The T cells in actinic reticuloid are of CD8 origin. In general, however, use of histology and immunohistochemistry to distinguish between early lesions of mycosis fungoides/Sézary syndrome in an erythrodermic patient and reactive erythroderma was not found to be useful by Vonderheid (2006). The lymph node biopsy often shows dermatopathic changes in reactive cases and can also show involvement by lymphoma if the cause of erythema is mycosis fungoides or Sézary syndrome.

Genetics, Molecular Findings, and Peripheral Blood Analysis

Examination of the peripheral blood is crucial in cases of erythroderma, which can often show an elevated erythrocyte sedimentation rate (ESR), increased white blood cell count, high level of C-reactive protein, and eosinophilia (Sigurdsson et al. 1996; Yuan et al. 2010). Atypical cerebriform lymphocytes (Sézary cells) may be present even in cases of reactive erythroderma. However, >20 % of the lymphocyte population or an absolute count of >1.0 K/uL can both indicate involvement by leukemia. Rarely, a high count of Sézary cells can be seen in reactive erythroderma (Vonderheid 2006), and the diagnosis should be confirmed to be reactive based on clinical findings. In addition, patients with Sézary syndrome have other abnormal blood findings. They may have a CD4/CD8 ratio >10, loss of CD7, evidence of a T-cell receptor gene rearrangement clone, or a chromosomally abnormal T-cell clone, and these would all be very unusual findings in reactive erythroderma. In addition, flow cytometry is used often to distinguish between reactive and malignant erythroderma. Malignant Sézary cells often have diminishment or loss of CD3, CD4, CD2, and CD5. In addition, loss of CD7 and CD26 has both been found to be present more often in malignant Sézary cells, and expansion of this group of atypical lymphocytes to amounts greater than 30–40 % of total number of lymphocytes is a significant finding that points to leukemia. Flow cytometric analysis of expression of Vβ proteins can also be performed, as restricted Vβ expression has been linked to Sézary syndrome; however, this finding is not thought to be specific (Vonderheid 2006; Russell Jones and Whittaker 1999). Molecular analysis of both skin and blood has been extensively studied in Sézary syndrome. Southern blot analysis was the approach of choice for analysis of the peripheral blood for T-cell receptor clones and was quite useful, as the detection threshold was relatively high (1–5 %). Using this method, detection of clones in reactive erythroderma was rare (Vonderheid 2006). PCR methodologies are used more commonly now; as these techniques are more sensitive, both reactive erythroderma and Sézary syndrome have been shown to demonstrate clones (Vonderheid 2006). In the skin, Southern blot detection of T-cell receptor clones is virtually diagnostic of Sézary syndrome, as this method does not usually detect clones in skin biopsies of reactive erythroderma. However, as in blood, PCR analysis for T-cell receptor gene rearrangement clones has replaced Southern blotting, primarily due to the fact that a lot of material is needed for Southern blot analysis and skin biopsies are small. However, given increased sensitivity with PCR analysis, false-positive results are often encountered (up to 25 %), as are false-negative results (Vonderheid 2006; Zhang et al. 2010). For this reason, clones detected in the skin are often compared to those in blood and vice versa for the most specific results in excluding reactive erythroderma. If matching clones are found, the results are indicative of Sézary syndrome, but it is important to note that such findings

Table 5.18 Clinical and morphologic comparisons between reactive erythroderma and erythrodermic mycosis fungoides/Sézary syndrome

	Reactive erythroderma	Erythrodermic mycosis fungoides/ Sézary syndrome
Ectropion	No	Yes
Alopecia	Yes	Yes
Associated skin lesions such as tumors, infiltrative plaques, and/or leonine facies	No	Yes
Spongiosis is present	Yes, mild	Yes, mild
Necrotic keratinocytes	Yes	Yes
Microabscesses	Langerhans cell	Pautrier's (tumor cells)
Cytologic atypia within T cells	No	Yes, but can be mild
Phenotype of T cells	CD4 (except in cases of actinic reticuloid)	CD4
Abnormalities in peripheral blood	Yes, low percentage of patients	Yes, high percentage of patients
Matching clones in the skin and blood	Very rare	Common

can also be seen in reactive erythroderma about 5 % of the time (Vonderheid 2006).

Prognosis and Clinical Course

While the prognosis of patients with reactive erythroderma is generally good, interestingly, men with reactive erythroderma were found to have a statistically significant shorter survival rate than age-matched men in the general population (Sigurdsson et al. 1996). The reason for this finding is unclear. Most patients with reactive erythroderma improved when their symptoms were treated and causes for the erythroderma removed (i.e., via drug withdrawal or sun protection) (Sigurdsson et al. 1996; Yuan et al. 2010).

Differential Diagnosis

The main differential diagnostic consideration is with erythrodermic mycosis fungoides and Sézary syndrome (Table 5.18). Patients with lymphoma or leukemia often have other skin lesions that would not be seen in reactive processes, such as tumors or leonine facies. Ectropion is also a good indicator of Sézary syndrome. In advanced cases, large atypical cells are seen in skin biopsies and peripheral blood of patients with Sézary syndrome. However, in early cases, the distinction between Sézary syndrome and reactive erythroderma is still quite difficult. Factors that favor Sézary syndrome include abnormalities in the peripheral blood demonstrated via morphology and flow cytometry of the T-cell population and matching T-cell receptor clones between skin and blood or skin, blood, and involved lymph nodes. Matching clones found over time in various synchronous or serially biopsied skin can also be helpful in confirming the diagnosis of Sézary syndrome.

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