T-Cell Pseudolymphoma Presenting in a Lichenoid and Nodular Pattern

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Lichenoid Keratosis

Introduction

Lichenoid keratosis (LK), otherwise known as lichen planus-like keratosis and benign lichenoid keratosis, was first described in 1966 by Lumpkin and Helwig as a solitary form of lichen planus (LP) (Lumpkin and Helwig 1966). Ackerman later that year described lesions as lichen planus-like keratosis in distinction with lichen planus (Shapiro and Ackerman 1966). LK is a common cutaneous entity that is often clinically confused with cutaneous malignancies such as basal cell carcinoma and squamous cell carcinoma. The pathogenesis is thought to involve a chronic inflammatory-mediated involution of a preexisting lentigo.

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Clinical Features

Epidemiology

LKs develop between the ages of 36 and 87 years with an average of 59.5 years. The gender distribution in a study of 1,040 cases included 760 females (76 %) and 250 males (24 %) with the majority of lesions occurring in Caucasians (Berger et al. 1984; Morgan et al. 2005).

Clinical Appearance of Lesions

LKs present as solitary pink to red-brown, often scaly, papules ranging from 5 to 20 mm in diameter (Morgan et al. 2005; Prieto et al. 1993). LKs are usually asymptomatic or mildly pruritic and resemble basal or squamous cell carcinoma. Lesions most commonly appear on the trunk and extremities with less frequent occurrences on the head and neck (Bolognia and Jorizzo 2008a; Morgan et al. 2005).

Histopathology

Pattern of Infiltration

LK typically consists of a pronounced band-like lichenoid chronic inflammatory infiltrate nearly indistinguishable from LP (Fig. 8.1a). LK may also

H.D. Cualing et al. (eds.), *Cutaneous Hematopathology*,
DOI 10.1007/978-1-4939-0950-6_8, © Springer Science+Business Media New York 2014

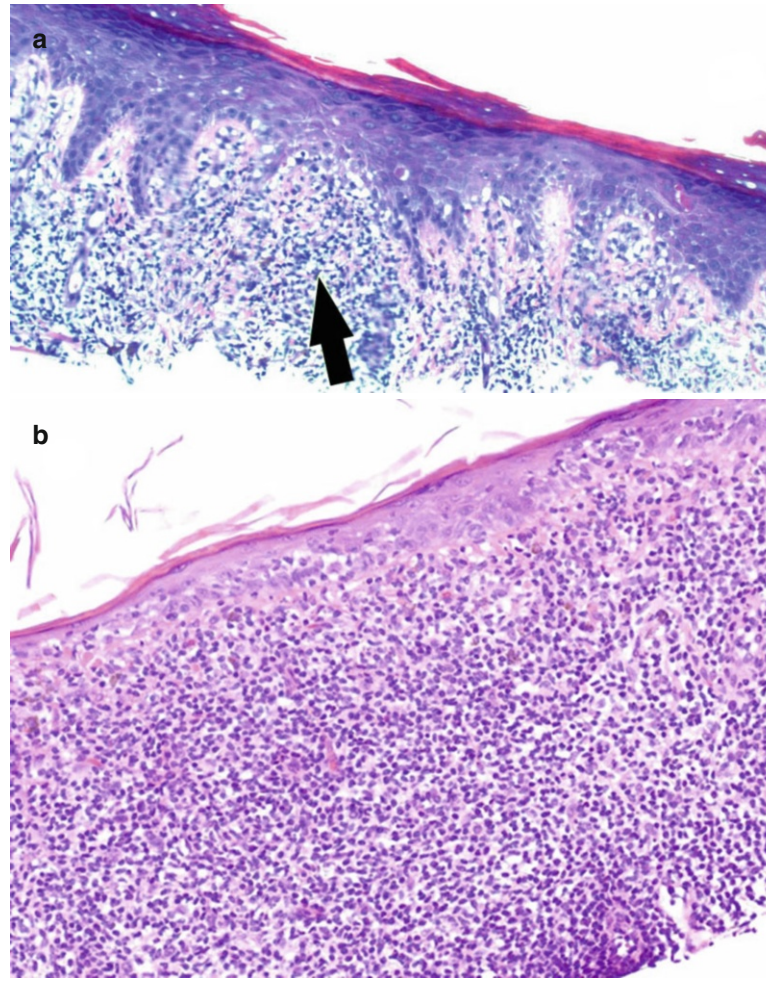

Fig. 8.1 (**a**) Lichenoid keratosis showing pronounced band-like (*arrow*) lichenoid chronic inflammatory infiltrate with exocytosis. (**b**) Lichenoid keratosis showing dense lichenoid and nodular lymphoid infiltrates

consist of dense lichenoid and nodular lymphoid infiltrates (Fig. 8.1b). As in LP, the epidermis often shows necrotic basilar keratinocytes, epidermal acanthosis, hypergranulosis, and hyperkeratosis (Fig. 8.2). Histological features that differentiate LK from LP include epidermal parakeratosis, an inflammatory infiltrate containing scattered eosinophils and plasma cells, and flanking epidermal foci of lentigo (Fig. 8.3) (Glaun et al. 1996; Jang et al. 2000; Prieto et al. 1993). The lesions of LK are classically divided into one of five histological variants, which include (1) classic form consisting of epidermal acanthosis and hyperkeratosis with an intense lichenoid lymphocyte-predominant inflammatory infiltrate and flanking epidermal foci of lentigo; (2) bullous form consisting of intra- or subepidermal nonacantholytic bullous cavities with a dense associated lymphocytic infiltrate; (3) an atypical form most readily confused with T-cell lymphoproliferative disorder and consisting of rare (less than 5 %) atypical lymphocytes defined by enlarged, hyperchromatic, and irregularly contoured nuclei that are CD3+ and CD30+ (Fig. 8.4); (4) early or interface form consisting of slightly acanthotic or normal epidermal thickness with lymphocytes aligned along the dermoepidermal junction and adjacent lentigo; (5) and atrophic or senescent form consisting of epidermal atrophy with papillary dermal scarring, patchy lymphocytic infiltrates, and melanin incontinence (Morgan et al. 2005).

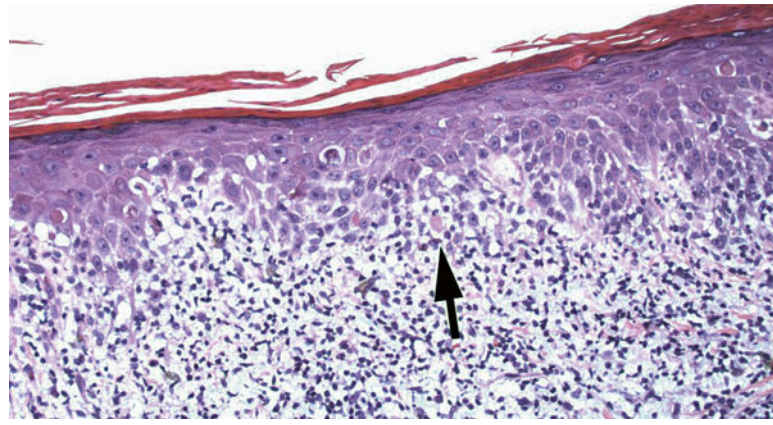

Fig. 8.2 Lichenoid keratosis showing necrotic basilar keratinocytes and exocytosis (*arrow*)

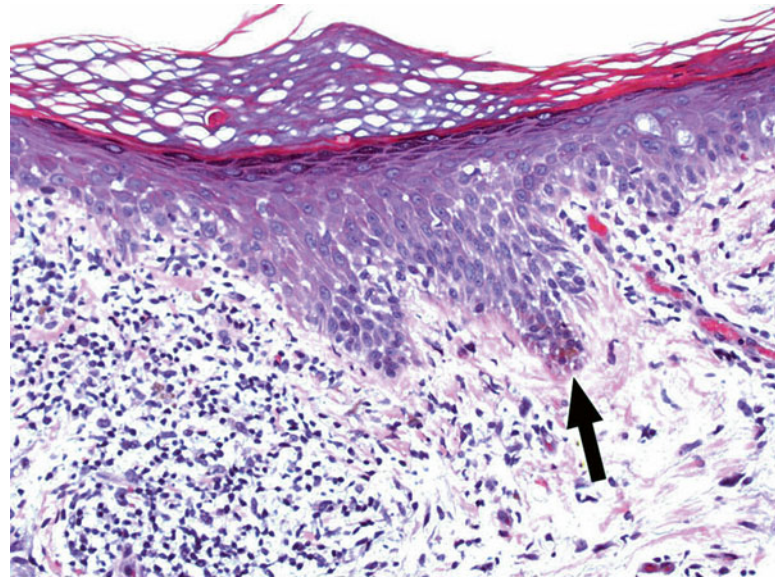

Fig. 8.3 Lichenoid keratosis showing distinguishing characteristics of epidermal parakeratosis, an inflammatory infiltrate containing scattered eosinophils and plasma cells, and flanking epidermal foci of lentigo (*arrow*)

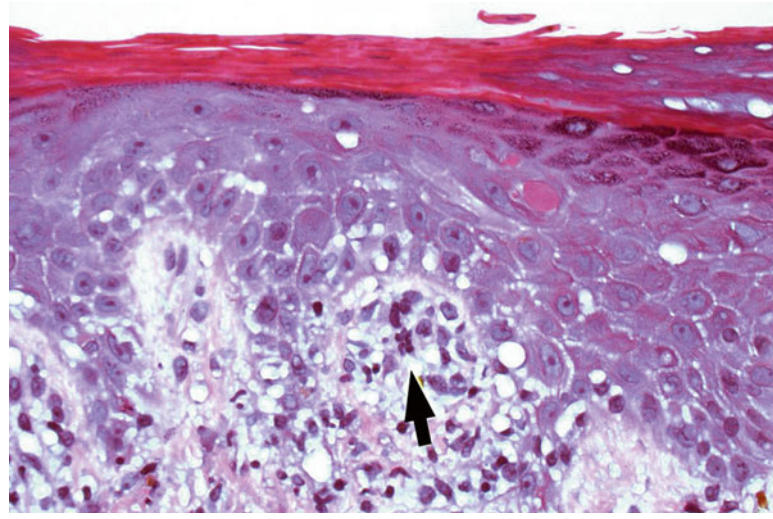

Fig. 8.4 LK showing atypical lymphocytes (*arrow*)

Cytomorphology

In a study of 1,040 cases of BLK, the classic form contained at least one apoptotic or Civatte body in every case (Morgan et al. 2005). The bullous form consists of more conspicuous numbers of apoptotic keratinocytes than the classic form associated with intraepidermal blister formation and subepidermal vesiculation (Morgan et al. 2005). The atypical form contains atypical lymphocytes characterized by enlarged, hyperchromatic, and irregularly contoured nuclei (Morgan et al. 2005).

Immunophenotype

An immunohistochemical study by Jang et al. of 17 patients diagnosed with LK revealed infiltrated epidermal and dermal lymphocytes of mainly CD8+ T cells and partly CD20+ B cells. CD4+ T cells were scarce in LK and cutaneous lymphocyte-associated antigen (CLA) was negative (Jang et al. 2000).

Genetics and Molecular Findings

A polyclonal population of cells was demonstrated by TCR gamma chain rearrangement analysis of 10 cases of benign LK (Smith et al. 2002).

Clinical Course

Clinical examination may not be able to differentiate LK from a solitary malignancy or inflammatory lesion; therefore, a biopsy is recommended. Lesions are usually removed with biopsy. Due to the benign nature of LK, remaining lesions may not require further surgery and may remain stable or undergo spontaneous regression.

Differential Diagnosis

LK can clinically mimic basal or squamous cell carcinoma, actinic keratosis, irritated seborrheic keratosis, melanoma, and nevus. Thus, a biopsy is warranted for accurate diagnosis of LK.

Lichen Aureus

Introduction

Lichen aureus (LA) is a rare variant of chronic pigmented purpuric dermatosis (PPD) first described by Marten in 1958 (Marten 1958). The PPD are a group of skin disorders with overlapping clinical and histopathological features (Graham et al. 1984; Newton and Raimer 1985; Ratnam et al. 1991). The etiologies of PPDs are unknown and the most common variant is Schamberg disease. Cutaneous T-cell lymphoma may begin with clinical lesions that resemble PPDs; thus, clinical and histopathological data is required for diagnosis.

Clinical Features

Epidemiology

Etiology of LA is unknown and lesions commonly occur in young adults and less frequently in children.

Clinical Appearance of Lesions

LA lesions present as one or multiple asymptomatic or mildly pruritic, golden- to rust-colored macules or lichenoid papules. The macules may coalesce into a patch and commonly appear on the lower extremities of young adults. Lesions have also been reported to occur on the trunk, upper extremity, and glans penis (English 1985; Kossard and Shumack 1989; Rudolph 1983). Lesions are frequently unilateral and persist unchanged for years (Graham et al. 1984; Price et al. 1985).

Histopathology

Pattern of Infiltration

LA is characterized by a dense band-like histiocytic and lymphocytic infiltration in the upper dermis; extravasation of erythrocytes and iron pigment in the histiocytes are often noticed. Early LA consists of a lymphocytic capillaritis with extravasated erythrocytes (Fig. 8.5) with mature

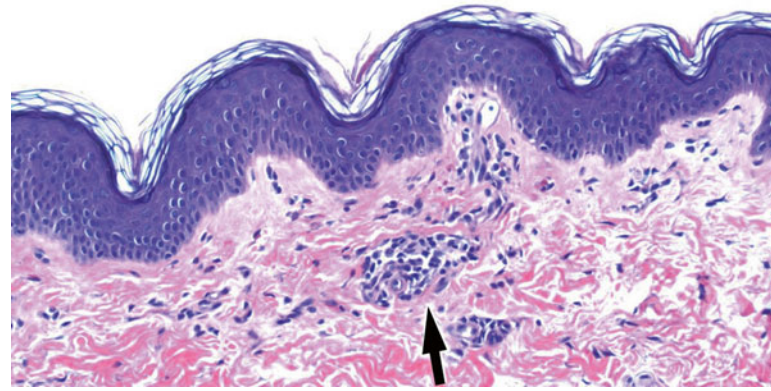

Fig. 8.5 Early LA consists of a lymphocytic capillaritis with extravasated erythrocytes (*arrow*)

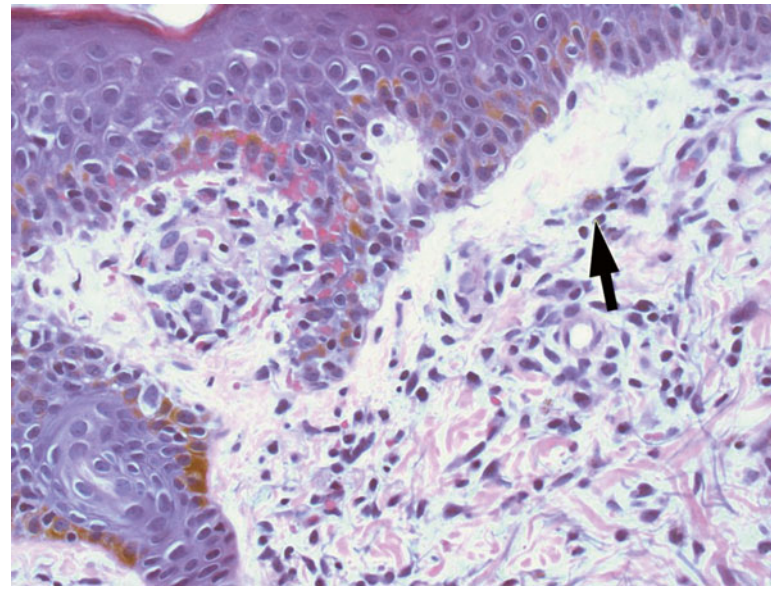

Fig. 8.6 LA mature lesions exhibiting a lichenoid tissue reaction with marked accumulation of hemosiderin-containing macrophages (*arrow*)

lesions exhibiting a lichenoid tissue reaction with marked accumulation of hemosiderin-containing macrophages (Fig. 8.6) dissimilar to conventional PPD (Price et al. 1985).

Cytomorphology

The infiltrate contains lymphocytes and histiocytes interspersed with extravasated erythrocytes. In one case report of LA, the histiocytes were characterized by convoluted or bean-shaped nuclei and a large amount of eosinophilic cytoplasm (Aoki and Kawana 2002). Additionally, large histiocytic cells consisting of cytoplasmic Birbeck granules were present among the lymphocytes in the upper dermis (Aoki and Kawana 2002). A thinning of the epidermis without evidence of spongiosis or epidermal exocytosis and an increased number of siderophores in the middermis have been observed (Murota and Katayama 2011).

Immunophenotype

The lymphocytic infiltration is predominately composed of T lymphocytes, a majority of which are CD4+, admixed with some reactive CD1a + dendritic cells (Aiba and Tagami 1988; Ghersetich et al. 1994; Smoller and Kamel 1991). Immunofluorescence studies are frequently negative, although one study demonstrated C3 and immunoglobulins present in vessel walls (Iwatsuki et al. 1980).

Genetics and Molecular Findings

T-cell receptor gene rearrangement (TCRGR) is not helpful in the diagnosis of LA. An analysis in 2008 by Fink-Puches et al. of the T-cell receptor gamma gene rearrangement performed in 16 cases of LA revealed an equal number of patients with monoclonal and polyclonal bands (Fink-Puches et al. 2008).

Clinical Course

LA belongs to the expanding spectrum of clonal dermatoses. Possible progression to mycosis fungoides (MF) has been reported in the literature; thus, patients require close follow-up (Brehmer-Andersson 1976; Cather et al. 1998; Guitart and Magro 2007; Martinez et al. 2001; Puddu et al. 1999; Ugajin et al. 2005). LA is difficult to treat and lesions typically remain stable or undergo spontaneous resolution. Anecdotal reports describe some benefit from the use of topical steroids if used for 4–6 weeks. PUVA (psoralen and ultraviolet A), narrow-band UVB, and immunosuppressive therapy have also demonstrated efficacy. If immunosuppression is considered, cutaneous T-cell lymphoma must be excluded (Bolognia and Jorizzo 2008b).

Differential Diagnosis

Angioma serpiginosum, MF, allergic contact dermatitis, non-allergic reactions to topical medications, drug eruptions, and hypergammaglobulinemic purpura of Waldenstrom are included in the differential diagnosis (Bolognia and Jorizzo 2008b). The differentiation between MF and PPDs is frequently challenging because of the overlapping histological and clinical features (Guitart et al. 1997). In the absence of cytological atypia, papillary dermal fibrosis and mild papillary dermal edema favor PPDs. Lymphocytic exocytosis can be seen in both lesions; however, the intraepidermal lymphocytes in MF demonstrate more atypical features than those of PPDs (Boyd and Vnencak-Jones 2003; Crowson et al. 1999; Smoller and Kamel 1991).

Actinic Reticuloid

Introduction

Actinic reticuloid (AR) is a chronic photosensitive dermatosis first described in 1969 by Ive et al. (1969). AR represents the most extreme variant of chronic actinic dermatitis and is characterized by cutaneous lesions simulating cutaneous T-cell lymphoma clinically and histologically. The following criteria must be met in the diagnosis of AR: (1) persistent infiltrated papules and plaques on sun-exposed skin, frequently extending to covered areas or generalized infiltrated erythroderma; (2) photosensitivity to a wide wave length spectrum including UVB, UVA, and some of the visible light spectrum; and (3) a dermal infiltrate with the inclusion of atypical lymphoid cells observed upon histological examination (Toonstra 1991). Cases lacking one or more of the above criteria are denoted with the general term “chronic actinic dermatitis” (Toonstra 1991). Chronic actinic dermatitis encompasses AR, persistent light reaction, photosensitive eczema, and chronic photosensitive dermatitis and is defined by the following criteria: (1) dermatitis of sun-exposed areas, (2) a histological profile resembling eczema or featuring lymphoma-like changes, and (3) a decreased minimal erythema dose (MED) to UVB (mJ/cm^2) and UVA (J/cm^2) (Clark-Loeser 2003; Frain-Bell et al. 1974; Khatri et al. 1994; Oliveira Soares et al. 2002).

The diagnosis and treatment of AR is particularly challenging for physicians as AR may easily be mistaken for the cutaneous T-cell lymphomas, Sézary syndrome (Pacheco et al. 2012; Toonstra et al. 1985), and mycosis fungoides (MF). While it has been demonstrated that a large number of patients with AR do not show an increased susceptibility to malignancy, (Bilsland et al. 1994) De Silva et al. suggest a progression of AR to MF in two patients (De Silva et al. 2000). They hypothesized that the transformation of AR into MF occurred from the chronic immunological stimulation of the skin combined with UV-induced cutaneous immunosuppression (De Silva et al. 2000). Additionally, Thomsen reports on the development of Hodgkin's lymphoma in a patient with AR (Thomsen 1977).

Clinical Features

Epidemiology

AR occurs predominantly in elderly men; however, it has also been shown to occur in young individuals and in women (Guardiola and Sanchez 1980; Healy and Rogers 1995; Kurumaji et al. 1994). AR is considered a rare, idiopathic disease with an incidence of approximately 1 in 6,000 (Ive et al. 1969; Khatri et al. 1994; Toonstra 1991). AR has been demonstrated to occur worldwide, with the greatest frequency in northwestern Europe, most notably, Holland (Healy and Rogers 1995; Toonstra 1991).

Clinical Appearance of Lesions

Erythema and edema on photoexposed areas, including the face, neck, ears, and arms, are common features at initial presentation. At later stages of AR, infiltrated, eczematoid, lichenified patches, plaques, and nodules may arise and extend into nonexposed areas. AR commonly presents in a papular form but has also been demonstrated to present in a nodular or lichenoid form (Evans et al. 2004; Grone et al. 2006; Yap et al. 2003). Patients may demonstrate a history of abnormal photosensitivity. Pruritus and burning are frequently associated with cases of AR. Generalized erythroderma and generalized lymphadenopathy have also been demonstrated to occur (Zak-Prelich and Schwartz 1999). Additional clinical symptoms include lichenoid hyperpigmentation, lichenoid purpuric lesions, palmoplantar hyperkeratosis onycholysis, and alopecia (Toonstra et al. 1989a). Patients with AR may also develop leonine facies, a dermatological condition characterized by deep furrowing of facial skin (Ravic-Nikolic et al. 2012).

Histopathology

Pattern of Infiltration

The histological pattern of AR shares similar features with cutaneous T-cell lymphoma. The infiltrate is present in the upper dermis and may also extend into the middle and lower dermis. Eosinophils, histiocytes, plasma cells, giant cells, IgE + cells with a dendritic morphology, and characteristic multinucleated stellate fibroblasts (Fig. 8.7) are typically present within the infiltrate (Zak-Prelich and Schwartz 1999). Exocytosis of lymphocytes and atypical mononuclear cells infiltrating the epidermis may simulate the Pautrier microabscesses of MF, thus making the diagnosis of AR particularly challenging. However, the atypical lymphocytes of AR are accompanied by conspicuous extracellular epidermal edema (spongiosis) (Fig. 8.8) and, unlike MF, lack pericellular vacuolization. It is also important to note that Pautrier's microabscesses are uncommon in early lesions of MF.

Psoriasiform epidermal hyperplasia may also occur, resulting in the presence of thickened collagen in the papillary dermis. A common histological change seen in AR is the presence of lichen simplex chronicus superimposed upon an inflammatory process; such changes are frequently useful in the differential diagnosis between AR and MF.

Cytomorphology

The infiltrate is perivascular or band-like, is frequently dense, and is composed of atypical mononuclear cells with a cerebriform nucleus (Fig. 8.9) (Clark-Loeser 2003; Ive et al. 1969; Toonstra et al. 1989a).

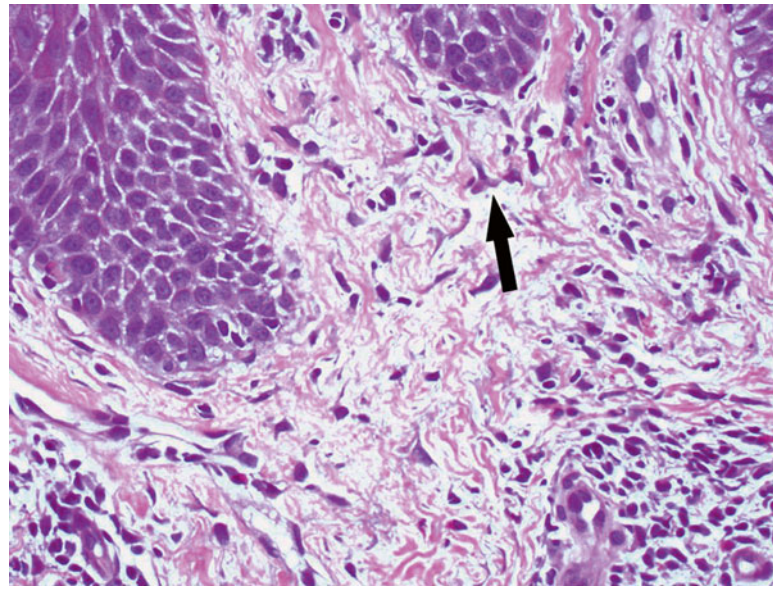

Fig. 8.7 AR showing characteristic multinucleated stellate fibroblasts (*arrow*)

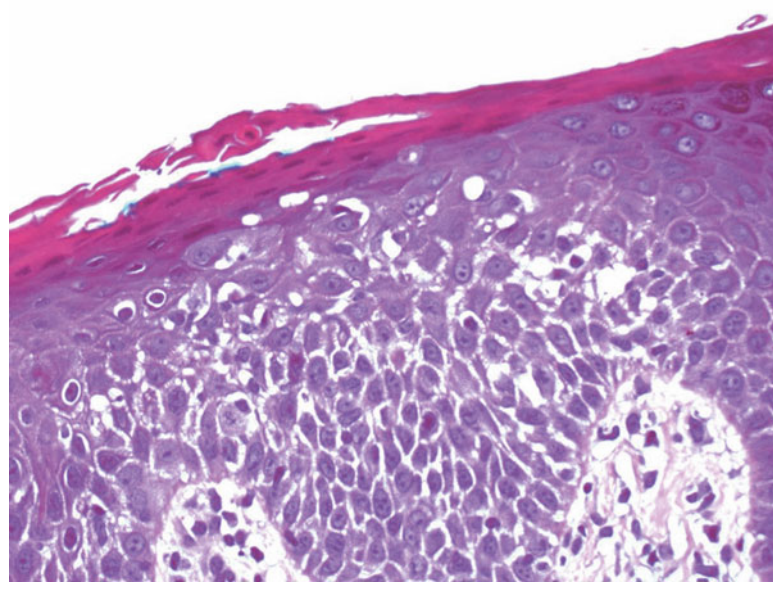

Fig. 8.8 AR showing atypical lymphocytes accompanied by conspicuous extracellular epidermal edema (spongiosis)

Immunophenotype

Immunohistochemical analysis of the cutaneous infiltrates demonstrates the presence of activated T cells, histiocytes, macrophages, and B cells (Toonstra et al. 1989b). A predominance of CD8+ lymphocytes is most frequently associated with AR, whereas a greater percentage of CD4+ cells is typical in individuals with MF (Toonstra et al. 1989a). An immunohistochemical analysis of 13 patients with AR demonstrated an inverse relationship between dermal infiltrate HLA-DR expression and the number of Leu CD8+ cells, thus indicating a negative correlation between a state of activation and Leu CD8+ cell concentration (Toonstra et al. 1989b). The infiltrate is composed

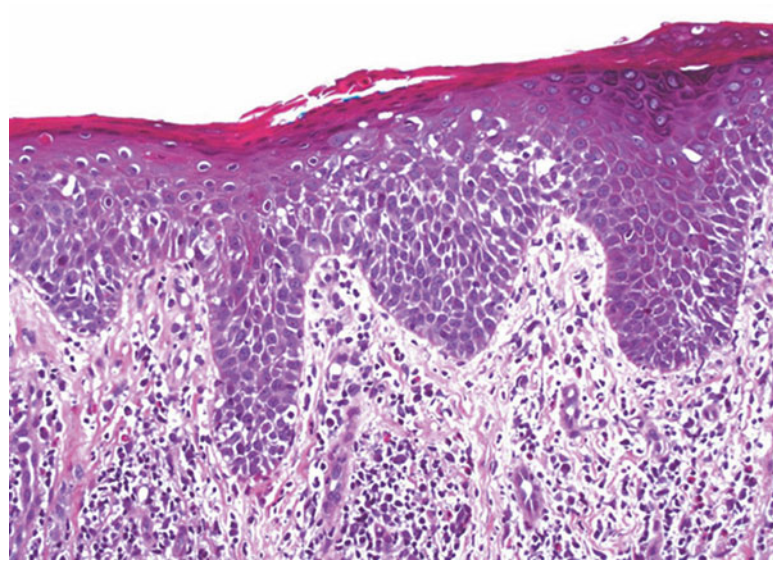

Fig. 8.9 AR showing psoriasiform epidermal hyperplasia, thickened papillary dermal collagen, and a band-like infiltrate with exocytosis composed of atypical mononuclear cells with a cerebriform nucleus

of polyclonal T lymphocytes, Langerhans cells, and HLA-DR + macrophages (Bakels et al. 1998; Toonstra et al. 1989a). The dermal infiltrate will demonstrate a combination of CD8+ cells and CD4+ cells, whereas the epidermal infiltrate will contain predominately CD8 + cells (Heller et al. 1994).

Genetics and Molecular Findings

Genotypic analysis of skin biopsies of patients with AR most frequently demonstrates a lack of T-cell gene receptor rearrangement; however, cases with monoclonal rearrangement have been reported in the literature (Melotti et al. 2008; Pacheco et al. 2012).

Clinical Course

The initial clinical presentation of AR mimics eczema, whereas the chronic stage of AR is characterized by a pseudolymphomatous appearance (Pacheco et al. 2012). Photopatch tests demonstrate one or more positive allergen responses in 75 % of AR cases and are often associated with musk ambrette, sulfanilamide, tetrachlorosalicylanide, lichen acid mix, and P-aminobenzoic acid (Oliveira Soares et al. 2002; Toonstra et al. 1989a). Increased photosensitivity to UVB, UVA, and part of the visible light spectrum should occur over a duration of at least 1 year for an accurate diagnosis of AR (Zak-Prelich and Schwartz 1999). Laboratory results including serum biochemistry and complete blood count measurements are predominantly normal (Zak-Prelich and Schwartz 1999). Contact allergy recognition and avoidance, photoprotection, photochemotherapy, and systemic immunosuppression may be used in the treatment of chronic AR. Rare cases of AR have demonstrated spontaneous remission (Toonstra 1991).

Differential Diagnosis

The differential diagnosis between AR and cutaneous T-cell lymphomas is significantly challenging for physicians because of the similar clinical and histopathological features between the disorders. Essential features of AR include photosensitivity to a wave length spectrum spanning UVB, UVA, and the inclusion of some of the visible light spectrum. Additionally, AR is characterized by mixed cellular infiltrates and a predominance of CD8+ T cells. Circulating atypical lymphocytes (Sézary-like cells) may occur in

both AR and MF; however, fewer numbers and a normal CD4/CD8 ratio are suggestive of AR. Positive patch and photopatch tests are correlated with a high frequency in AR, whereas no association has been shown to occur in MF (De Silva et al. 2000). While clonal T-cell receptor (TCR) gene rearrangement is frequently used in the differential diagnosis between AR and cutaneous T-cell lymphoma, a genetic rearrangement pattern of the beta chain T-cell receptor has been observed in patients with AR (Melotti et al. 2008; Pacheco et al. 2012); therefore, genetic rearrangement should not be used as a definitive marker for malignancy. An accurate diagnosis of AR involves the integrated synthesis of clinical, molecular, immunophenotypical, and morphological data.

Lymphomatoid Contact Dermatitis

Introduction

Lymphomatoid contact dermatitis (LCD) was first described by Orbaneja et al. in 1976 and is characterized as a chronic, persistent variant of allergic contact dermatitis that simulates the cutaneous T-cell lymphoma mycosis fungoides (MF) both clinically and histologically (Orbaneja et al. 1976). The immunological mechanism of LCD is hypothesized to occur from an antigenic stimulus resulting in the production and accumulation of activated lymphocytes that produce clonal selection, proliferate, and transform into blast cells (Evans et al. 2003). LCD is often a challenging disorder to diagnose due to the problematic nature of associating it with a specific allergen (Narganes et al. 2013). The allergens that have been reported to induce LCD include phosphorus, gold, nickel, cobalt, textile dyes, an exotic wood species (teak, *Tectona grandis* L.), benzydamine hydrochloride, para-phenylenediamine, para-tertyl-butyl phenol resin, isopropyl-diphenylenediamine, diaminodiphenylmethane, ethylenediamine dihydrochloride, methylchloroisothiazolinone, quaternium-15, and allergens in an ophthalmological preparation (Alvarez-Garrido et al. 2010; Braun et al. 2000; Calzavara-Pinton et al. 2002; Conde-Taboada et al. 2007; Danese and Bertazzoni 1995; Evans et al. 2003; Ezzedine et al. 2007; Fleming et al. 1997; Houck et al. 1997; Marliere et al. 1998; Mendese et al. 2010; Narganes et al. 2013; Nigro et al. 1988; Orbaneja et al. 1976; Park et al. 1999; Schena et al. 1995; Wall 1982).

Clinical Features

Epidemiology

LCD is observed in adults of both genders (Wood 2012).

Clinical Appearance of Lesions

LCD is characterized by erythematous, pruritic, scaly plaques and papules that may be discrete or confluent. Exfoliative erythroderma may be present. The lesions grow progressively and may exhibit periods of exacerbation and remission. LCD induced from gold earrings presents clinically as discrete nodules at the sites of contact (Fleming et al. 1997; Park et al. 1999). A nodular clinical presentation has also occurred in a case of LCD caused by an ophthalmological preparation (Braun et al. 2000).

Histopathology

Pattern of Infiltration

T-cell LCD demonstrates a band-like T-cell infiltrate in the upper dermis with prominent epidermotropism (Orbaneja et al. 1976). Superficial dermal (papillary) edema often accompanies the infiltrate permitting distinction with common forms of mycosis fungoides (Fig. 8.10a). Focal extension of the edema and infiltrate to periadnexal and perivascular areas may occur (Calzavara-Pinton et al. 2002). Epidermal spongiosis or spongiotic microvesiculation is typically present (Martinez-Moran et al. 2009) in addition to parakeratosis and acanthosis (Calzavara-Pinton et al. 2002; Ezzedine et al. 2007). Prominent tissue eosinophilia and lymphoid hyperplasia throughout the dermis and subcutaneous tissue were reported in a case of LCD caused by gold earrings (Park et al. 1999).

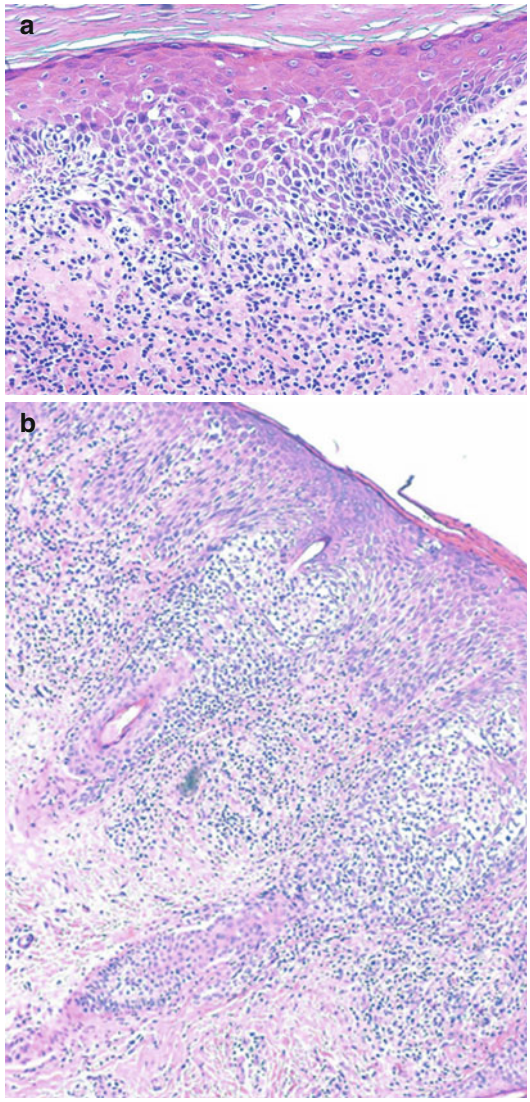

Fig. 8.10 (**a**) LCD showing a band-like T-cell infiltrate in the upper dermis with prominent epidermotropism and superficial dermal edema. (**b**) LCD showing spongiotic microvesiculations with Langerhans cells and few lymphocytes simulating "Pautrier's microabscesses"

Cytomorphology

Hyperchromatic and atypical lymphocytes with focal exocytosis are observed in LCD (Houck et al. 1997). The infiltrate is frequently composed of cells with large, hyperchromatic, convoluted nuclei (Calzavara-Pinton et al. 2002; Martinez-Moran et al. 2009). Multinucleated, giant cells showing birefringent inclusions have also been demonstrated (Conde-Taboada et al. 2007). The diagnosis of LCD is particularly challenging as the intraepidermal collections of lymphocytes frequently simulate the Pautrier microabscesses of MF (Fig. 8.10b) (Houck et al. 1997; Orbaneja et al. 1976).

Immunophenotype

Immunohistochemical analysis demonstrates a dominant phenotype of CD3+ and CD4+ cells (Evans et al. 2003; Ezzedine et al. 2007; Narganes et al. 2013). A dominance of C8+ cells over CD4+ cells has also been reported (Calzavara-Pinton et al. 2002). The presence of rare CD30+ and CD1a + cells has been observed (Martinez-Moran et al. 2009), in addition to CD2+, CD5+, CD7+, and CD45RO+, cells expressing cutaneous lymphocyte antigen (CLA) (Calzavara-Pinton et al. 2002).

Genetics and Molecular Findings

T-cell receptor gene analysis has demonstrated a lack of a clonal population of T cells (Evans et al. 2003; Ezzedine et al. 2007; Martinez-Moran et al. 2009).

Clinical Course

LCD may present as a localized form, where lesions develop in cutaneous regions in direct contact with the allergen, and as a generalized form, where the lesions are widely dispersed, exhibit an inclination to become erythrodermic and are frequently resistant to treatment (Haynes et al. 1982). Complete resolution of symptoms is most often obtained following removal of the antigenic stimulus. However, a lack of clinical remission despite allergic avoidance and potent topical steroid therapy has been reported (Ezzedine et al. 2007). In such cases, long-term follow-up is necessary as the disorder may evolve into a malignant lymphoma. This was demonstrated by Abraham et al. in their report of the

transformation of LCD into T-cell prolymphocytic leukemia (Abraham et al. 2006). However, the premise that these patients had lymphoma from the onset cannot be excluded.

Differential Diagnosis

The differentiation between LCD and mycosis fungoides (MF) remains challenging as the histological presentations of the two disorders may be indistinguishable. An accurate diagnosis of LCD should be made from the clinical and histological data, in combination with immunohistochemical, gene rearrangement, and patch-test analysis. The definitive diagnosis of LCD has been hypothesized to include four criteria: (1) a localized eruption indicating contact dermatitis clinically, (2) histological findings simulating cutaneous T-cell lymphoma, (3) positive patch-test results, and (4) resolution of symptoms following corticosteroid treatment and avoidance of the allergen (Orbaneja et al. 1976).

Lymphomatoid Drug Reactions

Introduction

Lymphomatoid drug reactions are cutaneous drug reactions resulting in atypical lymphoid infiltrates that simulate cutaneous T-cell lymphomas. Additional appellations for this entity include "lymphomatoid drug eruptions," "drug-induced cutaneous pseudolymphoma," and "drug-induced pseudolymphoma syndrome." A large number of drugs have been implicated in the induction of cutaneous atypical lymphoid infiltrates. The lymphomatoid drug reactions are divided into two main categories: (1) anticonvulsant-induced pseudolymphoma syndrome and (2) cutaneous pseudolymphoma induced by drugs other than anticonvulsants. Moreover, externally applied etheric plant oils have also been documented to induce lymphoproliferative reactions simulating malignant lymphomas (Cerroni et al. 2009). The most common anticonvulsant drugs inducing lymphomatoid drug reactions include phenytoin, primidone, mephenytoin, and trimethadione (Ploysangam et al. 1998). Other classes of drugs associated with lymphocytic eruptions include, but are not limited to, ACE inhibitors, antihistamines, beta blockers, antifungals, antiarrythmics, antirheumatics, and cytotoxics (Gupta et al. 1990; Henderson and Shamy 1990; Kardaun et al. 1988; Magro and Crowson 1995; Ploysangam et al. 1998; Rijlaarsdam and Willemze 1991).

Clinical Features

Epidemiology

Anticonvulsant-induced pseudolymphoma syndrome has been reported to occur more frequently in black patients than in white patients (Ploysangam et al. 1998). Cutaneous pseudolymphoma induced by drugs other than anticonvulsants affects male and females equally (Ploysangam et al. 1998).

Clinical Appearance of Lesions

Anticonvulsant-induced pseudolymphoma syndrome presents as solitary cutaneous plaques, papules, nodules, or macules, and less frequently, as multiple erythematous, pruritic lesions with a widespread distribution (Ploysangam et al. 1998). Cutaneous pseudolymphoma induced by drugs other than anticonvulsants result in localized papules, generalized papulonodular lesions, and single or multiple nodules and plaques (Ploysangam et al. 1998). Erythroderma simulating Sézary syndrome has been reported for both categories of lymphomatoid drug reactions (D'Incan et al. 1992; Souteyrand and d'Incan 1990).

Histopathology

Pattern of Infiltration

Lymphomatoid drug reactions are characterized by an infiltration of lymphocytes into the dermis in a dense band-like or nodular pattern (Rijlaarsdam and Willemze 1991). The band-like lichenoid pattern is the most frequent pattern and it may simulate MF. The nodular pattern may mimic non-Hodgkin's lymphoma (Crowson and

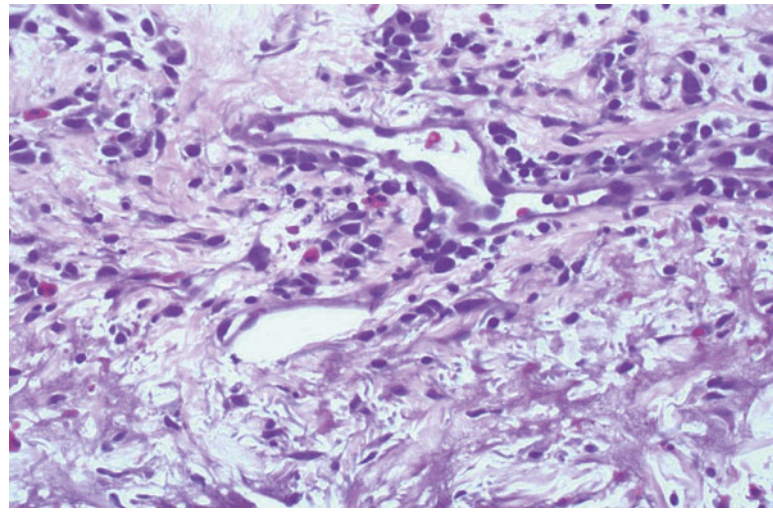

Fig. 8.11 Lymphomatoid drug reaction showing prominent superficial vasculature containing hypertrophied endothelia

Magro 1995; Dorfman and Warnke 1974; Kardaun et al. 1988; Luelmo Aguilar et al. 1992). A histological presentation compatible with the nodular pattern of pseudo T-cell lymphoma was demonstrated in a patient with pseudolymphoma syndrome due to carbamazepine (Saeki et al. 1999). The infiltrate is frequently composed of atypical nuclei with a cerebriform outline. Nodular lesions are often characterized by significant histiocytes. Eosinophils and plasma cells are typically conspicuous and, along with prominent superficial vasculature containing hypertrophied endothelia (Fig. 8.11), constitute important clues to their distinction with MF (Magro and Crowson 1995). Epidermotropism has also been reported in the literature (Callot et al. 1996).

Cytomorphology

The band and nodular infiltrates are frequently characterized by atypical cells with pleomorphic, hyperchromatic nuclei.

Immunophenotype

Immunohistochemical analysis demonstrates a predominance of T cells in the infiltrate that are CD4+. The predominance of B cells is a rare occurrence and is associated with antihistamines (Magro and Crowson 1995) and thioridazine (Luelmo Aguilar et al. 1992). Loss of pan-T-cell markers including CD2, CD3, and CD5 antigens has not been observed (Rijlaarsdam et al. 1992). The presence of CD3+, CD30+, and CD20+ atypical dermal lymphocytes was reported in an individual with carbamazepine-induced pseudolymphoma (Nathan and Belsito 1998). A polyclonal pattern of immunoglobulin light-chain expression is frequently observed.

Genetics and Molecular Findings

Molecular analysis of TCR genes most frequently demonstrates a polyclonal pattern.

Clinical Course

Patients with anticonvulsant-induced pseudolymphoma syndrome frequently develop symptoms within the first 2–8 weeks following drug intake (Ploysangam et al. 1998). These patients commonly develop generalized or localized lymphadenopathy, hepatosplenomegaly, fever, and erythematous eruptions (Ploysangam et al. 1998). Skin lesions often appear as solitary lesions; however, multiple nodules, papules, and plaques

may develop in a widespread distribution (Ploysangam et al. 1998). Circulating Sézary-like cells may be present (Ploysangam et al. 1998). Erythroderma may be present. A digitate dermatitis-like pattern has also been reported (Mutasim 2003). Other clinical symptoms of patients treated with anticonvulsants include arthralgia, leukocytosis, malaise, and severe facial edema. Patients with cutaneous pseudolymphoma induced by drugs other than anticonvulsants develop symptoms within 1–11 months following drug intake (Ploysangam et al. 1998). In most cases, withdrawal of the offending agent results in regression. In rare circumstances, the progression of lymphomatoid drug eruptions into malignant lymphomas may occur, most notably, following a sustained period of anticonvulsant drug therapy (Anthony 1970; Hyman and Sommers 1966; Isobe et al. 1980; Li et al. 1975; Rausing 1978). In such circumstances, withdrawal of the offending agent does not result in clinical remission.

Differential Diagnosis

The differential diagnosis between lymphomatoid drug reactions and cutaneous T-cell lymphomas involves clinicopathological, immunohistochemical, and clonal correlation. In some cases, follow-up data subsequent to the withdrawal of the inciting agent is the only definitive measure used to identify the benign character of the atypical lymphoid infiltrates. The cutaneous T-cell lymphomas involved in the differential diagnosis of lymphomatoid drug reactions include MF and Sézary syndrome.

Solitary T-Cell Pseudolymphoma

Introduction

Solitary T-cell pseudolymphoma was first described in 1986 by van der Putte et al. in their description of three cases of a small, solitary lesion characterized by nonepidermotropic band-like subepidermal infiltrates composed of large T lymphocytes (van der Putte et al. 1986). Since this original description, numerous appellations have been attributed to these solitary lesions composed of T-cell infiltrates, including "solitary lymphomatous papule, nodule, or tumor," "cutaneous lymphoid hyperplasia," "solitary nonepidermotropic T-cell pseudolymphoma," "pseudolymphomatous folliculitis," and "solitary small- to medium-sized pleomorphic T-cell nodules of undetermined significance" (Cerroni 2010). The description of this entity as a lesion of "undetermined significance" was suggested by Leinweber et al. due to inconsistency between the indolent clinical course and histopathological characteristics of the disorder, thus making a definitive diagnosis as precisely benign or malignant challenging (Leinweber et al. 2009).

Clinical Features

Epidemiology

Solitary T-cell pseudolymphoma has been reported to affect individuals of both genders (Leinweber et al. 2009).

Clinical Appearance of Lesions

Solitary T-cell pseudolymphoma presents as slightly elevated, round, erythematous, solitary lesions with a diameter of 1–2 cm (van der Putte et al. 1986). Lesions are commonly located on the head, neck, or trunk (Leinweber et al. 2009). Superficial erosion and ulceration have been observed (Leinweber et al. 2009).

Histopathology

Pattern of Infiltration

The infiltrate may exhibit a band-like subepidermal pattern characterized by large T lymphocytes (van der Putte et al. 1986). A nonepidermotropic, nodular, or diffuse infiltration of small- to medium-sized pleomorphic T lymphocytes was observed in a report of 136 cases of

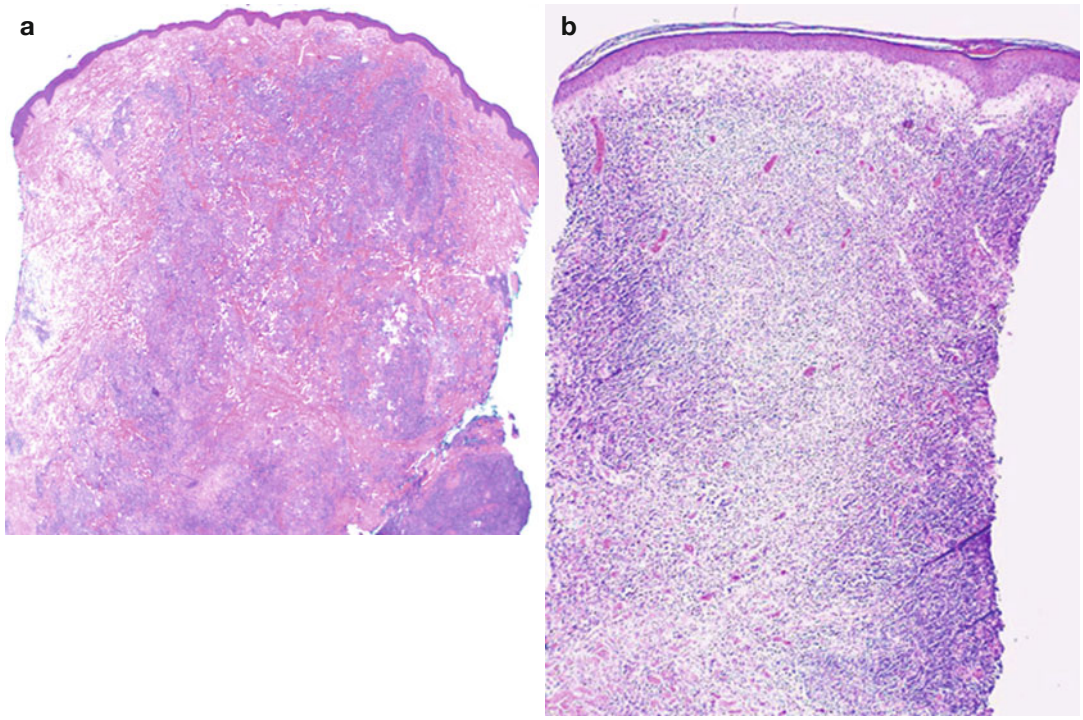

Fig. 8.12 (**a**, **b**) Solitary T-cell pseudolymphoma showing nonepidermotropic nodular or diffuse lymphoid infiltrates located in the entire dermis and with extension into the subcutaneous fat

SMPTCL (Beltraminelli et al. 2009). Dense, nodular, or diffuse lymphoid infiltrates located in the entire dermis and with extension into the subcutaneous fat are typical (Fig. 8.12a, b) (Leinweber et al. 2009). Dermoepidermal alignment or infiltration of the epidermis by lymphocytes is typically absent (Leinweber et al. 2009). Prominent vasculature consisting of hypertrophied or swollen endothelia containing cytoplasmic vacuolization is a helpful diagnostic feature (Fig. 8.13).

Cytomorphology

The lesions are typically composed of dense infiltrates of polymorphic cell population composed of a number of plasma cells, eosinophils, and many small non-atypical lymphocytes without atypia or without cerebriform nuclei (Figs. 8.14 and 8.15). Sheets of plasma cells and eosinophils may also be observed (Fig. 8.16). Adnexal structure effacement and/or angiodestruction, often observed with T-cell lymphoma, is typically not observed (Leinweber et al. 2009).

Immunophenotype

Immunohistochemical analysis has demonstrated a T-cell phenotype (CD3+) (Fig. 8.17a) and a T-helper phenotype (CD4+) admixed with CD8+/TIA-1+ cells, with variable proportions of B cells (CD20+) (Fig. 8.17b) (Leinweber et al. 2009). Scattered CD30+ cells representing less than 1 % of the infiltrate has also been observed (Leinweber et al. 2009).

Genetics and Molecular Findings

Although monoclonal rearrangement of the T-cell receptor gamma gene has been reported, these lesions usually are defined by lack of clonality upon T-cell surface receptor gene rearrangement study (Leinweber et al. 2009).

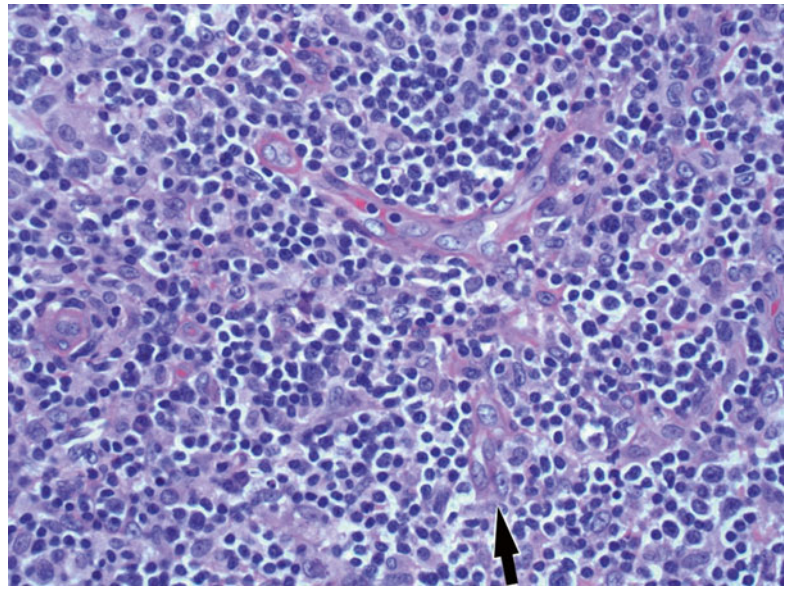

Fig. 8.13 Solitary T-cell pseudolymphoma showing prominent vasculature consisting of hypertrophied or swollen endothelia (*arrow*) containing cytoplasmic vacuolization

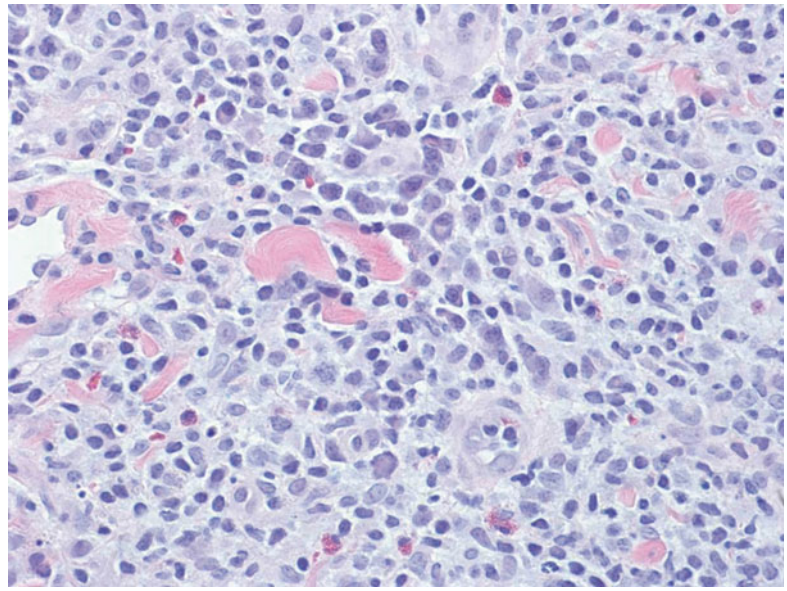

Fig. 8.14 Solitary T-cell pseudolymphoma showing sheets of plasma cells and eosinophils

Clinical Course

Patients often present with asymptomatic, solitary, red to purplish plaques or tumors. The lesions often exhibit a tendency to self-regress (van der Putte et al. 1986). Nonaggressive treatment modalities frequently result in an indolent clinical course without extracutaneous manifestations (Leinweber et al. 2009).

Differential Diagnosis

The differential diagnosis of solitary T-cell pseudolymphoma includes "primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma (PCSMTCL)." PCSMTCL is characterized by a histopathological profile of dense infiltrates of small- to medium-sized CD4 + pleomorphic T lymphocytes with a small proportion (up to 30 %)

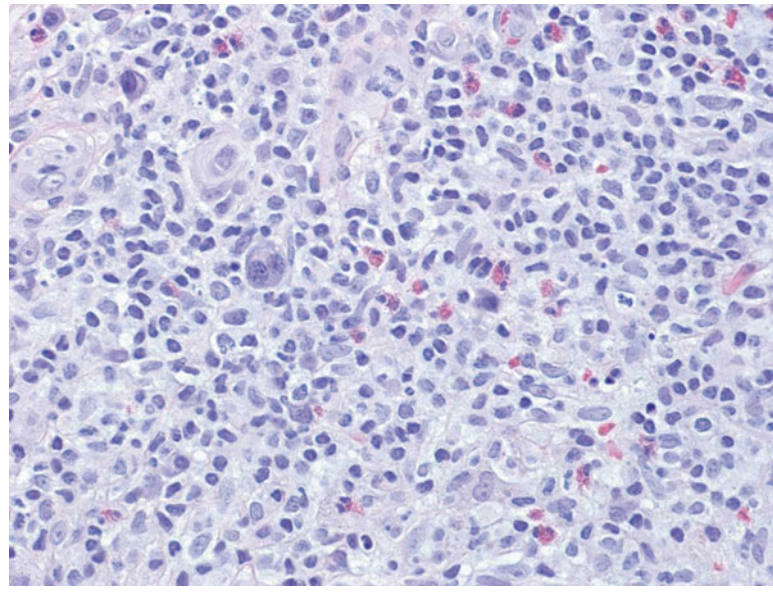

Fig. 8.15 Solitary T-cell pseudolymphoma showing binucleated reactive plasma cells and eosinophils

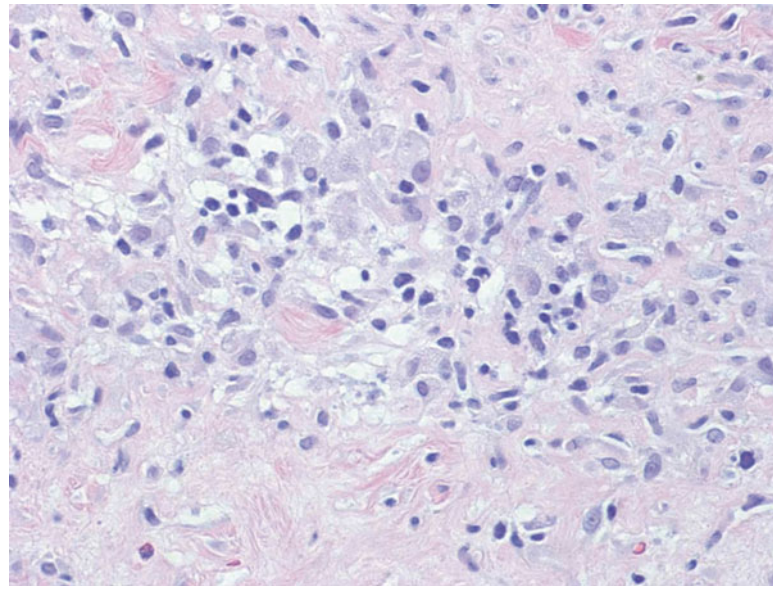

Fig. 8.16 Solitary T-cell pseudolymphoma showing clusters of foamy histiocytes

of large pleomorphic cells. The immunohistochemical profile of PCSMTCL is a CD3+/CD4+/CD8-/CD30- phenotype; however, CD8+ cases have also been described (Cerroni et al. 2004; Willemze et al. 2005). The difficulty in the diagnosis of PCSMTCL is highlighted by Lienweber et al. in their report on 26 cases that phenotypically and histopathologically met the criteria of PCSMTCL; however, the cases were characterized by excellent prognoses (Leinweber et al. 2009). Additional diagnostic challenges associated with solitary T-cell pseudolymphoma include the frequent predominance of small- to medium-sized pleomorphic T cells in mycosis fungoides (MF) and Sézary syndrome. Thus, the diagnostic criteria for PCSMTCL are limited to cases without

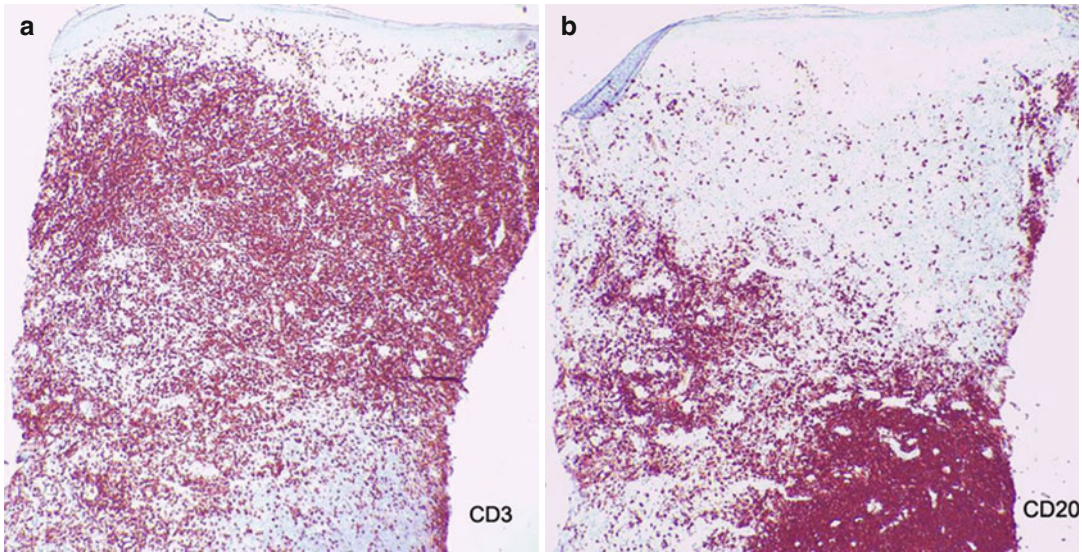

Fig. 8.17 (**a**, **b**) Solitary T-cell pseudolymphoma showing predominantly CD3+ T cells with variable proportions of CD20+ B cells. PCR analysis of TCRGR and IGH genes was negative

a history of MF or Sézary syndrome, without lesions that clinically simulate these disorders, and without distinct epidermotropism (Cerroni et al. 2004; Willemze et al. 2005).

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