Neoplastic Nodular T-Cell Pattern: An Approach to Diagnosis of Neoplastic Nodular T-Cell Lymphomas of the Skin

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Introduction

Primary cutaneous lymphomas have an estimated annual incidence of 1.0–1.5/100,000 and are the second most common group of extranodal lymphomas. Despite their relative rarity, there has been an increasing incidence of cutaneous lymphomas in the United States from 5 to 13 per million person-years over 25 years reported on 2005 (SEER data) (Bradford et al. 2009). Peripheral T-cell lymphomas comprise 12 % of all lymphomas, a minority compared to the more common non-Hodgkin B-cell lymphomas (Swerdlow et al. 2008). Diagnosis of these rare T-cell lymphomas, especially those that arise in the skin, is challenging. Of all peripheral T-cell lymphomas (PTCLs), four out of five are extranodal, and a majority of the peripheral location involves the skin (Groves et al. 2000).

Of the primary cutaneous lymphomas in the United States, primary cutaneous T-cell lymphomas (MF/Sezary syndrome (SS), PTCL-u, CD30 T-cell lymphomas, and the rare types) represent 71 % of all primary cutaneous lymphomas, whereas primary cutaneous B-cell lymphomas account for the remainder of cases (Bradford et al. 2009). Mycosis fungoides (MF) is the most frequent CTCL representing more than half of this group (Bradford et al. 2009). The overall annual age-adjusted incidence of CTCL was 6.4 per million persons. Incidence was higher among blacks (9.0×10^{-6}) than among whites (6.1×10^{-6}) and was higher among men (8.7×10^{-6}) than among women (4.6×10^{-6}). Incidence was correlated with high physician density, high family income, high percentage of population with a bachelor's degree or higher, and high home values. The incidence appears to be increasing both in North America and in Europe (Criscione and Weinstock 2007; Jenni et al. 2011). Although MF is an indolent disease, histologic and clinical progression is seen over time. Transformed MF occurs up to 7 % of early but up to 23 % in advanced cases, especially higher in tumor stage (Lai et al. 2012).

The term primary cutaneous T-cell lymphoma (pCTCL) refers to cases of cutaneous T-cell lymphomas that present in the skin without extracutaneous involvement at the time of diagnosis

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H.D. Cualing et al. (eds.), *Cutaneous Hematopathology*,
DOI 10.1007/978-1-4939-0950-6_10,

(Willemze et al. 2005). For prognostic and therapeutic reasons, this has to be differentiated from the similar other non-MF cutaneous T-cell lymphomas, identical-appearing secondary lymphomas, or even T-cell lymphomas masquerading as sarcoma (Alekshun et al. 2008; Rezania et al. 2007). Secondary lymphomas that involve the skin at presentation derived from systemic loci represent 25 % of all cutaneous lymphomas.

While mycosis fungoides generally presents with a protracted indolent course, the non-MF group of cutaneous PTCLs has a wide range of clinical behaviors. For example, primary cutaneous CD30+ anaplastic large cell lymphoma (c-ALCL) has good prognosis and rarely disseminates, with an estimated 5-year survival greater than 90 % (Bekkenk et al. 2000; Liu et al. 2003; Yu et al 2008), while primary cutaneous peripheral T-cell lymphoma, unspecified (PTCL-u), presents with a more aggressive generalized presentation that frequently spreads systemically and is often resistant to chemotherapy, with an estimated 5-year survival of 15 % (Beljaards et al. 1994; Grange et al. 1999; Bekkenk et al. 2003).

Some of the difference in frequency rates reported among PTCLs may be related to the use of less than precise terminology. For example, the relative frequency between cutaneous PTCLs reported by Bradford et al. differs from the WHO-EORTC data because the former used cutaneous PTCL as a group, while the latter used the more exact PTCL-u for that category. In the Surveillance, Epidemiology, and End Results (SEER) incidence rate data of 3,884 cutaneous lymphomas in the United States from 2001 to 2005, the primary cutaneous peripheral T-cell lymphoma (PTCL) group frequency is 20.8 %, and the CD30 lymphoproliferative group comprise 10.2 %, and the rare PTCLs like gamma-delta, angioimmunoblastic, subcutaneous panniculitic T-cell lymphoma, extranodal NK/T, and adult T-cell lymphoma/leukemia represent about 1 % of all cutaneous lymphomas (Bradford et al. 2009). In this regard, the terminology in the SEER study did not use PTCL, unspecified, but instead called this group " primary cutaneous PTCL" which is a heterogeneous group. In support of this observation is the reported longer overall 5-year survival rate in primary cutaneous PTCL category compared to the generally reported shorter rate in PTCL-u in most literature. In contrast, the frequency data used by WHO-EORTC was based on terminology PTCL-u; hence the CD30 + lymphoproliferative diseases are the second most common lymphoma after MF, instead of PTCL-u (Willemze et al. 2005).

Markers in Transformed MF

Additionally, a subset of these cells show increased expression of activation markers such as CD25 (interleukin 2 receptor family) and CD30 receptors (Zhang et al. 1996; Wasik et al. 1996). Activated B and T cells compose the transformed neoplastic tumor cells. These cells, usually medium or large in size, also express activation antigen CD30, a member of the tumor necrosis family (az-Cascajo 2001; Cepeda et al. 2003; Droc et al. 2007; Eckert et al. 1989; Edinger et al. 2009; Gallardo et al. 2002; Gniadecki and Rossen 2003; Kadin 2006; Kempf et al. 2012; Kikuchi et al. 1992). Similarly, the interleukin-2 family of receptors (Boehncke et al. 1993; Jakob et al. 1996; Kelley and Parker 2010) is noted to be present. Both antigens are seen in certain T- and B-cell lymphomas of the skin. In addition, high levels of Bcl2 proteins are expressed in transformed MF (Benner et al. 2009; Adachi and Horio 2008).

Follicle Helper T Cell as Putative Origin of Nodular T-Cell Lymphomas in the Skin

Germinal or follicle center T cells co-localize in B-cell-dominant germinal centers recognizable as rounded nodules in the dermis or subcutis. This T helper subset expresses follicle helper T-cell markers CD279, CD10, CD4, BCL-6, and CD57. Programmed death-1 (PD1, CD279a)-positive T cells localize in the ridge between germinal centers and the mantle and are an often used marker of follicle helper T cells (Blank and

Mackensen 2007; del Rio et al. 2005; Kantekure et al. 2012; Wang et al. 2007).

Many of the nodular neoplastic T-cell tumors discussed here that arise from helper T cells, the follicle helper T cells, the CD30 + T cells, and the gamma-delta T-cell subset, have putative histogenetic origin from lymph nodes to the skin via homing receptors cutaneous lymphocyte antigen (CLA) and cell chemokine CCR10 as part of the innate or adaptive immune system (Kim et al. 2006; Hudak et al. 2002; Kabelitz and He 2012; Kabelitz et al. 2005; Lanier et al. 1986; Lanier 2005). T-cell lymphomas that present in a nodular or follicular pattern may have this growth pattern presumably owing to their expression of follicle helper phenotype such as CD10 or PD-1. This group, which comprises the tumors forming the neoplastic nodular pattern, is postulated to include angioimmunoblastic T-cell lymphoma (AITCL), CD4 + pleomorphic T-cell lymphoma, the nodular subsets of PTCL-U, or cutaneous ALCL (Battistella et al. 2012; Ferenczi 2009; Gammon and Guitart 2012; Gaulard and de Leval 2011; Hu et al. 2012; Huang et al. 2009). In parallel, the cutaneous gamma-delta T-cell lymphoma is seen to localize following the normal predilections in the subcutaneous, dermis, and follicle epidermis via other idiopathic means.

Pathogenesis: Genotypic and Cellular Signal Pathway Profiles

For the majority of T-cell lymphomas, the pathogenesis is uncertain, although recent DNA profiling studies suggest that immunophenotypic profile and the T helper cytokine profile of the malignant T cells drive the pathogenesis and lead to dysregulation of normal immunity.

Gene expression profiling results show distinct signatures that predispose some types to stay within the skin environment and other genes predispose to dissemination and more aggressive course, as previously noted with MF and Sezary cells, but are also seen in skin-trophic c-ALCL and systemic-trophic cPTCL, also refered to as cPTCL, NOS or cPTCL, u (Ballabio et al. 2010; van Kester et al. 2010, 2011, 2012; Tracey et al. 2002, 2003). Increasing evidence also suggests that genetic and epigenetic profiles are key to clinical and biological behavior. There is evidence for epigenetic instability and promoter methylation in CTCL as well as their aggressive forms (Scarisbrick et al. 2003). *DNA profiling* studies showed inactivation of tumor suppressor genes (Scarisbrick et al. 2002), cell cycle dysregulation, defective DNA repair, disruption of apoptosis signaling, and, in advanced tumor stage MF, promoter hypermethylation of the *p16* gene (Navas et al. 2000). Tumor promotion in MF is postulated to be due to a combination of apoptosis signaling breakdown through increased tumor necrosis factor expression and promotion of apoptosis through inhibition of signal caspases. More practically, increased T-cell proliferation (higher *Ki67* expression) occurs in transformation of patch/plaque stages to advanced IIb tumor stage (Tracey et al. 2003; Wozniak et al. 2009).

Discussion of Individual Entities

Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

Definition

All cutaneous peripheral T-cell neoplasms that do not fit the better defined subtypes of PTCLs entities under the WHO-EORTC classification (Willemze et al. 2005) and that could be delineated from the provisional categories of pleomorphic CD4 + T-cell lymphoma, cutaneous gamma-delta, and epidermotropic CD8-positive T-cell lymphoma. Morphologically, PTCL-u comprise at least 30 % large cells and, phenotypically, lack CD30 surface membrane antigen (Bekkenk et al. 2003; Zucca and Zinzani 2005; Fink-Puches et al. 2002).

Epidemiology

PTCL-u affects middle-aged to elderly individuals (median age 68 years, range 20–87 years), with a male to female ratio of 2.5:1 (Bekkenk et al. 2003; Beljaards et al. 1994). In the WHO-EORTC classification, PTCL-u ranks third in incidence, after the CD30+ lymphoproliferative disease, which is the second most common after

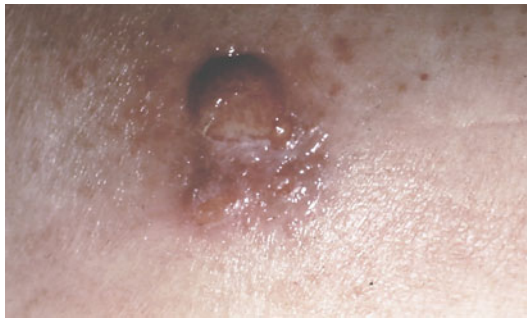

Fig. 10.1 Peripheral T-cell lymphoma, unspecified, showing clustered pustular plaque/nodule with satellite lesions

MF/Sezary syndrome (Willemze et al. 2005). PTCL-u cases have concurrent extranodal disease in 78 % of which skin involvement comprises about a fifth of cases so a diagnosis of PTCL-u in the skin requires a search for disseminated disease elsewhere including bone marrow disease (Savage et al. 2004).

Clinical Appearance of Lesions

Localized but more frequently generalized plaques or nodules are usually present (Fig. 10.1). These cases may be associated with systemic lymphoma, especially upon relapse (Willemze et al. 2005; Bekkenk et al. 2003; Zucca and Zinzani 2005).

Pattern of Infiltration

Diffuse and nodular (82 %) or band-like pattern (18 %) infiltrates occur in the dermis (Fig. 10.2a–c). Epidermotropism (27 %) is generally limited or absent. In less than 10 % of these cases, folliculotropism was present with less than 15 % with angiodestructive pattern (Bekkenk et al. 2003) (Fig. 10.3a–c).

Cytomorphology

For the designation of PTCL, the large cells (the neoplastic cells in which the nuclei are larger than macrophage nuclei or alternatively at least 4× the nuclear diameter of small lymphocytes) (Fig. 10.4a, b) represent at least 30 % of the total tumor cell population. Mitosis is frequent (Beljaards et al. 1994; Zucca and Zinzani 2005; Savage et al. 2004). This characteristic delineates pleomorphic small- and medium-sized CD4+ T-cell lymphomas (also called primary cutaneous small and medium-sized T-cell lymphoma) which show less than 30 % large cells. There is variable admixture with small lymphocytes and histiocytes and less commonly with sparse eosinophils and plasma cells (Bekkenk et al. 2003) (Fig. 10.5).

Immunophenotype

The neoplastic cells are often CD4 positive and by definition lack CD30, the latter delineating this heterogeneous group from CD30-positive T-cell lymphomas. And in many cases, one or more "mature" T-cell antigens are coexpressed, absent, or diminished (Fig. 10.6) (Savage et al. 2004; Bekkenk et al. 2003). Rare CD56 expression is seen, but a third of the cases express cytotoxic proteins (granzyme B, TIA-1) (Bekkenk et al. 2003). CD8+, double CD4-/CD8-negative, or CD4-/CD8-positive cases account for a minority (Fig. 10.7) (Bekkenk et al. 2003). Admixed B cells (5–10 %) were observed in less than 10 % of biopsies (Bekkenk et al. 2003), and sometimes tumor cells are weakly coexpressing CD20 or CD79a (Fig. 10.8). The prognostic significance of Th1 or Th2 chemokine receptor expression appears to divide PTCL-u into favorable and unfavorable groups. Those with expression of CCR4 (Th2), which correlates with CD25 expression, appear to have poorer clinical outcome than those with a Th1 profile (Tsuchiya et al. 2004; Ishida et al. 2004; Ishida and Ueda 2011).

Cytogenetics and Molecular Findings

TCR genes are clonally rearranged, but no specific karyotypic lesions are found (Bekkenk et al. 2003).

Clinical Behavior

Although primary cutaneous form is seen in practice, this disease presents in a largely systemic fashion with advanced tumor stage, albeit with a high frequency of the extranodal and skin involvement at presentation (Savage et al. 2004). Prognosis is poor, with a 5-year survival rate of less than 20 % (Willemze et al. 2005). No difference has been observed between patients who present with solitary and those who have generalized skin involvement (Bekkenk et al. 2003).

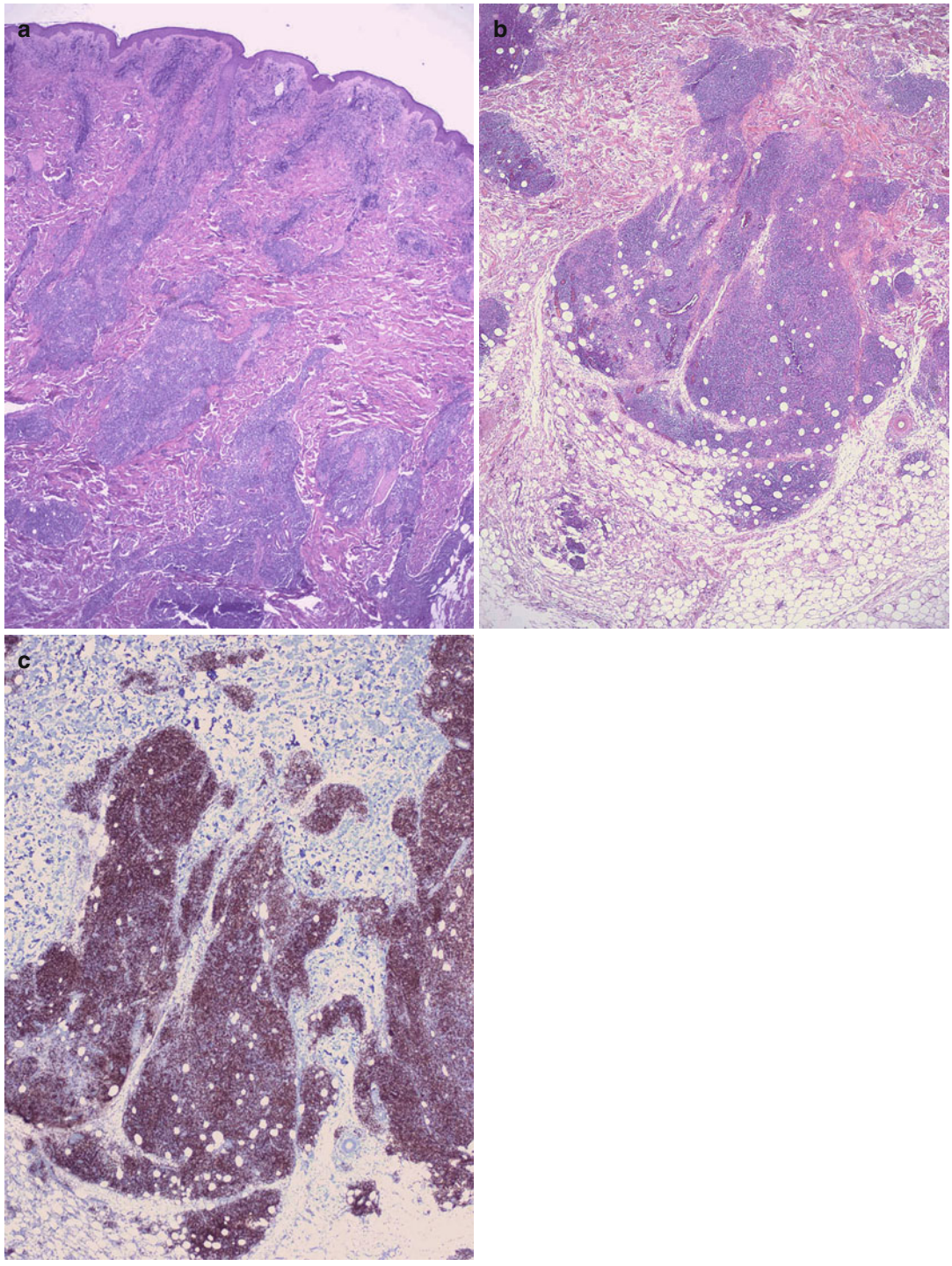

Fig. 10.2 The low-power histologic patterns of lichenoid with dermal (**a**), nodular, and diffuse (**b**) as well as CD3+ T-cell immunostain (**c**) in peripheral T-cell lymphoma, unspecified

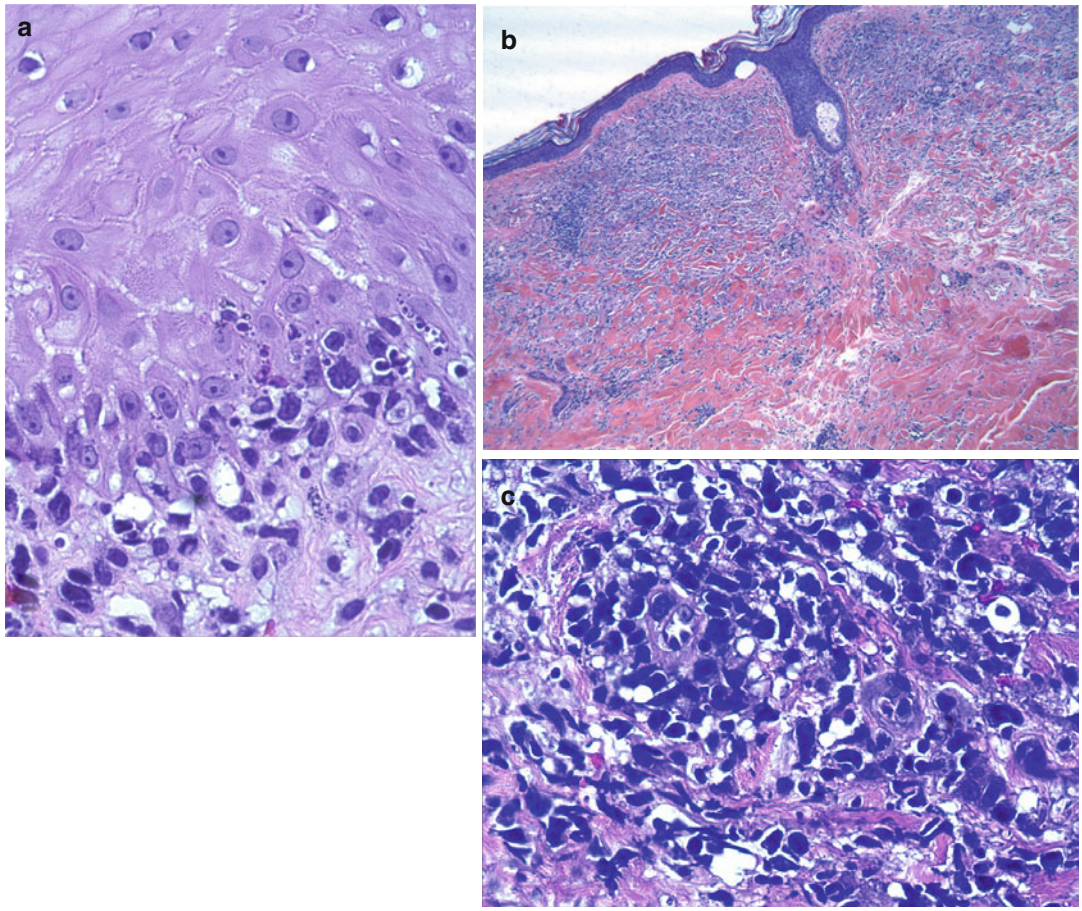

Fig. 10.3 (**a**) Epidermotropism, (**b**) folliculotropism, and (**c**) angiodestructive pattern in PTCL-u are also sometimes seen

Differential Diagnosis

MF transformed type, primary cutaneous small- and medium-sized T-cell lymphoma, or other aggressive cutaneous peripheral T-cell lymphomas (Rezania et al. 2007) (see Tables 10.1 and 10.2) or systemic lymphomas involving the skin are included in the differential diagnosis. Please refer to the discussion of the above entities within this chapter. Systemic PTCL-u has to be considered in the differential, especially considering that this predominantly nodal or viscerotropic lymphoma has predilection for skin involvement (Zucca and Zinzani 2005).

Systemic PTCL-u or Peripheral T-Cell Lymphoma, NOS

This group has an incidence rate of about 6 % of all non-Hodgkin lymphoma (Rudiger et al. 2002) and accounts for about a third of all PTCLs in western countries (Agostinelli et al. 2008; Rizvi et al. 2006). Patients are usually adults with 2:1 male to female ratio and present with nodal or visceral disease as the main clinical picture (Swerdlow et al. 2008). There is heterogeneity in pathology, and about half show morphological and molecular variability that echoes the term

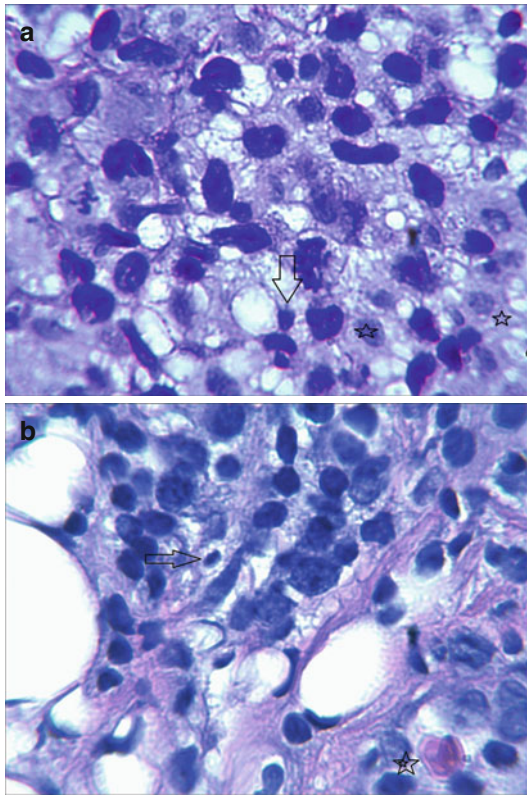

Fig. 10.4 PTCL-u. (**a**) The large neoplastic cell nuclei are larger than macrophage nuclei (*stars*) or (**b**) alternatively at least 4× the nuclear diameter of small lymphocytes (*arrows*) and represent at least 30 % of the cells. Note the atypical mitoses

"not otherwise specified" (Agostinelli et al. 2008; Went et al. 2006). Hence, diagnosis is made when other specific T-cell lymphomas are excluded. Tumor cells are invariably positive for βF1 and variably express CD4+, CD52+, and CD8 +/– immunophenotypes, with frequent antigen loss; double positive or negative CD4/CD8 are seen in more than half and Ki67 in greater than 80 % (Went et al. 2006). CD56 is seen in neoplastic T cells (Went et al. 2006). CD30, CD15, and CD20 are aberrantly seen in less than 10 % suggesting Hodgkin and B-cell non-Hodgkin in the differential (Quintanilla-Martinez et al. 1994, 1999; Yao et al. 2001). There is a high predilection to involve extranodal sites such as the liver, bone marrow, gastrointestinal tract, soft tissue, and skin (Zucca and Zinzani 2005; (Alekshun et al. 2008). The 5-year overall survival is 30–35 %, an intermediate rate, using standard chemotherapy (Savage et al. 2004). Extranodal presentations predict an even poorer prognosis. For example, cases with skin involvement as a primary that have progressed to systemic disease have a poorer prognosis, with a 5-year overall survival rate of less than 20 % (Willemze et al. 2005). No difference has been observed in patients presenting with solitary or generalized skin involvement (Bekkenk et al. 2003).

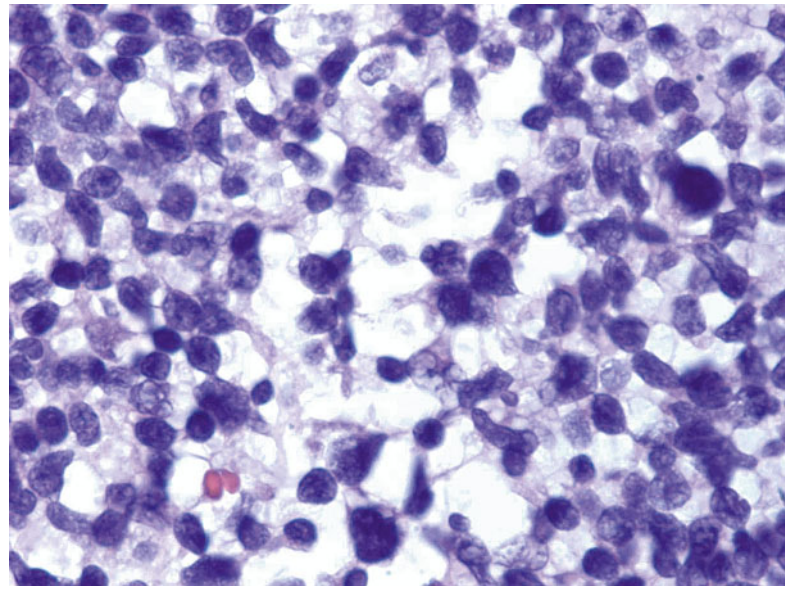

Fig. 10.5 PTCL-u. Variable admixture with small lymphocytes, histiocytes, and less commonly with sparse eosinophils and plasma cells

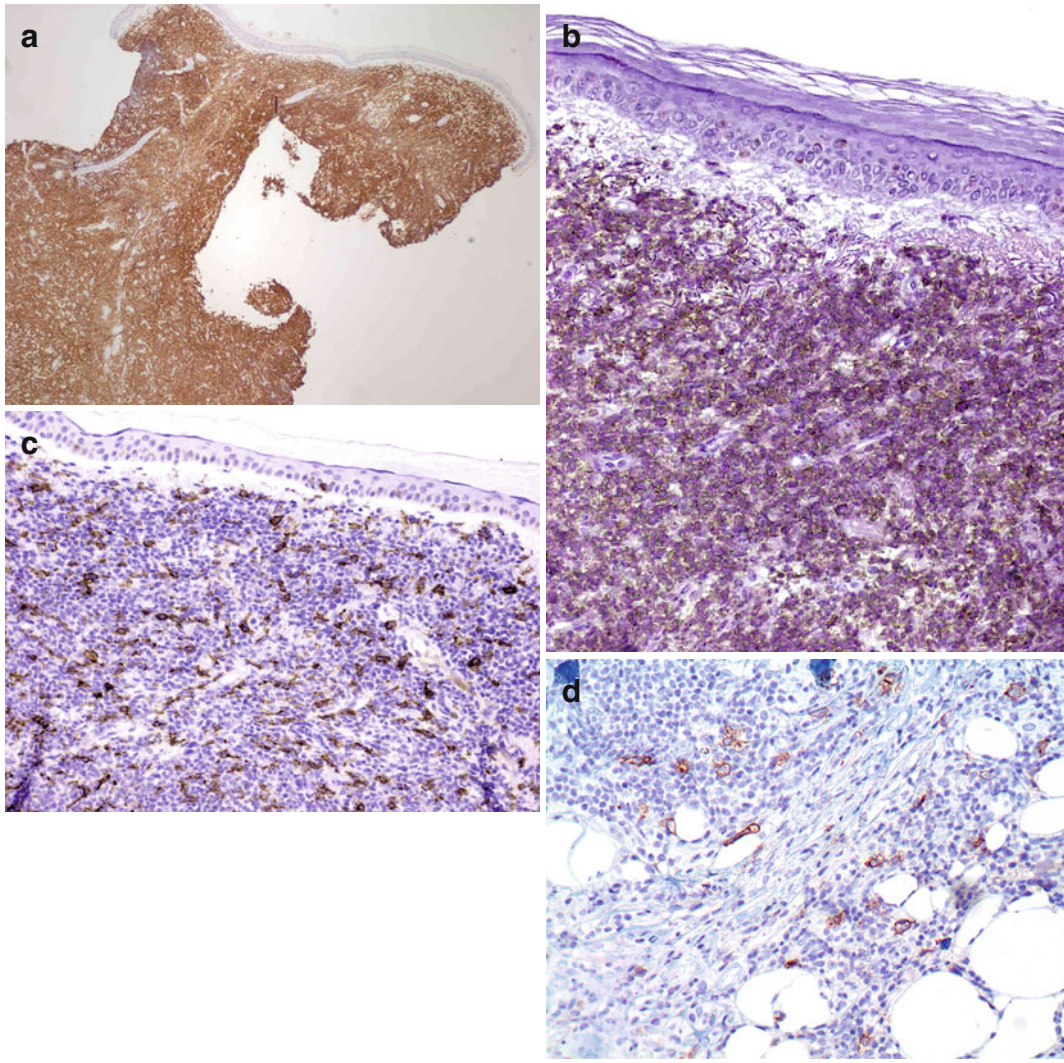

Fig. 10.6 PTCL-u with aberrant T antigens: CD7 positive (**a**), CD5 weak (**b**), lacking CD4 (**c**), and by definition CD30 negative or sparse (**d**)

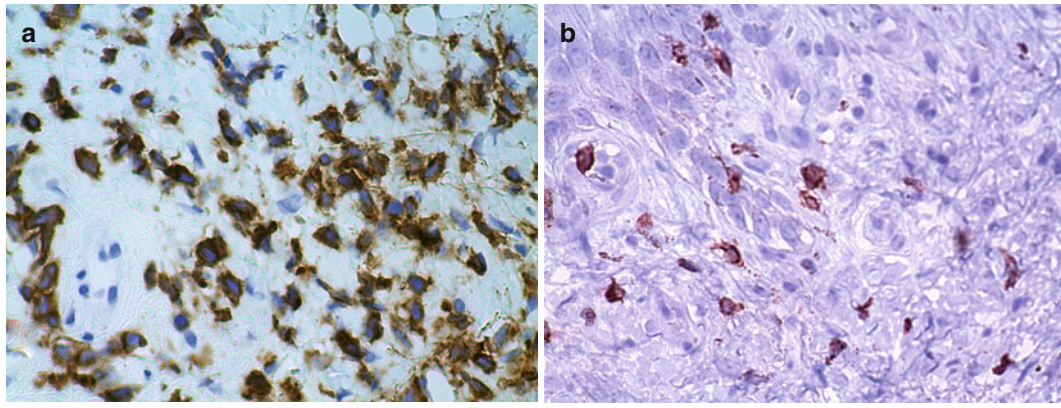

Fig. 10.7 CD8-positive PTCL-u cases are not infrequent (**a**). One or more "mature" T-cell antigens are aberrantly decreased or lost; (**b**) in this case, CD3-positive cells are much decreased

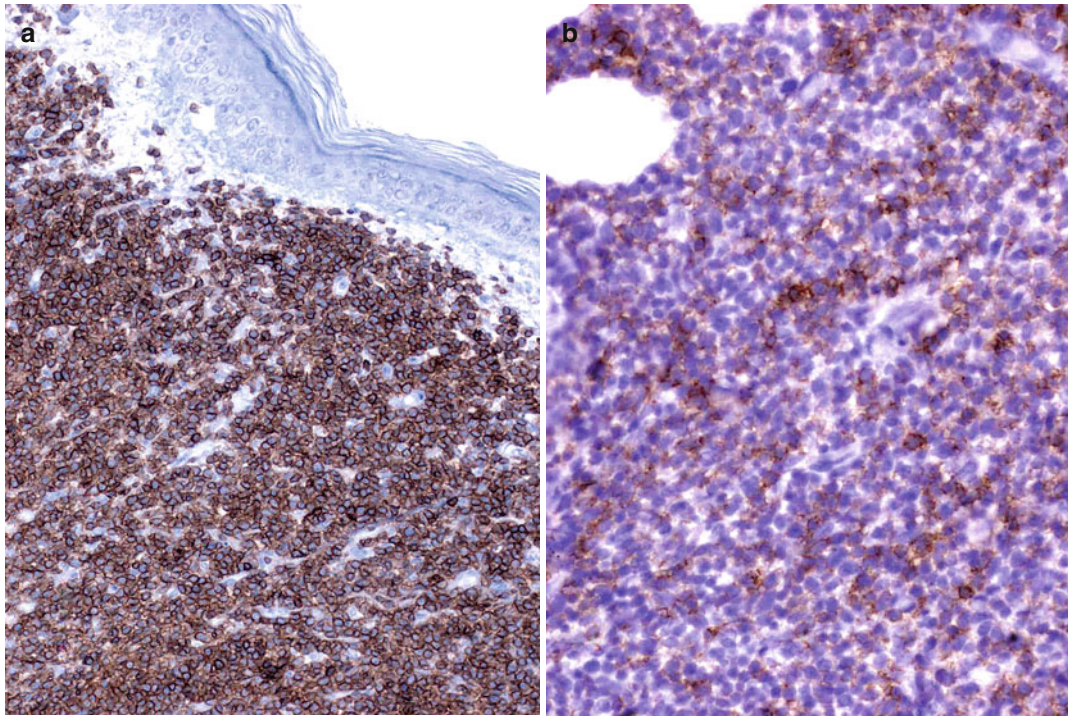

Fig. 10.8 (**a**) CD4-positive PTCL-u with (**b**) coexpression aberrantly of B-cell antigen, CD20

Table 10.1 Pathology, cytogenetics, and molecular biology of rare subtypes of mature T/NK-cell lymphoma

Lymphoma type	Morphology	Immunophenotype	Cytogenetics	Molecular biology	References
Cutaneous γδ T-cell lymphoma	Epidermal, dermal, subcutaneous perivascular cytophagic histiocytes, psoriasiform epidermal hyperplasia	CD3+/CD2+/ CD56+/ cytotoxic proteins+ (TIA-1, granzyme B, and perforin/CD4–/CD8±/ βF1± γ/δ +/CD5–)	Nonspecific	TCR genes are rearranged, EBV absent	Willemze et al. 2005 Toro et al. 2000
Primary cutaneous peripheral T-cell lymphoma, unspecified	Medium- to large-sized pleomorphic or immunoblast-like >30 %	CD4+/CD30–	Nonspecific	TCR genes are rearranged	Willemze et al. 2005 Bekkenk et al. 2003
Primary cutaneous small- to medium-sized T-cell lymphoma	Nodular infiltrates, small to medium lymphocytes <30 % large pleomorphic cells	CD3+/CD4+/CD8–/ or CD8+/CD30–/cytotoxic proteins–(granzyme B, TIA)	Nonspecific	TCR genes are rearranged	Willemze et al. 2005 Bekkenk et al. 2003
Extranodal NK/T-cell lymphoma, nasal type	Angiodestructive necrosis, polymorphous infiltrate admixed with inflammatory cells	CD56+/CD2+/cytoplasmic CD3ε+/cytotoxic granule proteins+(TIA-1, granzyme B, and perforin)/sCD3–/ CD4–/CD8–	del 6(q16–q27), del 13(q14–q34)	TCR genes are germ line, EBV+, mutations of k-*ras*	Willemze et al. 2005 Santucci et al. 2003

Table 10.2 Clinical features of rare subtypes of mature T/NK-cell lymphoma

	Cutaneous γδ T-cell lymphoma	Primary cutaneous peripheral T-cell lymphoma, unspecified	Primary cutaneous T-cell lymphoma CD4+ small/medium	Extranodal NK/T-cell lymphoma, nasal type
Median age, years (range)	61 (25–91)	68 (20–87)	53 (3–90)	50
M/F ratio	1.5	2.5	1:1	3.2
Clinical presentation	Disseminated plaques, nodules, tumors with ulceration, necrosis	Solitary or generalized nodules, tumors	Solitary plaques tumors, papules	Localized: destructive tumor of nasal cavity/nasopharynx Disseminated: plaques, tumors ± ulceration
Therapy	Systemic combined CT (chemotherapy)	Anthracycline-based combined CT ± RT	Solitary lesion: excision, RT (radiotherapy) Disseminated: PUVA, IFN-α, cyclophosphamide	Limited stage: RT ± CT Disseminated: CT or CT+RT
5-year disease spec survival rate	0 %	20 %	75 %	17–40 %
Median overall survival (months)	15–31	22	See text	45 (skin only)

Transformed Mycosis Fungoides

Introduction

Transformation of cutaneous T-cell lymphoma was first described by Lukes and Collins (1974). Because of the adverse effect on prognosis, a number of reports have been published since then to better identify and diagnose these cases. The presence of tumor MF clinically is not a sine qua non for a diagnosis of large cell transformation, and tumor MF may not show histologic evidence of transformation (Cerroni et al. 1992). Indeed, large cell transformation could be seen in both early and advanced MF (Lai et al. 2012). Hence, the diagnosis of large cell transformation of mycosis fungoides always requires histologic and cytological confirmation (Salhany et al. 1988; Dmitrovsky et al. 1987).

Tumor MF is one of the three facets of clinical progression; the others include nodal or visceral dissemination. Biopsy may show diffuse to nodular infiltrates with histologic evidence of large cell transformation of small cerebriform cells, which are sometimes referred to as "blastic" cells (Kamarashev et al. 2007), or histology may not contain a significant number of large cells in close to half of cases of tumor MF (Cerroni et al. 1992). Hence, accurate diagnosis of large cell transformation requires the histopathologist to count the number of large cells.

Definition

Large cell transformation is defined as having large cells (nuclei ≥4 times the size of a small lymphocyte) (Vergier et al. 2000), in 25 % or more of the dermal infiltrate or as cohesive nodules composed of large cells. Similar dire prognosis is noted if large cells comprise greater than 25 % or 50 % of cells (Vergier et al. 2000). This distinction from MF is very important since the course of MF is generally protracted except when superimposed with large cell transformation, development of tumors, or dissemination.

Epidemiology

About 8–55 % of MF patients undergo transformation, with 65 years as the average age at transformation (Vergier et al. 2000; Salhany et al. 1988; Greer et al. 1990; Cerroni et al. 1992). The incidence of transformation of mycosis fungoides varies according to the stage, being very rare in early stage MF reported to be from 0.5 to 7 % (Lai et al. 2012) to as much 31 % in stages IIB–IV and as much as 46 % in those with T3 tumors

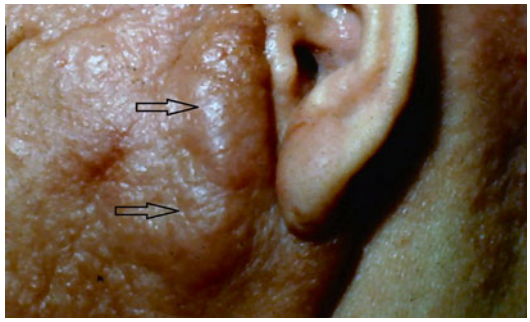

Fig. 10.9 Mycosis fungoides tumor stage (*arrows*) with histologic large cell transformation commonly occurs in the skin, here with antecedent macules, plaques, and papules

(Diamandidou et al. 1998). Tumor stage T3 has the highest incidence of transformation.

The median time to transformation from the time of initial diagnosis was reported to range from about a year to 6.5 years, dependent on varying length of clinical follow-up (Greer et al. 1990; Vergier et al. 2000). About a quarter presented before 2 years from diagnosis. The cumulative probability of transformation is 39 % happening between 1 year and about 12 years (Diamandidou et al. 1998).

A clinically advanced stage higher than tumor stage IIB predict up to 31 % will have large cell transformation versus 14 % in the lower stages. Once transformation occurs, the survival from disease of patch, plaque, and tumor stages was 7.2, 2.3, and 1.8 years, respectively (Kamarashev et al. 2007). The proposed ISCL/EORTC classification revision requires the size of at least one tumor to be at least 1.5 cm in diameter to meet the definition of tumor in T_3 (Olsen et al. 2007). However, biopsy is needed early on as transformed MF may be seen in 13 % of MF patients without clinical evidence of tumor formation (Vergier et al. 2000).

Clinical Appearance of Lesions

The most common location of transformation occurs in the skin (Fig. 10.9), but other uncommon sites like CNS are reported. Transformation often occurs in lymph nodes, where transformation is detected first in 35 % (Salhany et al. 1988; Vergier et al. 2000). In the skin, transformed MF are usually associated with multiple skin lesions and plaques or tumors (Cerroni et al. 1990) or rarely as solitary nodules (Vergier et al. 2000; Greer et al. 1990). Painful: ulcerations that may be reddish, indurated, or elevated, and pruritic; and dry well-demarcated tumors are observed. These tumors are usually located in sun-unexposed areas such as the abdomen, breast, buttocks, trunks, or neck (Berger et al. 2011; Greer et al. 1990). True de novo transformed MF at presentation is reported but probably very rare, considering that 18 % (Vergier et al. 2000) to 36 % (Diamandidou et al. 1998) of cases that presented within months of diagnosis as MF transformation have had a long history of dermatitis that were suggestive of MF.

Extracutaneous disease noted in about 1 % of a large multivariate survival study is associated with clinical evidence of tumors (T3 stage) in 61 %, noted commonly in the lung, oronasopharynx, and central nervous system (Agar et al. 2010).

Pattern of Infiltration

Most of the transformed cases showed a diffuse pattern (Fig. 10.10), sometimes forming micronodules, with lichenoid and patchy pattern in the minority (Diamandidou et al. 1998). Other reports show tumor nodules or large cells located in upper dermal to subcutaneous tissue (Vergier et al. 2000). There is often a decrease in epidermotropism and increased large cells, usually away from hair follicles or epithelia but within the dermis or subcutis (Salhany et al. 1988). The large transformed cells in the dermis often extend from the dermal-epidermal interface into the subcutaneous tissue. A narrow grenz zone, sometimes with reactive fibrosis, frequently separates the epidermis from the dermal tumor in the central portion of the mass. Epidermis may be ulcerated, rarely show Pautrier's microabscesses, and if present usually are comprised of cerebriform cells and large transformed cells (Fig. 10.11) (Salhany et al. 1988).

Cytomorphology

The large cells have round to oval vesicular nuclei, large nucleoli, and moderately abundant amphophilic cytoplasm; sometimes these cells show nuclear irregularity, and along with conspicuous

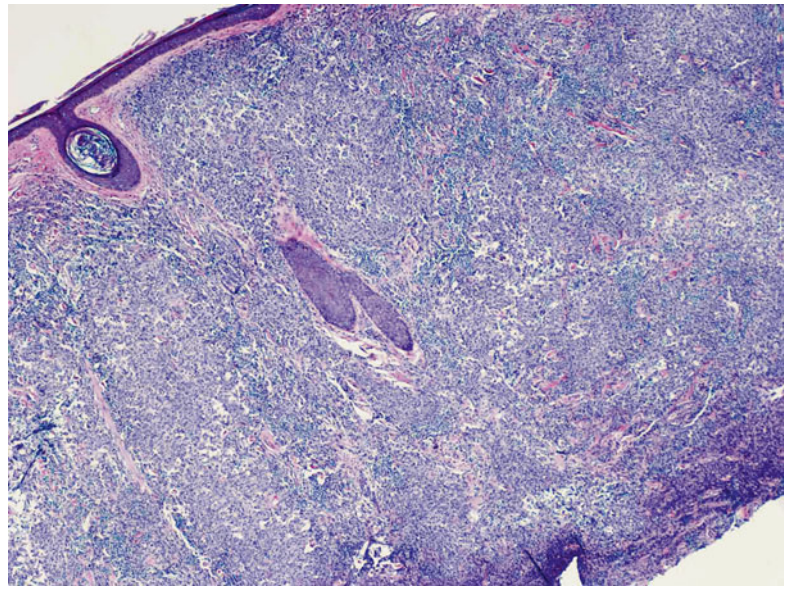

Fig. 10.10 Transformed tumor stage MF, histologically with a diffuse pattern

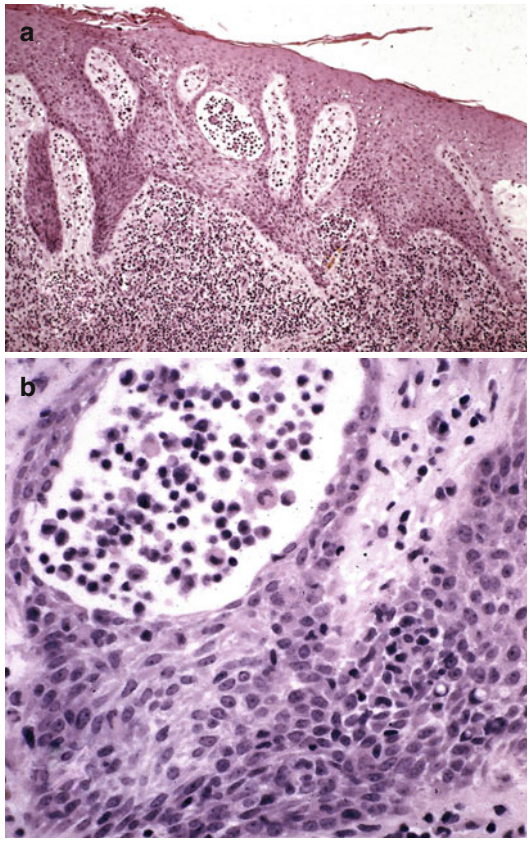

Fig. 10.11 Transformed tumor stage M. (**a**) Pautrier's microabscesses overlying lichenoid pattern. (**b**) Closer view of microabscess with hyperchromatic cerebriform and large transformed cells with lobated nuclei

nucleolus, these cells appear as multinucleated or Reed-Sternberg-like cells although classic Reed-Sternberg cells are rare (Fig. 10.12) (Salhany et al. 1988). The cytopathology of transformed cells appears variously as either medium to large pleomorphic, anaplastic, immunoblastic, or unclassified (Fig. 10.13) (Cerroni et al. 1992). Mitoses are often numerous. Admixed histiocytes along with Langerhans cells are always seen within the dermal infiltrates but must be differentiated from tumor cells. The number of large cells has to be counted, because of similarly bad prognosis of patients with 25–50 % of large cells (Fig. 10.14). Large cells could be defined as above or more precisely greater than 35 μm (Salhany et al. 1988) or more conventionally as greater than the size of macrophage nuclei. Small to large cerebriform or atypical "dysplastic" cells are scattered or easily seen along the periphery of the dermal mass (Salhany et al. 1988), and this salient feature may differentiate transformed MF from similar neoplasm such as ALCL or PTCL-u.

Immunophenotype

Similar to other cutaneous peripheral T-cell lymphomas, transformed MF may lose or gain some T-cell antigens such as CD7, CD5, CD3, or betaF1. Transformed MF often have CD3+ T

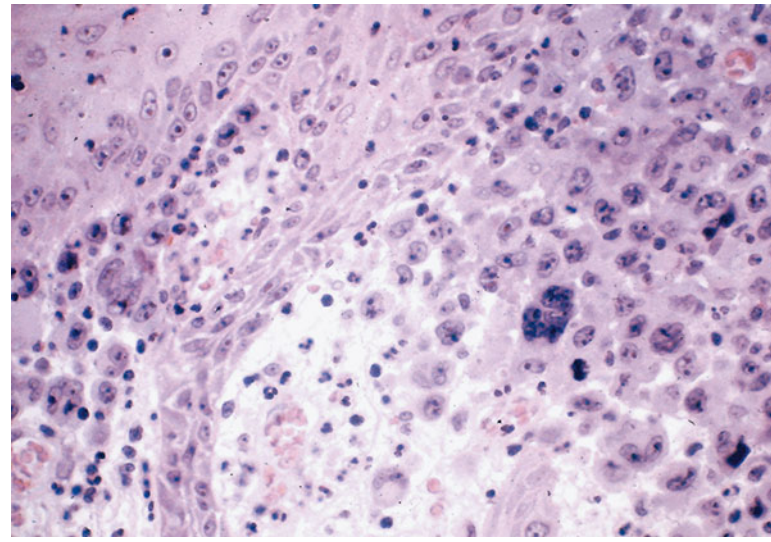

Fig. 10.12 MF with large cell transformed lymphoma cells showing lobated irregular nuclei, with conspicuous nucleoli, with occasional Reed-Sternberg-like cells although classic Reed-Sternberg cells are rare

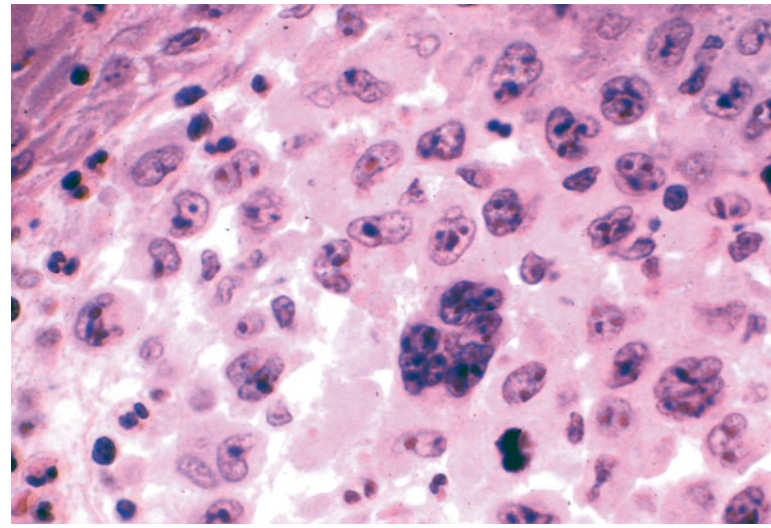

Fig. 10.13 The transformed cells in MF appear variously as either medium to large pleomorphic, anaplastic, immunoblastic, or unclassified, with frequent mitosis, all represented here

helper phenotype expressing CD4 in 70 % of cases, CD8 in 19 %, and absent CD4 and CD8 in 4 %; and most have partial loss of one or more T antigens and, in 4 %, aberrant expression of B-cell antigens CD20 and CD79 (Benner et al. 2012b).

A decreased intensity or diminution of total number of positive cells may be seen in CD7, CD26, CD45RO, CD5, or CD3 (Jones et al. 2001; Salhany et al. 1988). Absent or diminished pan-T antigens can be observed, while CD30, CD15, or CD75 (LN2) may appear as aberrant additional antigens simulating that seen in Reed-Sternberg cells, each noted in about half of the cases (Salhany et al. 1988). CD25 may be expressed weakly in all of the few cases tested (Diamandidou et al. 1998). Varying expression of CD30 in the large transformed cells (Fig. 10.15) from 31 to

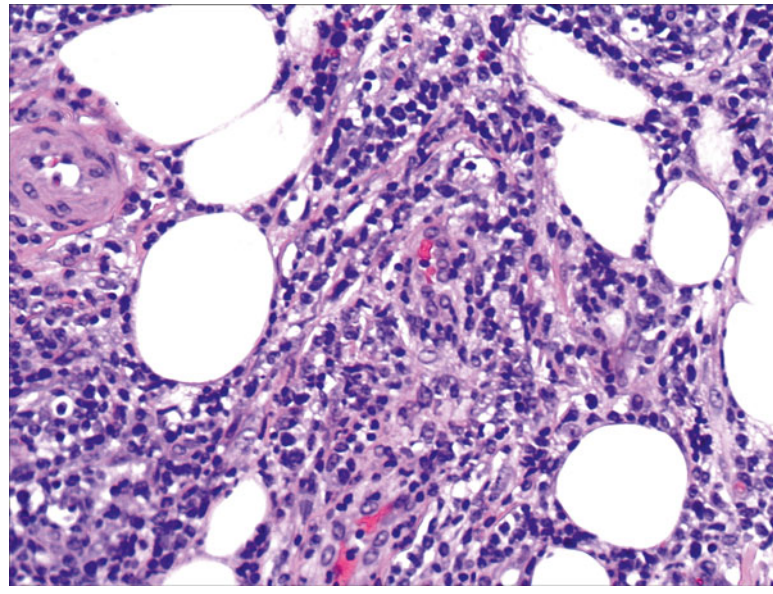

Fig. 10.14 Deep subcutaneous tissue is often involved as in this case

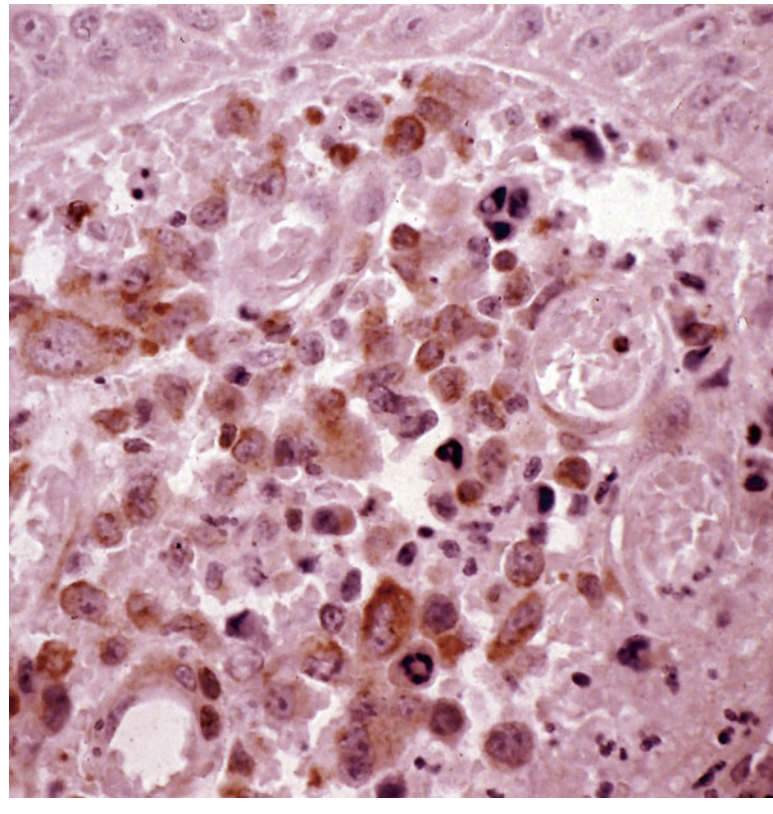

Fig. 10.15 CD30-positive transformed MF cells with cytoplasmic and surface *brown* staining

50 % is seen (Olsen et al. 2007; Arulogun et al. 2008; Barberio et al. 2007; Vergier et al. 2000). High expression (greater than 75 % CD30-positive cells) is seen in 15 % (Vergier et al. 2000) to 39 %, while low level (less than 5 %) noted in 45 %, with the remainder of cases (Benner et al. 2012b) showing intermediate expression. Interestingly, Benner et al. reported that CD30 expression in transformed MF is associated with a significantly better survival (Benner et al. 2012b). Their finding raises the question of whether the improved prognosis of those patients was due to inclusion of ALCL masquerading as T-MF.

Immunophenotypes of large cell lymphoma arising from MF are similar to the original MF. The small cerebriform malignant cells gave rise to large cell lymphoma in transformed MF because both cells contain identical T-cell surface v-beta antigens as detected by flow cytometry technique using a set of monoclonal antibodies to T-cell receptor V-beta region families (Wolfe et al. 1995).

Cytogenetics and Molecular Findings

A majority of T-cell gene rearrangement results in MF/SS (84 %) show a clonal T-cell population using PCR or GeneScan capillary electrophoresis (Ponti et al. 2005, 2008). Furthermore, this clone of MF and its large cell transformation are singular. They show identical clones upon V-beta or PCR nucleotide sequences, using molecular genetics of the low grade and its transformed lesion years apart (Wood et al. 1993). Hence, transformation is an evolution instead of an emergence of new malignant clones.

In untransformed MF, an abnormal cytogenetics is found in 66 %, ranging from hypo- to hypertetraploid, with same malignant clones found in the skin, blood, and lymph nodes (Nowell et al. 1982). Losses and gains of chromosome materials are also documented likewise using comparative genomic hybridization with most frequent loss in chromosomes 1p, 17p, 10q, and 19 and gains in chromosomes 4q, 18, and 17q (Mao et al. 2002). FISH analysis documented evidence of chromosome 1 and 17q rearrangements in a third of Sezary syndrome cases. Similarly, multicolor FISH (SKY) detected structural and recurrent chromosomal abnormality in 47 % with chromosome 10 showing the most frequent abnormality (Batista et al. 2006).

However, conventional cytogenetics data on large cell transformation is surprisingly scant when compared with the molecular genetics and nucleotide profiling analysis data. Using gene profiling analysis, a total of five genes are significantly upregulated in tumor stage compared with patch/plaque stage MF. Tumorigenesis is here associated with upregulation of antiapoptotic and inhibition of proapoptotic pathways leading to growth advantage via TRAF1 and tumor necrosis factor receptors (Tracey et al. 2003). In addition, using microRNA profiling, there are different miRNAs expressed in tumor stage MF that allows differentiation from nontumor MF and ALCL (Benner et al. 2012a; van Kester et al. 2011, 2012; Berger et al. 1988; Karenko et al. 2007). Inflammatory versus MF gene expression profile has also been reported (van Kester et al. 2012). Of targeted therapy significance, genes associated with Th1 immune response and cytotoxicity are downregulated, while CD52 and interleukin seven genes were upregulated in mycosis fungoides/Sezary syndrome (Hahtola et al. 2006).

Clinical Behavior

The 10-year disease-specific survival of MF shows an indolent course with over 80 % surviving, while development of tumor reduces survival to 42 % (Agar et al. 2010; van Doorn et al. 2000) and presence of large cell transformation reduces survival to between 2 and 36 months in most series (Dmitrovsky et al. 1987; Greer et al. 1990; Salhany et al. 1988; Vergier et al. 2000; Barberio et al. 2007; Arulogun et al. 2008; Diamandidou et al. 1998; Benner et al. 2012b) and in a specially large series (Agar et al. 2010) up to 100 months. Similarly, a cohort of patients with tumors in contrast to those with plaques/patches fared poorly (Suzuki et al. 2010b). The presence or absence of large cell transformation in all patients that *already had tumor stage* did not show difference in survival (Vonderheid et al. 1981; Benner et al. 2012b).

Early transformation less than 2 years from diagnosis, advanced stage (IIB–IV vs. I–IIA) (Diamandidou et al. 1998; Berlingeri-Ramos et al. 2007), and extracutaneous dissemination are poor prognostic signs. In patients with disease limited to only skin lesion at transformation, findings of folliculotropic MF, lack of CD30 in large cells, and extracutaneous disease are significantly associated with reduced survival (Benner et al. 2012b). In contrast when studying earlier stages of MF, Edinger found that increasing numbers of CD30+ cells conferred a worse prognosis, as did increased numbers of Ki-67+ cells, although the two markers were independent of each other (Edinger et al. 2009). Increased serum levels of soluble CD30 are also associated with a poorer survival for patients with early (stages 1–IIa) MF (Kadin et al. 2012).

Differential Diagnosis

1. CD30 anaplastic large cell lymphomas: It is important to have an accurate measurement of the CD30-positive cells to differentiate transformed MF from the CD30-positive (ALCL) lymphomas. The diagnosis of T-MF with CD30 + large cells instead of a de novo CD30 + lymphoma is made if clinical evidence of patch and/or plaque skin lesions compatible with MF precedes the transformation, along with a morphology composed of a pleomorphic types from small cerebriform to large cells. This diagnosis is supported if there are less than 75 % CD30-positive large cells among the T cells, but differentiation cannot be made reliably if more than 75 % of large cells are CD30 (Vergier et al. 2000). Beylot-Berry reported that perforin expression by large cells is significantly more frequent in ALCL complicating MF than in T-MF (personal communication 2nd World Congress on Cutaneous Lymphomas, Berlin, Feb 6–10, 2013).
2. Histiocyte-rich or granulomatous MF, histiocytic clusters: Histiocyte-rich or granulomatous MF is characterized by nodules of large histiocytic cells mimicking large lymphoma cells. It is important to separate this type with large cell transformation of tumor cells composed of T lymphocytes because the clinical course of "histiocyte-rich MF" or "granulomatous MF" parallels MF without transformation (Vergier et al. 2000). In contrast to the latter, histiocytes or granulomatous nodules mark with CD68 (KP1 or PGM1 clones) instead of pan-T antibodies. In one series of transformed MF, upwards of 67 % of these cases show clusters of histiocytes (Vergier et al. 2000). CD68 staining for histiocytes should be performed in suspected transformed MF. This is because if using routine histology only in the assessment of large cells, these cells may not be of T-cell origin but of macrophage lineage. Although the nuclei of macrophage are also large like tumor cells, there are subtle clues to tell them apart. Histiocytic cells are morphologically different from T cells, the former showing scant to very pale and sparse heterochromatin vesicles while the latter tend to have thicker darker chromatin and prominent chromocenters. Macrophages tend to have round to oval thin pinkish nuclear membranes and small nucleolus, while transformed MF may have thick irregular, lobated membranes and prominent nucleolus. However, when clusters of histiocytes are closely admixed with large tumor cells, their differentiation from neoplastic cells may be difficult.
3. Large B-cell lymphoma: The presence of sheets of B cells could be seen in transformed MF and hence may cause confusion with B-cell lymphomas. Clusters of large cells in MF may not be T cells as up to 45 % has been found to be of CD20+ B cells in origin. Hence, CD20 staining for B cells is also an essential panel for working these cases (Vergier et al. 2000). Interpretation is further complicated by the aberrant expression of B-cell antigens, e.g., CD20 by tumor T cells in some T-MF (Merlio communication) (2nd World Congress on Cutaneous Lymphomas, Berlin, Feb. 6–10, 2013).
4. *Tumor d' emblée*: Although the classic Alibert description of MF (Alibert 1806) included

patches, plaques, and progression to ulcerated tumors, a number of literature reports beginning with Vidal-Bronc in 1805 (Habermann and Pittelkow 2007) to the beginning of the twentieth century (Pernet 1912; Pringle 1914) and in the 1950s (Olivier 1951; Pernet 1912; Pringle 1914) described *tumor d' emblée* as an initial presentation of MF. However, current CTCL classification raises concern that *tumor d' emblée* could largely represent a type of nodular cutaneous PTCL, instead of a variant of MF, when seen in a setting that is not accompanied by a long-standing MF. The prevailing view is that when a patient initially presents with only tumor without previous or current patches or plaques, a diagnosis of MF is not likely, but may instead be diagnostic for other T-cell lymphomas infiltrating the skin (Willemze et al. 2005) or perhaps a variant of a systemic peripheral T-cell lymphoma that involves the skin.

Early series of MF tumor stage study include tumor MF detected at presentation (Salhany et al. 1988), but more recent case series excluded "tumor d' emblée" cases. Vergier et al. excluded cases that present without clinical history or histologically confirmed MF if the initial presentation was a large T-cell lymphoma without proven previous clinical and histologic MF (Vergier et al. 2000). In a review of the historical evolution of cutaneous lymphoma classification, Kempf noted that the WHO-EORTC classification (Willemze et al. 2005) excluded *d' emblée* form of MF and in those presenting with tumor should instead consider other T-cell lymphomas such as cutaneous PTCL, unspecified (Kempf and Sander 2010).

5. Non-MF subtypes of CTCL: For patients presenting with tumors, it is important to differentiate tumor stage MF from non-MF subtypes of CTCL such a pleomorphic CD4 small- and medium-sized T-cell lymphoma and PTCL-U (see discussions on each type in this chapter).

Primary Cutaneous Small- to Medium-Sized T-Cell Lymphoma (PCSM-TCL)

Introduction

This provisional entity in the 2008 WHO and 2005 WHO-EORTC classification was called primary cutaneous CD4-positive small/medium T-cell lymphoma (Swerdlow et al. 2008; Willemze et al. 2005). Subsequent case series addressing whether this is a valid entity have indicated that this "entity" may be heterogeneous (Garcia-Herrera et al. 2008; Williams et al. 2011). Hence, phenotypically this group may present as CD8 + tumors, or the CD4 + type may be seen presenting as one of these categories: (1) "solitary… T-cell nodules of undetermined significance" that overlap with reactive pseudolymphomas (Beltraminelli et al. 2009; Leinweber et al. 2009), (2) indolent T-cell lymphoma (Garcia-Herrera et al. 2008; Williams et al. 2011), and (3) a more aggressive subset that may clinically simulate PTCL-u with an adverse course (Garcia-Herrera et al. 2008; Williams et al. 2011).

Because of the nodular T-cell-rich immunohistology and its indolent course, this disease group overlaps with the wide variety of T-cell pseudolymphomas (Beltraminelli et al. 2009; Leinweber et al. 2009) and presents a diagnostic challenge. Accurate diagnosis may require an optimal combination of morphology with accurate large cell identification, immunohistology, clonality, and clinical features for adequate distinction (Williams et al. 2011). A histologic subset of PCSM-TCL with eosinophilia and recurrent skin nodules reported by Campo and the Barcelona group (Garcia-Herrera et al. 2008) may especially mimic allergic/drug-induced T-cell nodular form of pseudolymphoma or cutaneous lymphoid hyperplasia.

Definition

Primary cutaneous small- and medium-sized T-cell lymphoma (PCSM-TCL) presents most commonly as a solitary nodule and histologically

as nodules of "pleomorphic" small and medium cells admixed with less than 30 % large or immunoblastic cells (Willemze et al. 2005; Kempf and Sander 2010; Beljaards et al. 1994; Swerdlow et al. 2008). As part of the definition, there should be no clinical evidence of patches and plaque seen in MF. For convenience, we will use the term pleomorphic T-cell lymphoma interchangeably with PCSM-TCL.

A unifying list of criteria for diagnosis may include the following criteria as modified from Cerroni et al. (2009), Garcia-Herrera et al. (2008), and Williams et al. (2011):

1. Absent history or lesions diagnostic of MF or marked epidermotropism.
2. Molecular evidence of monoclonal T lymphocytes.
3. T cells expressing CD3/alpha-beta (either CD4 or CD8), not gamma-delta TCR framework.
4. Absent CD30 (to exclude CD30 lymphomas).
5. Nodular or diffuse infiltrate of neoplastic small- and medium-sized T cells.
6. Admixture of many reactive B, reactive T, histiocytes, eosinophils, and polyclonal plasma cells.
7. Histologic evidence of fewer than 30 % large cells (to exclude PTCL-u).
8. Accurate quantification of proliferative count of Ki67 of less than 25 % and in CD4 tumors with less than 10 % CD8 reactive T cells will exclude the aggressive variant of PCSM-TCL (Garcia-Herrera et al. 2008; Williams et al. 2011) which were clinically recommended to be included with and may behave like a PTCL-u (Garcia-Herrera et al. 2008; Williams et al. 2011).

Epidemiology

A rare disease accounting for 2 % of all CTCLs (Willemze et al. 2005). There is a wide age range of presentation with a median age of 53 years (range 3–90 years), with a male to female ratio of 1:1 (Beltraminelli et al. 2009; Leinweber et al. 2009).

Clinical Appearance of Lesions

The most common locations are in the head and neck, upper trunk, and rarely lower extremities (Bekkenk et al. 2003; Garcia-Herrera et al. 2008) (Fig. 10.16).

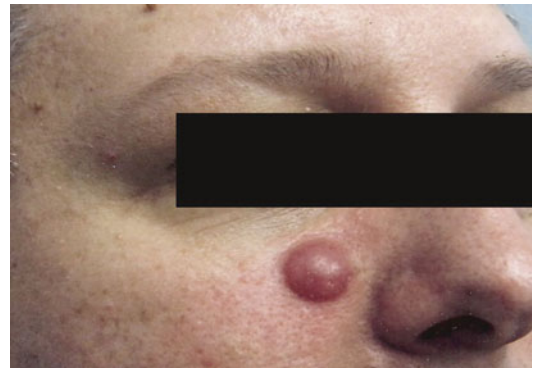

Fig. 10.16 Primary cutaneous small- and medium-sized T-cell lymphoma showing as a solitary reddish nodule on the face

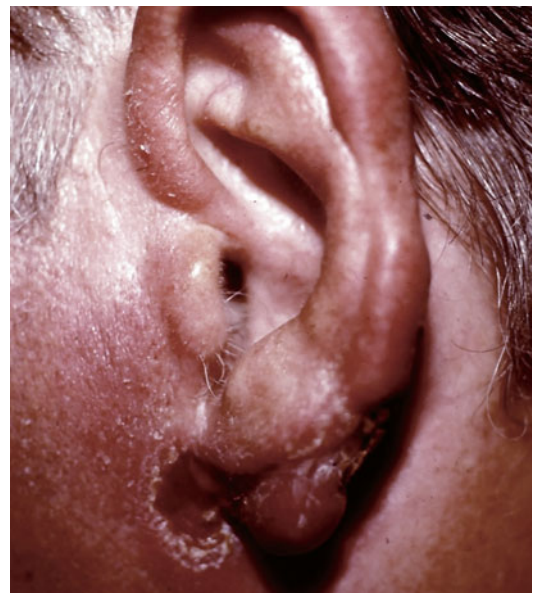

Fig. 10.17 The CD8+ variant of PCSM-TCL has predilection for the ear

The CD8+ type has predilection for the ear (Fig. 10.17) as described below. A minority of clinical presentations include multiple nodules or large tumors; otherwise systemic symptoms are usually not present (Beltraminelli et al. 2009; Garcia-Herrera et al. 2008; Leinweber et al. 2009).

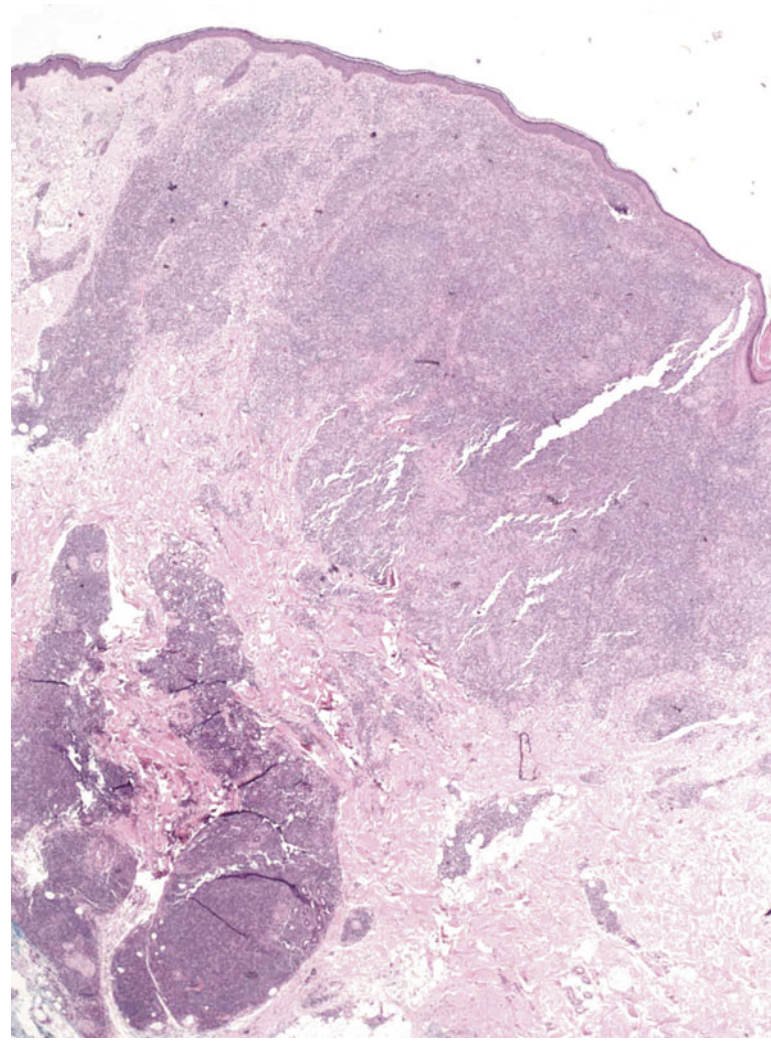

Fig. 10.18 Primary cutaneous small- and medium-sized T-cell lymphoma showing a dense nodular involvement throughout the upper and deep dermis close to subcutaneous tissue

Pattern of Infiltration

Infiltrates are dense, diffuse, or nodular within the dermis (Fig. 10.18), with a tendency to infiltrate the upper portions of the subcutaneous tissue (Fig. 10.19). There is minimal or no epidermotropism (Fig. 10.20). Significant epidermotropism should raise consideration of MF and higher magnification evaluation for typical cerebriform morphology for exclusion of the latter.

Cytomorphology

Cells are pleomorphic composed of majority of small- to medium-sized lymphocytes with scattered or more specifically less than 30 % large cells (Fig. 10.21). Reactive small lymphocytes, many eosinophils, and histiocytes may also be seen (Fig. 10.22) (Bekkenk et al. 2003). A subset with intense eosinophilia has been described as a possible histologic variant of this disease (Garcia-Herrera et al. 2008). The term pleomorphic is

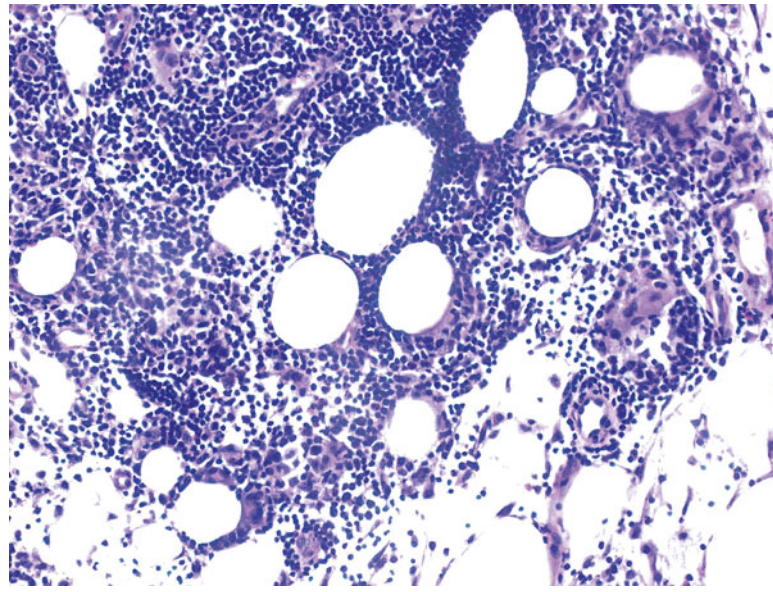

Fig. 10.19 Primary cutaneous small- and medium-sized T-cell lymphoma with focal spread to the upper portions of the subcutaneous tissue

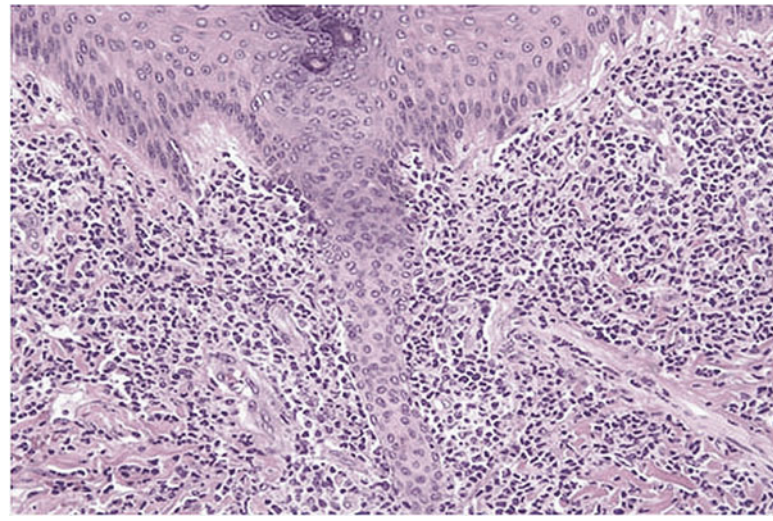

Fig. 10.20 Primary cutaneous small- and medium-sized T-cell lymphoma with minimal to absent epidermotropism, unlike that seen in mycosis fungoides

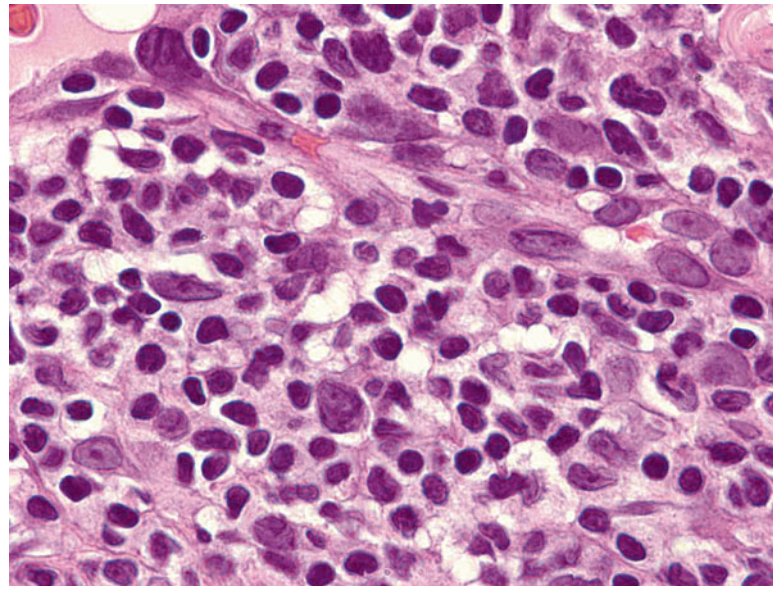

Fig. 10.21 Primary cutaneous small- and medium-sized T-cell lymphoma cells are pleomorphic composed of small- to medium-sized lymphocytes with less than 30 % large cells

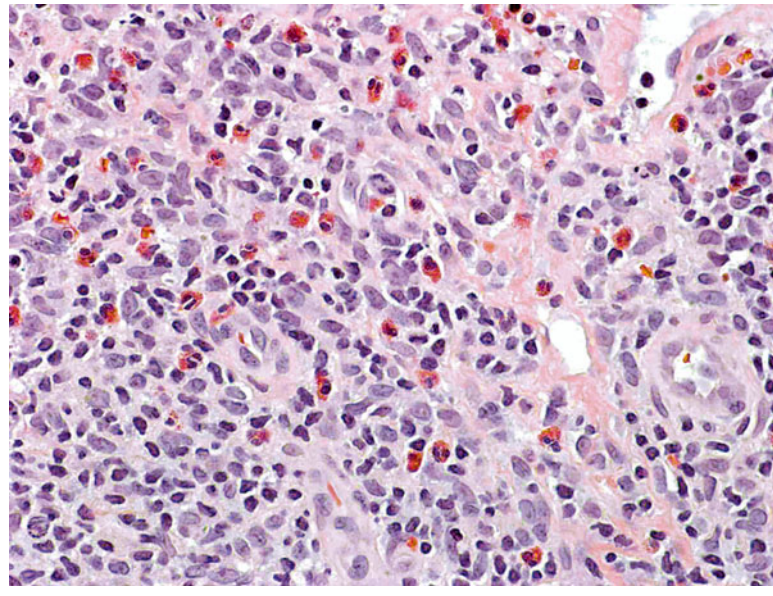

Fig. 10.22 Some primary cutaneous small- and medium-sized T-cell lymphoma cases may show a mixture of small lymphocytes, few plasma cells, many eosinophils, scattered histiocytes, and many capillaries and vessels

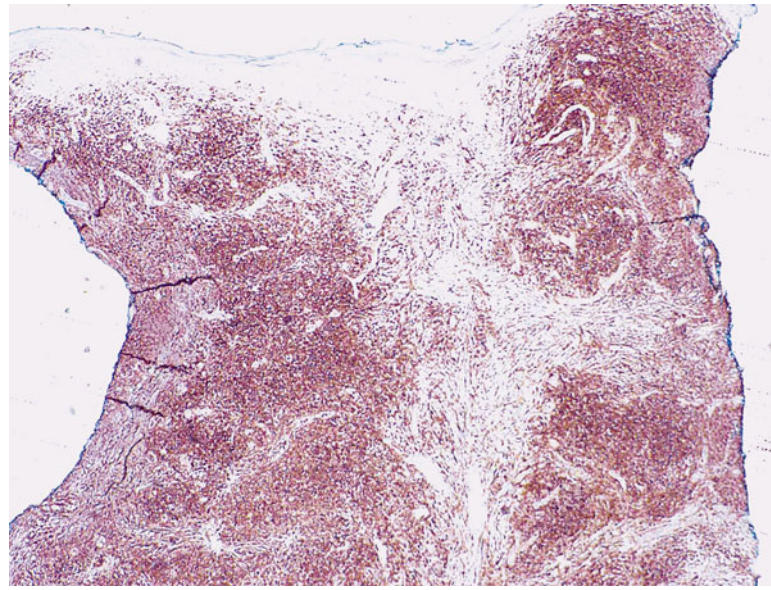

Fig. 10.23 Primary cutaneous small- and medium-sized T-cell lymphoma cells are usually positive for CD4, in diffuse and nodular pattern

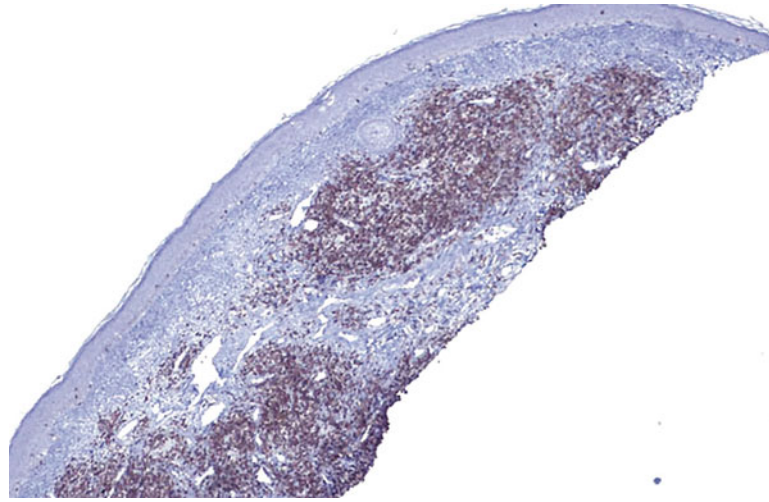

Fig. 10.24 PCSM-TCL may present as a variant composed of CD8-positive tumor cells, particularly when the nodules are located in earlobes

mostly included in the diagnostic terms but have also been substituted by (SM) small- and medium-sized descriptors and the presence of less than 30 % large cells (Beljaards et al. 1994).

Immunophenotype

The neoplastic cells are positive for CD3 and CD4 (Fig. 10.23) in most cases and positive in CD8 in a minor subset, usually localized in the ear (Fig. 10.24). Cytotoxic proteins (granzyme B, TIA) and Epstein-Barr virus and CD30 and CD56 antigens are not seen in CD4 + tumor cells, and T-cell antigens are aberrantly lost in some cases (Garcia-Herrera et al. 2008; Von Den and Coors 2002).

Originally described as showing only CD4-positive T cells, a collection of recent reports suggest a primary cutaneous small- and medium-sized

T-cell lymphoma may have CD8 immunophenotype. Almost uniformly, the reports described an indolent, nonepidermotropic, pleomorphic nodular tumor in the ear, with CD8 immunophenotype (Geraud et al. 2011; Beltraminelli et al. 2010; Petrella et al. 2007; Swick et al. 2011; Suchak et al. 2010). Hence, if accepted as part of this group, more recent terminology of PCSM-TCL is notable for absence of the CD4 descriptor. Despite the similar CD8 immunophenotype, this former group is not to be confused with the aggressive and epidermotropic CD8+ T-cell lymphoma, often with ulcerated skin lesions and localized in other skin regions (Berti et al. 1999; Gormley et al. 2010; Nofal et al. 2012).

Along with the dominant neoplastic T cells, admixed reactive CD20 + B cells and polyclonal plasma cells, dotted with eosinophils and histiocytes, are findings that overlap with pseudolymphoma or cutaneous lymphoid hyperplasia (Sterry 1986; Sterry et al. 1992).

Cytogenetics and Molecular Findings

Diagnosis requires molecular genetic analysis and positive TCR gene rearrangement for unequivocal diagnosis of PCSM-T-cell lymphoma versus the similar-looking T-cell pseudolymphoma. TCR genes are rearranged in 60 % (Beltraminelli et al. 2009) to 100 % of reported cases (Grogg et al. 2008; Rodriguez Pinilla et al. 2009). In practice, we tend to consider TCR-negative cases as T-cell pseudolymphoma and positive cases as PCSM-TCL.

Clinical Behavior

The WHO 2008 classification of lymphomas included two provisional categories under PTCL-u. Of these two, only primary cutaneous small- and medium-sized pleomorphic CD4+ T-cell lymphomas have a good prognosis (Swerdlow et al. 2008; Willemze et al. 2005). Localized lesions have a good prognosis with local treatments. A disease-specific 5-year survival rate of up to 75 % and an overall 5-year survival rate of 45 % have been reported (Bekkenk et al. 2003). A large series with long follow-up revealed most were alive without lymphoma after a median follow-up of 63 months (Beltraminelli et al. 2009).

About 200 cases of this provisional entity have been reported, and despite the presence of clonal T cells in many reported cases, the indolent behavior of these lesions perhaps has earned them a recommendation to consider the term "cutaneous nodular proliferation of pleomorphic T cells of undetermined significance" in lieu of small and medium pleomorphic T-cell lymphoma (Von Den and Coors 2002; Bekkenk et al. 2003; Friedmann et al. 1995; Grogg et al. 2008; Beltraminelli et al. 2009; Leinweber et al. 2009; Garcia-Herrera et al. 2008; Sterry et al. 1992; Rodriguez Pinilla et al. 2009; Kim and Vandersteen 2001).

However, a group of five cases with clinical and histologic features of PCSM-TCL was described that followed an aggressive clinical outcome, with a median survival of 23 months, akin to PTCL-u (Garcia-Herrera et al. 2008). Although others believe these cases are different from PCSM-TCL, by using histologic criteria alone, these cases appear to fit that category if one were to exclude one case with an associated nodal Langerhans cell sarcoma (Garcia-Herrera et al. 2008). What sets this group apart from the typical course for PCSM-TCL and may perhaps be useful in practice to exclude these cases from the indolent PCSM-TCL are the following: differences in clinical behavior, high proliferative rate, and different tumor-reactive microenvironments. The markers were scored objectively using commercial image analysis techniques as previously described (Carreras et al. 2006). Hence, this group is characterized by having rapidly growing large tumors (>5 cm) versus less than 3 cm in the indolent group, high mitotic index with median Ki67 % of 22 (15–43) versus 9 % (range 1–20) and low CD8 infiltrating lymphocytes (0.3–8 %) versus 20 % (range 9–47) in indolent, respectively, and, finally, sparse B cells versus nodules of B cells in indolent (Garcia-Herrera et al. 2008).

Because of the clinical difference, a proposal to lump this set in the PTCL-u disease category, instead of as a variant of PCSM-TCL, appears reasonable (Williams et al. 2011). However, to accurately delineate this group, an accurate count of immunomarkers was done by the Barcelona group (Garcia-Herrera et al. 2008). This is

Table 10.3 T-cell lymphoma versus T-cell pseudolymphoma

	Nodular PCSM-TCL	Nodular pseudo-T-cell lymphoma	PTCL, unspecified
Clinical	Solitary, rare multiple	Solitary, rare multiple	Multiple, rare solitary
Course	Indolent	Benign	Aggressive with high mortality
Pattern	Nodular diffuse, nonepidermotropic, dermal to focal subcutaneous tissue	Nodular, also may be band-like or perivascular, usually just dermal	Diffuse and nodular, dermal to subcutaneous tissue
Cytology	Small and medium size, less than 30% large cells	Small and medium size, with immunoblasts and histiocytes	Large cells > 30% of cells
T and B clonality	Monoclonal T	Polyclonal T and B	Monoclonal T
Phenotype	CD4, rare CD8, few or CD30 negative; loss of T-cell antigens; Ki67 increased >25%	CD4,CD8 mixed with CD20 sheets, scattered CD30,ki67 wide range low to less than 40%	CD4, CD8, some CD20 aberrant, loss of T-cell antigens,CD30 negative or few; ki67 increased 60 % of more
Reactive components			
Plasma cells	Few	Few or many sheets	Few
Eosinophils	Few	Few or many sheets	Few
Histiocytes	Few	Many diffuse or granulomas	Few
CD20	Few	Sheets or clusters	Few
CD8, if CD4 tumor	Few	Increased	Few

because by using histologic criteria alone (of less than 30 % large cells) and without using immunomarkers, this aggressive group may inadvertently and unfortunately be assigned to the category of PCSM-TCL. To nullify this heterogeneity and standardize the criteria for diagnosis of PCSM-TCL, clinical and immunomeasurement analysis (immunometric or hematometric analysis) may be used. Those that are aggressive appear to present with a large rapidly growing tumor bigger than 5 cm and decreased CD8 and CD20 cells. A validated 2-D image analysis computerized tools that perform the function of cell population statistic automation applied to fixed tissue immunostains may be helpful in this regard (Nielsen et al. 2012; Baatz et al. 2009; Cualing et al. 2007; Carreras et al. 2006, 2009; Garcia-Herrera et al. 2008).

Differential Diagnosis

T-cell nodular pseudolymphoma – the most important differential diagnosis is from the nodular and diffuse type of T-cell pseudolymphoma. Two major histo-architectural types of T-cell pseudolymphoma include the MF-like band and the nodular T-cell pattern (Smolle et al. 1990; Wirt et al. 1985). Clinically, a clear-cut etiology from either a recent drug intake, insect bite, or chemical exposure though uncommon may lead to an easy diagnosis. However, since most pseudolymphomas are idiopathic, a thorough correlation for clinical regression on follow-up along with a biopsy for immunohistology, morphology, and molecular genetics may all be useful. See Table 10.3 (Rijlaarsdam et al. 1992; Adams 1981; Albrecht et al. 2007; Arai et al. 1999; Bakels et al. 1997; Barr-Nea et al. 1976; Bendelac et al. 1986; Bergman 2010; Bernstein et al. 1974; Bignon and Souteyrand 1990; Blazejak and Holzle 1990; Blumental et al. 1982; Bocquet et al. 1996; Brodell and Santa Cruz 1985; Cerroni and Goteri 2003; Delaporte et al. 1995; Good and Gascoyne 2009; Griesser et al. 1990; Kulow et al. 2002; Landa et al. 1993; McComb et al. 2003; Rijlaarsdam and Willemze 1994; Smolle et al. 1990; Sterry 1986; Tallon et al. 2010; Van Der Putte et al. 1986; Wirt et al. 1985).

In general, pseudo-T-cell lymphomas may show a nodular pattern (Fig. 10.25) and minimal nuclear atypia of lymphocytes and, by immunostains, show increased number of reactive lymphoid cells in clusters positive for CD8 T cells or

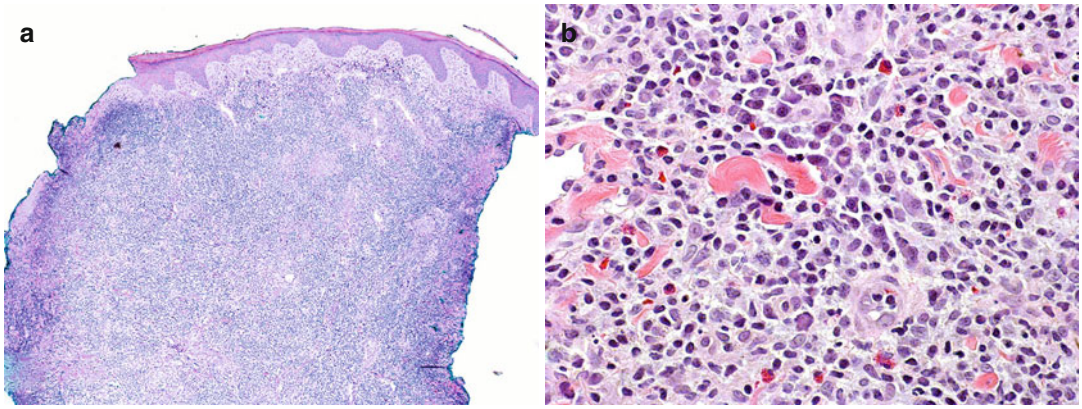

Fig. 10.25 (**a**) Pseudo-T-cell lymphomas mimic PCSM-TCL because they may also often present as a solitary nodule and histologically may likewise show a diffuse to nodular pattern. This biopsy is from a coin-sized nodule on an arm close to an IV drug line, the reactive nature confirmed by polyclonal T and B cells demonstrated with negative TCR and IgG gene rearrangements. (**b**) On high power, there are many capillaries with histiocytes, eosinophils, and clusters of plasma cells

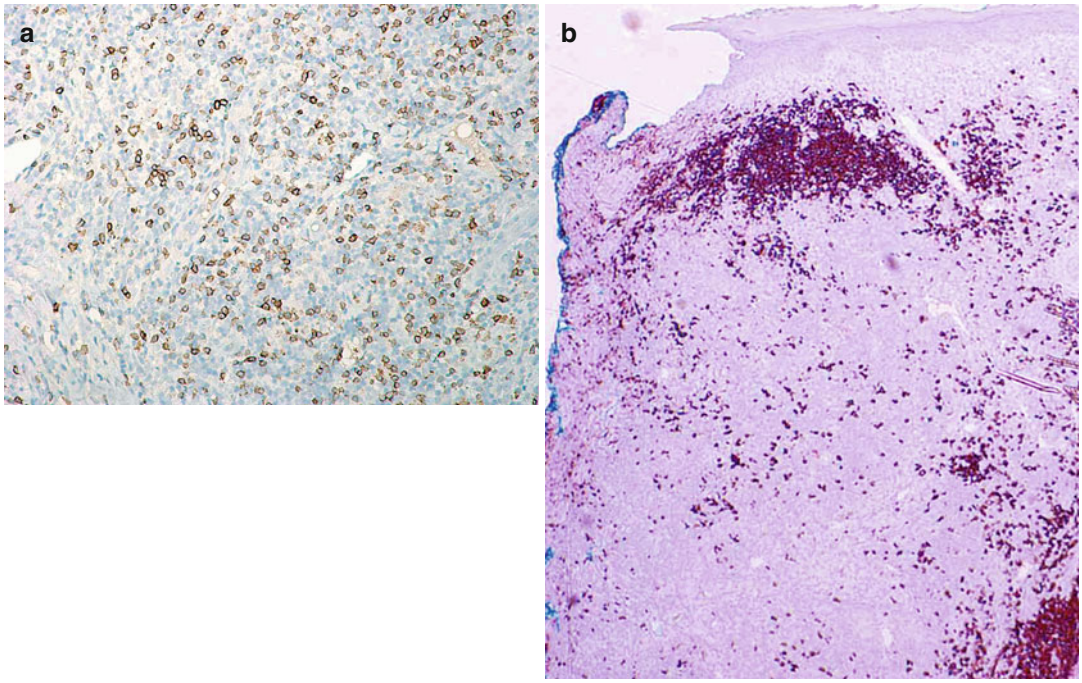

Fig. 10.26 T-cell pseudolymphoma with increased number of reactive cells positive for CD8 T cells (**a**) and CD20 B cells in clusters (**b**)

CD20 B cells (Fig. 10.26), and low Ki67 (Fig. 10.27) as well as increased in eosinophils or plasma cells (Fig. 10.28) and CD68+ histiocytes (Fig. 10.29), sometimes with histiocytic clusters and granulomas (Smolle et al. 1990; Wirt et al. 1985; Rijlaarsdam et al. 1992), and tend to be polyclonal (Bakels et al. 1997). In a comparative series on CD4+ T-cell pseudolymphomas, the CD8+ small T cells ranged between 15 % and 60 % (median, 25 %) compared to between 2 %

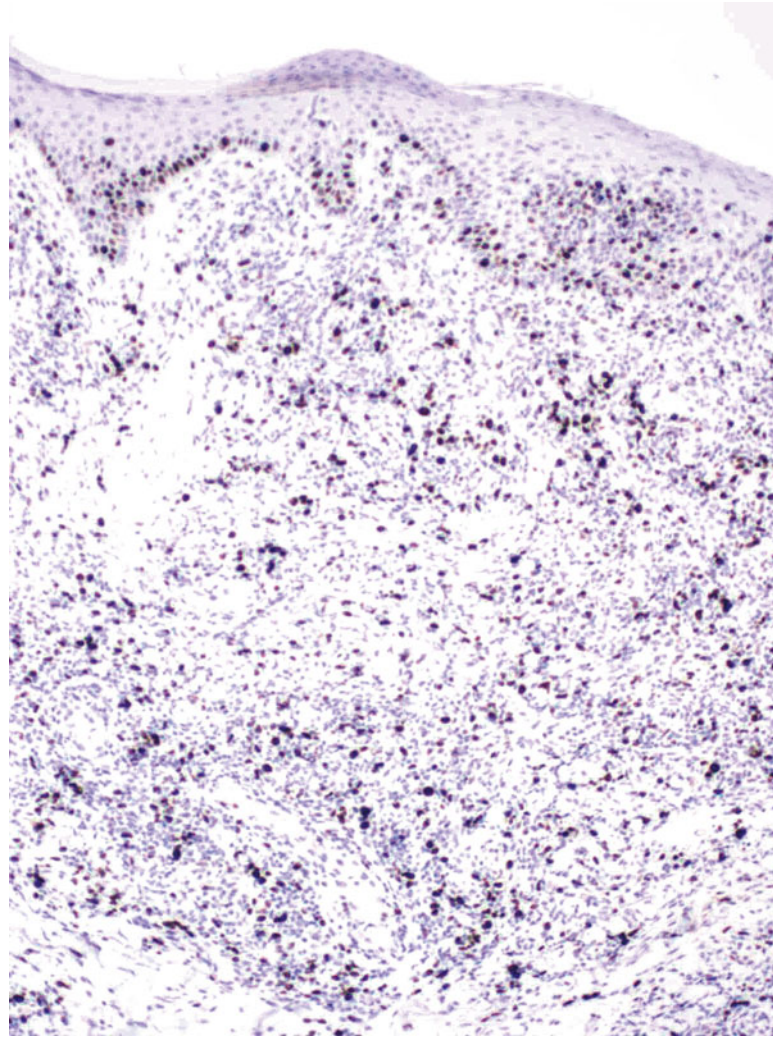

Fig. 10.27 T-cell pseudolymphoma with low Ki67

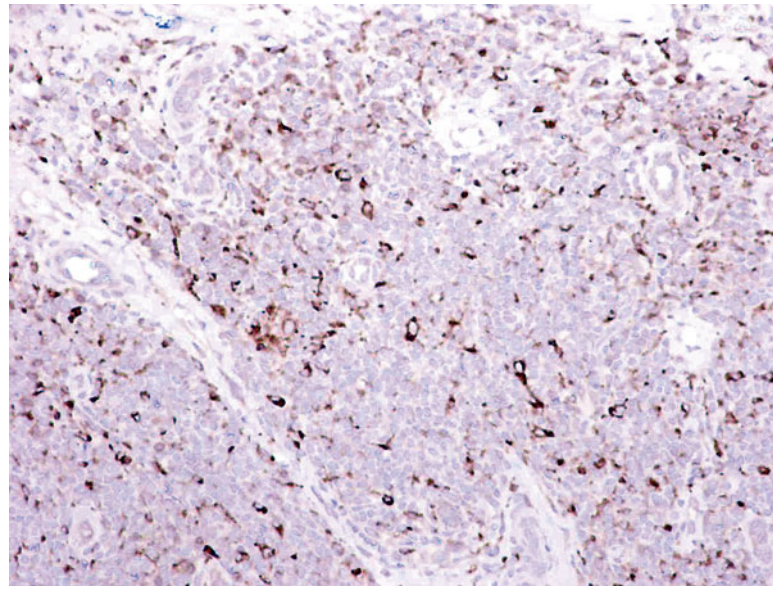

Fig. 10.28 T-cell pseudolymphoma with single and clusters of CD68+ histiocytes

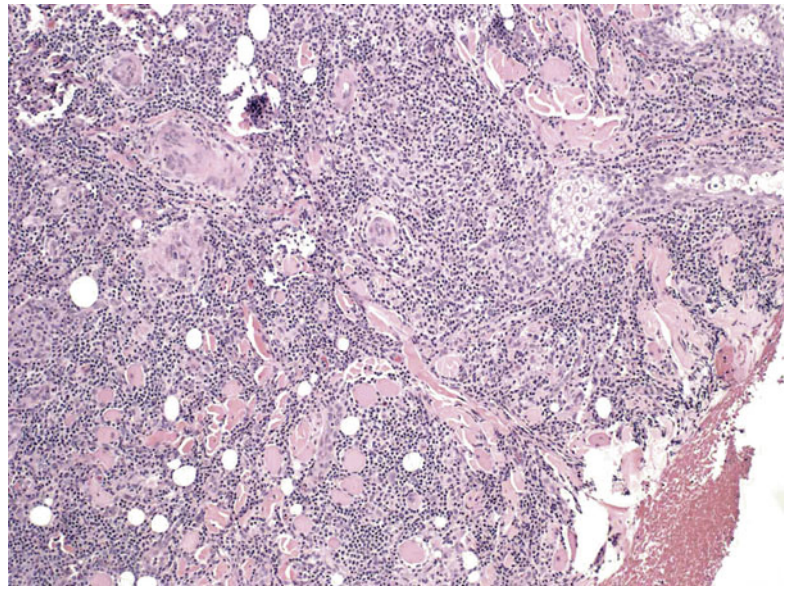

Fig. 10.29 T-cell pseudolymphoma with clusters of histiocytes and small granulomas

and 15 % (median, 5 %) in transformed MF and between 1 % and 10 % (median, 2 %) in the aggressive PTCL-u. In indolent nodular pleomorphic T-cell lymphoma, however, the CD8 + T cells overlap with the nodular pseudo-T-cell lymphoma (15 and 35 % CD8+). Similar pattern has been observed in the proportion of CD20+ B (Bakels et al. 1997).

Despite utilizing all these tools for diagnosis, distinction may not be possible since it is widely understood that there is a spectrum of clonal benign dermatitis to frank clonal malignant lymphoma (Wood 2001; Kulow et al. 2002; Gniadecki 2004; Gniadecki and Lukowsky 2005; Burg et al. 2005; Guitart and Magro 2007).

PTCL, unspecified, is also a differential diagnosis since some of these cases may rarely present as solitary or few nodules presenting a clinical challenge from PCSM-TCL. The distinction is mainly histopathologic, with the accurate evaluation of the presence of more than 30 % large cells in PTCL-u and less than 30 % in small- and medium-sized T-cell lymphoma. Here the large cells have been variously defined as having nuclei greater than 4×, the size of small lymphocyte nuclei or in those terminologies borrowed from hematopathology lymph node workup as those cells with nuclei larger than macrophage nuclei. See Table 10.1.

The relation of PCSM-TCL with the few cases described as "primary cutaneous follicle center T cell lymphoma" (Battistella et al. 2012) must be clarified because of the clinical and immunohistologic overlap with PCSM-TCL especially if Bcl6, PD1, and CD10 immunostains are routinely performed. This distinction may not be possible since a number of reports indicated the PCSM-TCL of CD4 type may be of follicle center cell derivation. Hence, the CD4 PCSM-TCL tumors show expression of a subset identified with the follicle helper T cells, typically forming rosettes around B immunoblasts (Rodriguez Pinilla et al. 2009). Follicular T helper cells express PD1 (CD279), Bcl6 (follicle center cell), and CXCL13 (Rodriguez Pinilla et al. 2009). Programmed death-1 (PD1) expression, normally associated with germinal center cells (Fig. 10.30), may be used in workup of these tumors. The PD1 immunoreactivity is decreased or lacking in MF, PTCL-u, CD30 lymphomas, and aggressive CD8 epidermotropic lymphomas but note that PD1 will not separate from the immunophenotypically similar PD1 expression in T-cell pseudolymphomas (Cetinozman et al. 2012).

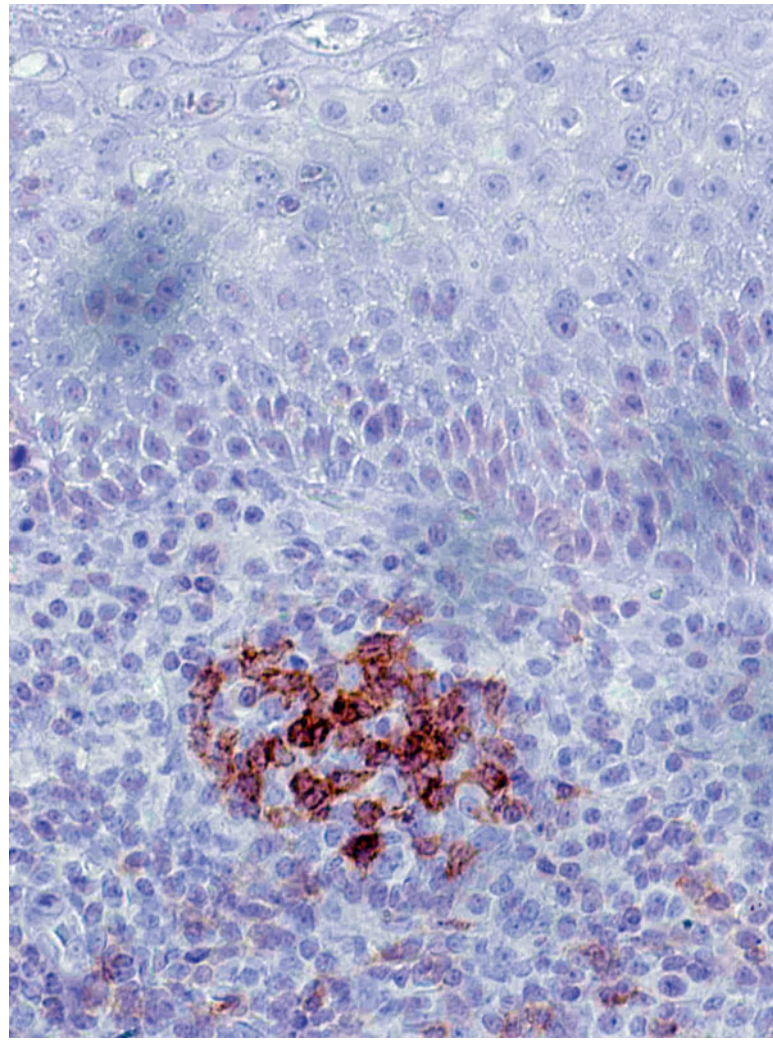

Fig. 10.30 PD1 expression in germinal center T cells in subepidermal location. Note the weaker staining scattered interfollicular T cells

Cutaneous Gamma-Delta T-Cell Lymphoma

Introduction

Primary cutaneous γδ T-cell lymphoma is a rare subset of cutaneous T-cell lymphoma that needs to be delineated from the more common CTCLs and from the similar hepatosplenic lymphoma because of its unique presentation, adverse course, and its hematologic complications (Kadin 2000; Guitart et al. 2012). It has to be noted that both mucosal and cutaneous T γδ lymphomas are different from the hepatosplenic γδ T-cell lymphomas, which are derived from immature γδ T cells and which are positive for TIA-1, but negative for granzyme B and perforin (Toro et al. 2000). Hepatosplenic γδ T-cell lymphomas do not involve the skin. They cause splenomegaly, hepatomegaly, and relatively minimal lymphadenopathy. They usually affect middle-aged men and cause pancytopenia and early death. They are characterized by specific chromosomal abnormalities including isochromosome 7q (Gaulard et al. 2003).

Although primary cutaneous γδ T-cell lymphoma is a provisional entity under the WHO-EORTC (Willemze et al. 2005), it has been included in the WHO 2008 (Swerdlow et al. 2008) under the umbrella of primary cutaneous peripheral T-cell lymphoma, rare subtypes (Gaulard et al. 2008).

It would be useful to review the nosology of this rare cutaneous lymphoma. The T-cell membrane cell surface is specified by a CD3 complex in association with either a T-cell alpha-beta (T αβ) or a T gamma-delta (T γδ) protein subset (Bluestone et al. 1995; Bluestone and Matis 1990). The either/or exclusivity of these markers in normal T cells has been a given for decades, and the presence of TCR βF1 is assumed to identify alpha-beta T cells and exclude T γδ cells, but recent reports suggest a group of cytotoxic T-cell lymphomas may express both. Using an anti-T γδ immunoreactive with human paraffin tissue suggests that TCRT γ expression in primary cutaneous T-cell lymphoma may not be mutually exclusive, and therefore some of these tumors may express both T αβ and T γδ (Rodriguez-Pinilla et al. 2013).

Nevertheless, in human physiology, the majority of mature T cells express T αβ heterodimer framework, but about 5 % of normal T cells express the T-cell γδ framework. The function of the T γδ cells in the skin appears to be protective, has cytotoxic effector properties, and can secrete lymphokines or proliferate (Girardi 2004; Kabelitz 1995; Kabelitz et al. 2000; Kabelitz and Wesch 2003). These cells can be detected by antibodies to T-cell δ1 (TCR delta1) and lack βF1 (antibody to framework beta 1) (Kabelitz 1995). These are mature T cells that express cytotoxic TIA-1 and release granzyme B and perforin causing apoptosis. Most T γδ cells lack both CD4 and CD8 surface markers, but in the human peripheral blood, some are CD8+. This skin and mucosal distribution of disease reflects their role in normal epithelial immune responses, but extracutaneous presentation in lung, nasolaryngeal, and intestinal (Arnulf et al. 1998) as well as splenic and liver sites (Cooke et al. 1996, 1996; Garcia-Herrera et al. 2011; Gaulard et al. 2003) has been well documented.

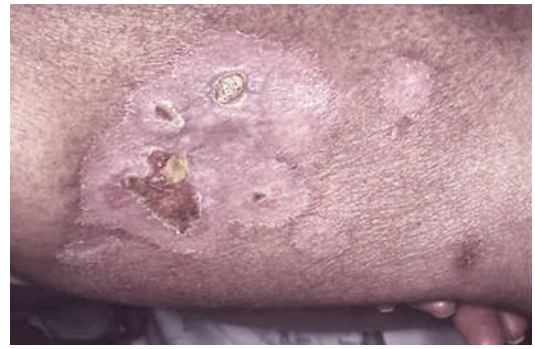

Fig. 10.31 Primary cutaneous T γδ tends to form nodules that ulcerate

Definition

Cutaneous γδ T-cell lymphomas are composed of clonally activated γ/δ T cells with a cytotoxic phenotype, with a dermotrophic and deep subcutaneous pattern of infiltration, and present with ulceronecrotic skin plaques, deep nodules, and aggressive panniculitis-like tumors and hemophagocytic syndrome in less than 10 % of cases (Koch et al. 2009; Toro et al. 2000, 2003; Willemze et al. 2005; Guitart et al. 2012). Whether this is a pure category identified by immunostaining characteristics alone is controversial.

Epidemiology

Young to middle-aged, presenting with skin lesion of a median duration of 1.25 years, and with a median age of 61 years (25–91 range) (Guitart et al. 2012), and a male to female ration of 1.5:1 (Toro et al. 2003).

Clinical Appearance of Cutaneous Lesions

Presentations include most commonly scaly deep plaques resembling panniculitis, or patches resembling MF, as well as nodules or tumors which tend to ulcerate (Fig. 10.31). These are commonly located on the lower and upper extremities, followed by the torso (Guitart et al. 2012). Solitary lesions are seen in 15 % and in those with limited disease; about half are associated with fever, malaise, fatigue, chills, and weight loss (Guitart et al. 2012). Systemic involvement has been reported, but rare with low

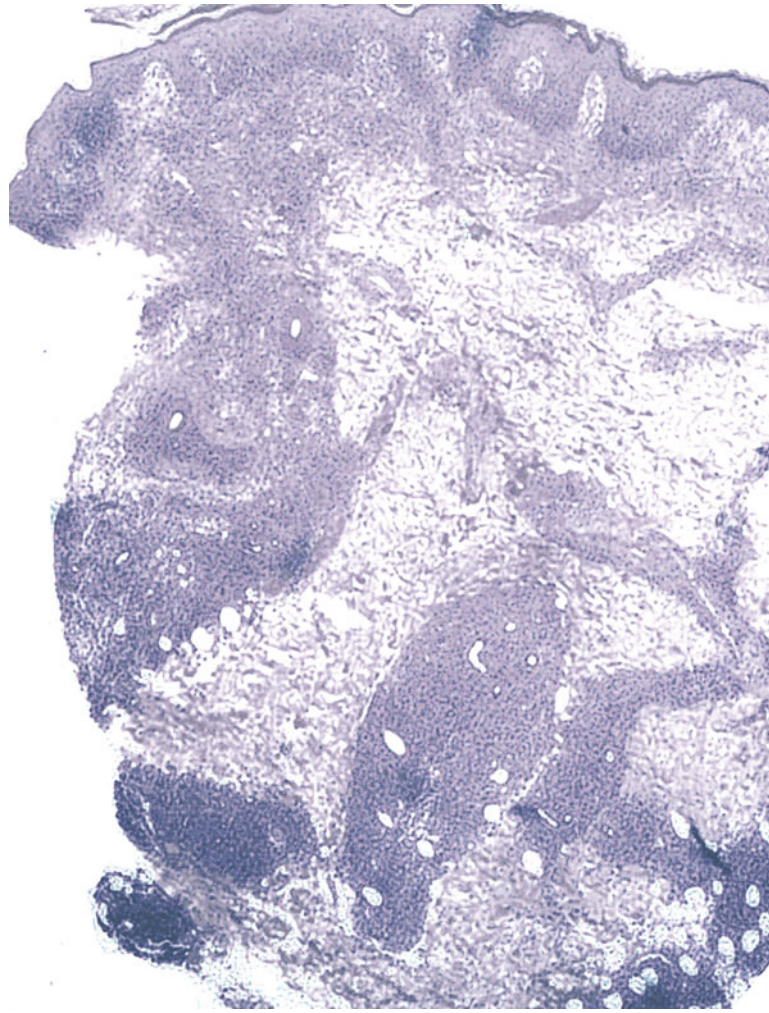

Fig. 10.32 Cutaneous T γδ lymphoma shows a mixed epidermal, mid-dermal, periadnexal, and subcutaneous pattern

frequency of involvement of the lymph nodes, spleen, or bone marrow. LDH is elevated in more than half of the cases (Kadin 2000; Toro et al. 2003).

Pattern of Infiltration

In the early stages, the pattern is mid-dermal, periadnexal, and perivascular (Fig. 10.32) (Salhany et al. 1998). In later stages, dense lymphocytic infiltrates are located in the mid-dermis, with variable epidermotropism and nodular extensions into subcutaneous fat and ischemic necrosis of overlying skin (Fig. 10.33). Necrosis and psoriasiform epidermal changes are common (Koch et al. 2009). Pagetoid pattern has been described (Guitart et al. 2012). There are frequently mixed histologic patterns: epidermotropic and subcutaneous panniculitic-like, associated with dense dermal involvement. All cases involved the subcutis with extension upwards into the dermis and epidermis (Fig. 10.34) (Garcia-Herrera et al. 2011; Toro et al. 2000, 2003; Salhany et al. 1998).

Cytomorphology

These tumors have a range of cytomorphology (Rodriguez-Pinilla et al. 2013; Salhany et al. 1998), composed of either small-/medium-sized

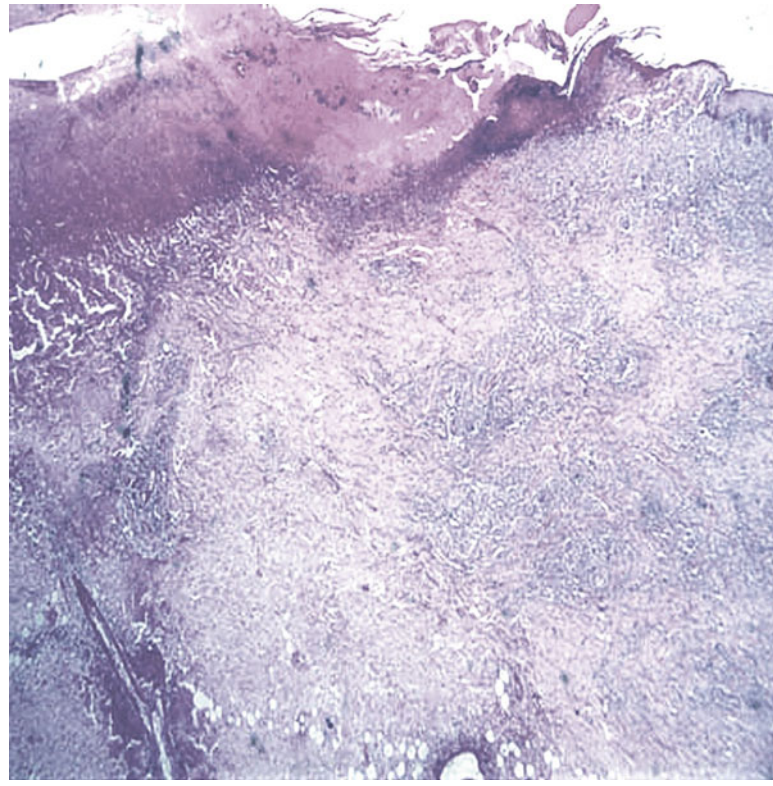

Fig. 10.33 Cutaneous T γδ: perivascular and nodular extensions into dermis, hair adnexa, and subcutaneous fat and ischemic necrosis of overlying skin

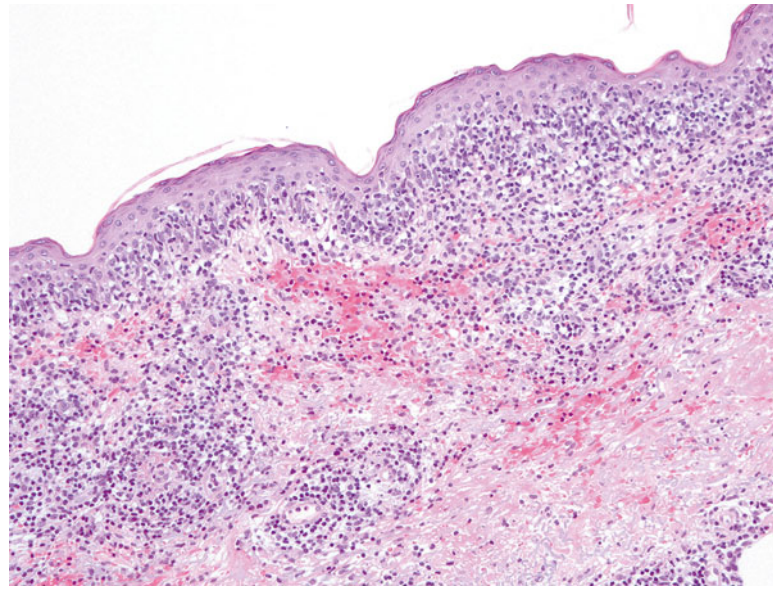

Fig. 10.34 Cutaneous CD8 + T γδ lymphoma involving the epidermis, dermis, and focally subcutis

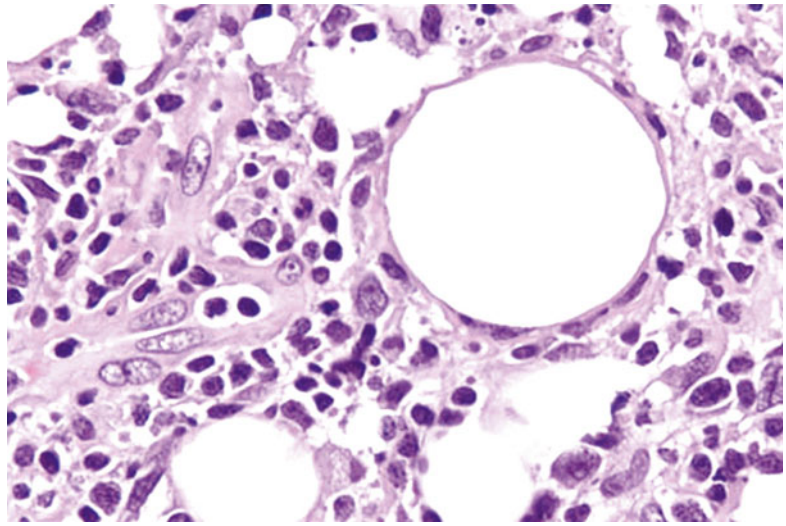

Fig. 10.35 Cutaneous T γδ lymphoma composed of medium-sized or large atypical lymphocytes with irregular hyperchromatic nuclei and coarse chromatin, with small nucleoli and a few large blastic cells which are localized in between fat globules and not rimming the fat cells

atypical lymphocytes (Garcia-Herrera et al. 2011) or medium-sized or large atypical lymphocytes with irregular hyperchromatic nuclei and coarse chromatin, with small nucleoli and a few large blastic cells with vesicular nuclei and conspicuous nucleoli (Toro et al. 2000). Most cases do not show rimming of fat cells as characteristic of subcutaneous panniculitic-like T-cell lymphomas, although rare cases had predominant subcutis infiltrate, some with rimming (Rodriguez-Pinilla et al. 2013) (Fig. 10.35). Cerebriform nuclei are not seen (Toro et al. 2000, 2003; Kadin 2000). Numerous apoptosis are described. In those cases, with cytophagic histiocytes or hemophagocytic syndrome, histiocytes phagocytizing red and white blood cells and platelets may be present in the skin and bone marrow (Craig et al. 1998; Toro et al. 2003; Salhany et al. 1998).

Immunophenotype

Many cutaneous T γδ cases, as originally described, are CD56 + (Fig. 10.36), lacking both CD4 and CD8 and sometimes lose CD5 and variably positive for CD8 and CD7 (Arnulf et al. 1998; Boulland et al. 1997) and negative for CD20, CD79a, and CD30. The γδ expression and the subcutaneous localization of primary cutaneous T γδ define adverse prognostic parameters so it is important to be certain (Toro et al. 2003). The lack of betaf1 (βF1) may be due to T antigen loss and cannot be equated with a T γδ lymphoma. T-cell δ1 expression is further defined as positive if more than 80 % of cells have *membrane* expression (Toro et al. 2003).

In a series of eight primary cutaneous T γδ tumors cases (Garcia-Herrera et al. 2011), using paraffin-reactive antibodies to T-cell receptor (TCR) delta (δ) portion of the heterodimer γδ on CD3 T-cell complex (antihuman TCRδ constant region) (Human Pan TCRγδ1, clone 5A6.E9, Thermo Scientific, IL), primary cutaneous T γδ tumors were described to have an activated cytotoxic phenotype, of which six cases were double negative for CD4 and CD8 and two cases expressed CD8. CD56 immunoreacted in three of seven patients. In TCR γδ-positive cases, expression was evaluated by membranous staining for TCRδ chain and additionally for TCRγ chain (using paraffin-reactive monoclonal antibody TCR 1153 clone γ3.20, Thermo Scientific, IL), in which the TCRγ immunoreactivity was previously characterized (Roullet et al. 2009).

Nevertheless, in many previous other studies, these T cells are usually positive for CD3, CD43,

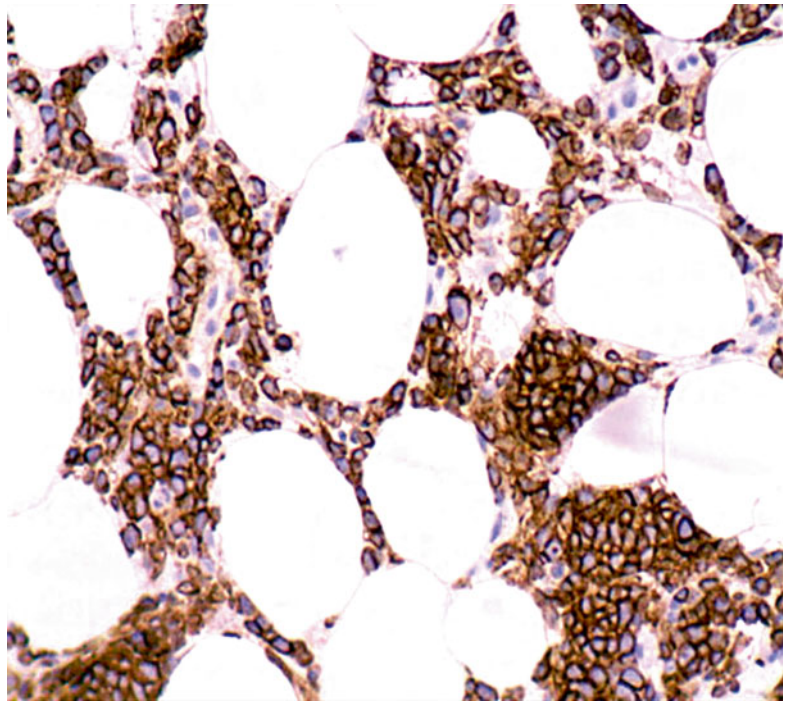

Fig. 10.36 CD3 + CD56 + T cells (*below*) are the typical coexpressed markers

and T-cell δ1, with cytotoxic markers TIA-1 and granzyme B (Salhany et al. 1998; Toro et al. 2003; Go and Wester 2004; Koch et al. 2009). These or similar tumors with overlapping features with primary cutaneous CD8 epidermotropic T-cell lymphoma have been described to be variably positive for βF1, CD4, and CD8 (Guitart et al. 2012). Most reports in which EBER was done showed absence of Epstein-Barr virus (Salhany et al. 1998; Toro et al. 2003; Go and Wester 2004; Rodriguez-Pinilla et al. 2013). High Ki67 expression upwards of 70 % has been reported (Koch et al. 2009).

Cytogenetics and Molecular Findings

TCR (γ/δ) genes are rearranged. There is no specific karyotypic abnormality (Toro et al. 2003. EBV is absent (Salhany et al. 1998; Go and Wester 2004).

Clinical Behavior

Generally characterized as aggressive with progressive clinical course resistant to various chemotherapies (Toro et al. 2000, 2003). The median survival is 15 (Toro et al. 2003) to 31 months (Guitart et al. 2012). If there is hemophagocytic syndrome with resulting pancytopenia, the prognosis is especially poor (Salhany et al. 1998). Patients with subcutaneous fat involvement may fare worse than those with only dermal involvement (Salhany et al. 1998; Toro et al. 2000, 2003).

Differential Diagnosis

The expression of TCRγ may not be confined to primary cutaneous T γδ and include other CTCLs of mycosis fungoides type, lymphomatoid papulosis type D, tumor MF, or MF with large cells, and hence caution is warranted in using one positive parameter alone (Rodriguez-Pinilla et al. 2013). In this report, TCRγ can be found in other CTCLs other than primary cutaneous γδ.

The neoplastic cells show overlapping features with primary cutaneous CD8 epidermotropic T cell (Guitart et al. 2012) and other cytotoxic primary cutaneous lymphoma and had

coexpression of TCR αβ with TCR γδ (Rodriguez-Pinilla et al. 2013). Interestingly, Rodriguez-Pinilla et al., using different clones and methodology, showed dual cytoplasmic instead of surface membranous immunostaining pattern, in tumor cells with positivity for both TCR T αβ and TCR γδ. (Paraffin-immunoreactive monoclonal antibodies 8A3 Endogen, Dako autostainer with protease, and Gamma 3.20 Thermo, Dako autostainer, Tris EDTA, both antigen retrieved using said reactants, were used for detecting TCR αβ- and TCR γδ-positive cells, respectively.) (Rodriguez-Pinilla et al. 2013) In 5 of 12 of primary cutaneous γδ cases, coexpression of TCR αβ and TCR γδ markers was noted, which indicated possibly an aberrancy of marker expression in a neoplasm such as cutaneous T-cell lymphomas, in contradistinction with the exclusive expression of these markers in normal cells (Bluestone and Matis 1990; Kabelitz 1995).

Primary cutaneous aggressive CD8+ cytotoxic lymphoma is a challenging differential, if CD8 or CD56 are coexpressed, but one clue may be that cutaneous γδ lymphomas tend to have more subcutaneous involvement. Whether there is a subset of cutaneous γδ which are not distinguishable from primary cutaneous CD8 epidermotropic type is still a standing question given that recent studies indicate an overlap between these groups (Guitart et al. 2012). Although CD8 epidermotropic CTCL can form *nodular patterns*, because of its eponymic label and its current evolving nosology, that particular type is discussed in Chap. 6 (see Fig. 6.24).

Another group to differentiate include lymphomas in the skin with prominent subcutaneous involvement, such as PTCL-u, subcutaneous panniculitic T-cell lymphoma, and nasal-type extranodal NK/T-cell lymphoma and CD30 lymphomas (Koch et al. 2009; Toro et al. 2000, 2003) which all can present with deep subcutaneous tumors. For each of the above categories, an accurate evaluation for the number of large cells, a dominant subcutis tumor infiltrate pattern with no dermal tumor, EBV positivity, and strong CD30 decorated large cells may be useful clues, respectively. CD30 lymphomas are notable differential especially if CD56 and cytotoxic markers are strongly expressed as is known to be so for this group (Chang et al. 2000; Bekkenk et al. 2001).

The subcutaneous panniculitic T-cell lymphoma expressing T αβ appears to have a predominant subcutaneous distribution, rimming of fat by tumor cells, and prominent apoptosis, whereas the cutaneous T γδ shows pandistributed epidermic, dermic, and subcutaneous infiltration (Kumar et al. 1998; Salhany et al. 1998). Because of the involvement of the subcutaneous fat on histology alone, benign conditions mainly that of lupus erythematosus profundus and other reactive panniculitis are in large part the benign differential diagnosis. In this regard, an absence of clonal T cells or clinical features may distinguish reactive processes from T-cell lymphomas with fat involvement (Aguilera et al. 2007).

Finally, when there is intense epidermotropic component, MF has to be ruled out since MF has been described to also present with a CD56+ (Wain et al. 2005), CD4-negative, and CD8-negative phenotype and may involve the subcutaneous tissue as well, especially on progression.

Cutaneous Angioimmunoblastic T-Cell Lymphoma (cAITL)

Skin involvement is often not primary and often occurs in patients with generalized disease. Primary cAITL has been described in about 10 % of cases (Martel et al. 2000) and documented in many case reports and few series (Smithberger et al. 2010; Batinac et al. 2003; Bayerl et al. 2010; Bernstein et al. 1979; Brown et al. 2001; Ferran et al. 2006; Huang and Chuang 2004; Martel et al. 2000; Suarez-Vilela and Izquierdo-Garcia 2003).

Four main histologic patterns, in the order of frequency, are seen in cutaneous involvement of AITL (Martel et al. 2000), and the findings may be similar to that of primary cAITL:

1. Vascular hyperplasia, with "high" endothelial vessels (HEVs) associated with sparse superficial perivascular atypical lymphoid infiltrates. Endothelial cells are plump and protrude into the lumina. Atypical lymphocytes are pleomorphic with large RS-like cells (Fig. 10.37a, b).

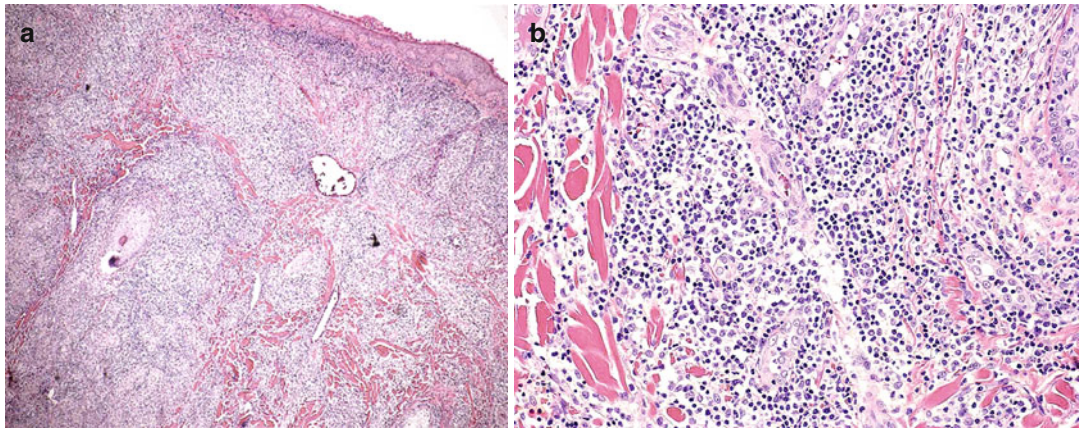

Fig. 10.37 (**a**) Cutaneous angioimmunoblastic T-cell lymphoma with vascular hyperplasia, with prominent "high" endothelial vessels (HEVs) associated with perivascular atypical lymphoid infiltrates. (**b**) High-power view of venules with many endothelial cells which are plump and protrude into the lumina

2. Vascular hyperplasia with dense pleomorphic atypical lymphoid infiltrate in superficial and deep dermis.
3. Vasculitis with no pleomorphic atypical lymphocytes.
4. Capillary hyperplasia, mild perivascular infiltrate in superficial dermis of non-atypical lymphocytes associated with eosinophils (Fig. 10.38a–c).

Systemic *Angioimmunoblastic T-Cell Lymphoma* (*AITL*): This lymphoma primarily presents in lymph nodes but often at a disseminated stage with involvement of the liver and spleen and clinically associated with hypergammaglobulinemia and B symptoms such as fever and malaise (Frizzera et al. 1975; Sallah and Gagnon 1998; Attygalle et al. 2004, 2007; Dogan et al. 2003). Originally included in the atypical lymphoproliferative disorders, this entity is now firmly included in the WHO monograph under the PTCLs based on typical clonal molecular and karyotypic findings (Swerdlow et al. 2008).

The pathologic distinction from cPTCL-u can be difficult, but salient morphological and phenotypic features may be useful (Agostinelli et al. 2008). The main findings in favor of AITL, primary or cutaneous, include prominent or arborizing vascularization, expansile CD21+ dendritic cell networks, and coexpression of CD10 (a precursor and follicular lymphoma-associated antigen) and other follicle center helper T-cell markers by the neoplastic T cells (Grogg et al. 2005; Attygalle et al. 2004, 2007; Dogan et al. 2003). Immunoblasts of varying size along with clear medium-sized cells are present (Swerdlow et al. 2008). EBV association has been described with secondary oligoclonal or monoclonal EBV + B-cell lymphomas in some patients (Attygalle et al. 2004, 2007; Dogan et al. 2003).

The neoplastic cells are often CD4 positive with variable loss of T-cell antigens and expression of follicular T helper cells which show immunoreactivity to CD10, BCL6, CXCL13, and PD1 (de Leval and Gaulard 2011; Gaulard and de Leval 2011; Attygalle et al. 2004, 2007; Dogan et al. 2003). Clonal T-cell gene rearrangements with strong, distinct bands with oligoclonal pattern favor AITL over reactive angioimmunoblastic proliferation (Attygalle et al. 2004, 2007; Dogan et al. 2003).

AITL is found mostly in the elderly and has an aggressive clinical course. The 5-year overall survival rate, as well as the 3-year median survival rate, is about 30 % (Savage et al. 2004).

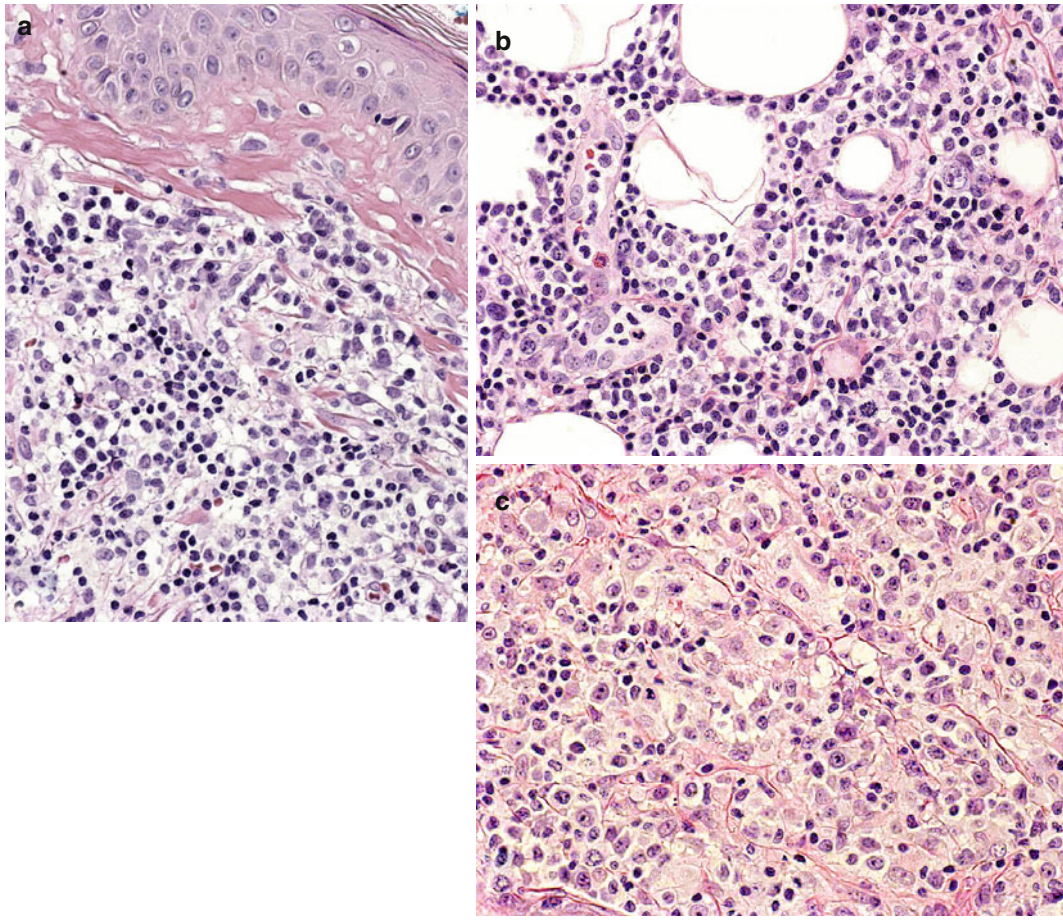

Fig. 10.38 Cutaneous angioimmunoblastic T-cell lymphoma with (**a**) capillary hyperplasia, mild perivascular infiltrate in superficial dermis, (**b**) lymphocytes associated with eosinophils, and (**c**) high-power view with atypical pleomorphic lymphocytes with mitosis, some with scattered large nucleolated mononuclear cells. Note the "clear-" appearing cytoplasm of cells

"Extanasal (Cutaneous)" Subtype of Extranodal NK/T-Cell Lymphoma, Nasal Type

Definition

This is an extranodal lymphoid neoplasm of NK cells or, less commonly, from cytotoxic T cells (Chan et al. 1997; Mraz-Gernhard et al. 2001). Skin involvement may be a primary or secondary manifestation of the disease, but the "extranasal" type is often associated with skin lesions (Gniadecki et al. 2004). Nasal cases and extranasal cases are two major types of extranodal NK/T--cell lymphomas designated as "nasal type" (Swerdlow et al. 2008; Willemze et al. 2005).

Extranodal NK/T-cell lymphoma, nasal type, has also been synonymous with past cases described as "lethal midline reticulosis, polymorphic reticulosis." For our purposes here, we will focus on the extranasal (cutaneous) NK/T-cell lymphomas with skin involvement instead of the extranodal NK/T-cell lymphoma, nasal type (with frequent upper aerodigestive tract involvement).

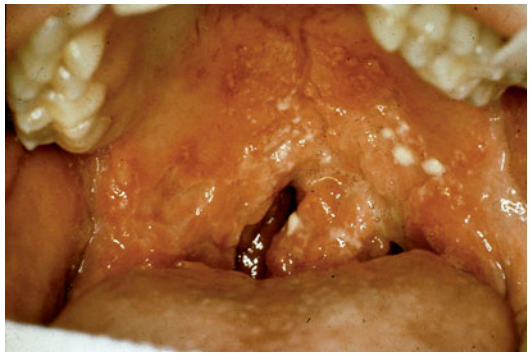

Fig. 10.39 Extranodal NK/T-cell lymphoma, nasal type, oropharyngeal lesions with pustular deformed uvular ulcerated mucosa

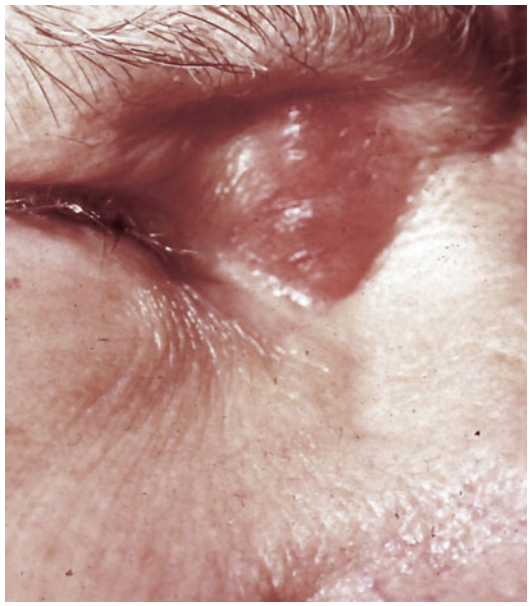

Fig. 10.40 Skin involvement of extranodal NK/T-cell lymphoma, nasal type, adjacent to the nose

Epidemiology

The whole spectrum of diseases that include extranodal NK/T-cell lymphoma (nasal and extranasal) and aggressive NK-cell leukemia is rare. The "nasal" type comprised 4 % of the peripheral T-cell lymphomas in Europe (Gallamini et al. 2004). Mostly adults of middle age to elderly (median age 50 years), with a male to female ratio of 3:2, are described (Mraz-Gernhard et al. 2001; Savage et al. 2012). Rare pediatric cases with cutaneous involvement have been reported (Pol-Rodriguez et al. 2006).

Race Predilection

The nasal and extranasal types were originally described in Oriental/Asian patients, but patients of Mexican and South American descent (Chan et al. 1997; Cheung et al. 2003), as well as European Caucasians (Assaf et al. 2007; Bekkenk et al. 2003, 2004; Bekkenk and Willemze 2001), have also been reported as well as individual reports of patients from North America (Aladily et al. 2012; Summers et al. 2011; Wood et al. 2011).

Clinical Appearance of Lesions

Oropharyngeal lesions (Fig. 10.39), may present without skin lesions or be concurrently associated with cutaneous lesions (Fig. 10.40). Skin lesions appear in about a third of the cases (Chan et al. 1997) and, although rare, are increasingly recognized (Mraz-Gernhard et al. 2001; Natkunam et al. 1999; Savoia et al. 1997; Ansai et al. 1997). Clinical features include confluent or multiple reddish plaques, tumors, or nodules that may ulcerate, but flat lesions have been described. Lesions may be located on the extremities, trunk, and, less frequently, head and neck (Chan et al. 1997). Rare cases with bruise-like skin lesions have been reported (Dummer et al. 1996). Systemic symptoms such as weight loss, malaise, and fever may be present, and cytopenia due to hemophagocytic syndrome has been reported in some cases (Brodkin et al. 2008; Takahashi et al. 2001).

Pattern of Infiltration

Nodules and ulcerated skin along with dermal and subcutaneous angiocentric lymphoid infiltrate are seen (Fig. 10.41). Epidermotropism may be present (Fig. 10.42). A dense infiltrate in the dermis may be seen extending to the subcutaneous tissue, with associated angiodestructive growth pattern and occlusion of the blood vessel lumens by lymphoid cells, which are both common but not evident in all cases (Fig. 10.43). Vascular occlusion can cause ischemic necrosis of both tumor cells and normal tissue (Fig. 10.44).

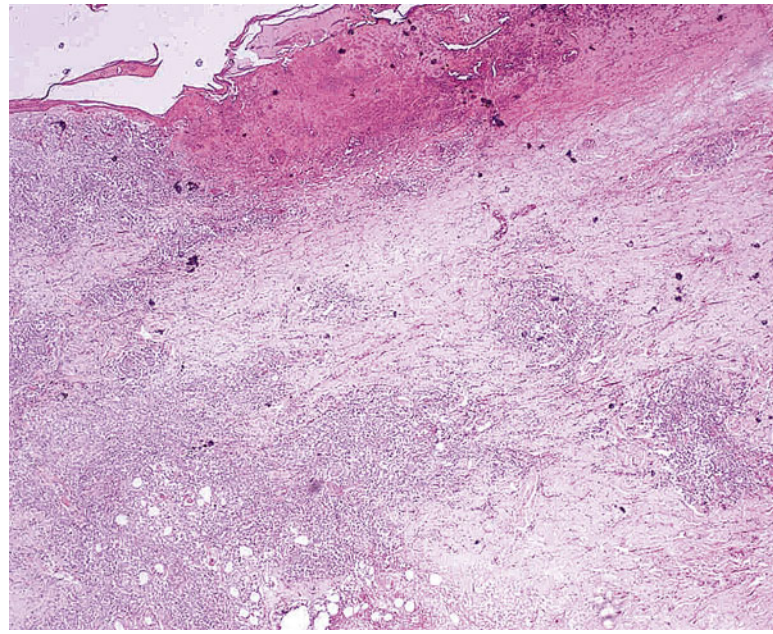

Fig. 10.41 Extranodal NK/T-cell lymphoma, nasal type. A dense infiltrate of perivascular atypical lymphocytes which extends from the ulcerated epidermis to the dermis and into the subcutaneous tissue is seen

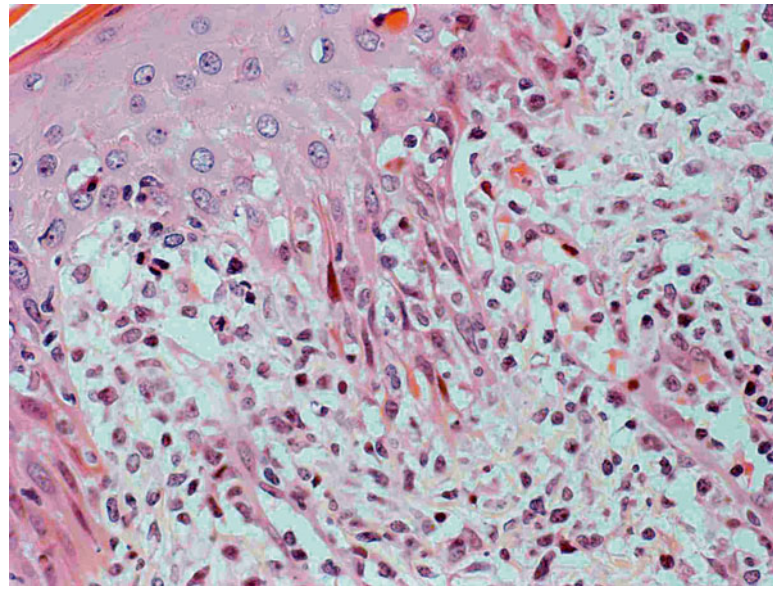

Fig. 10.42 Extranodal NK/T-cell lymphoma, nasal type. Epidermotropism may be present

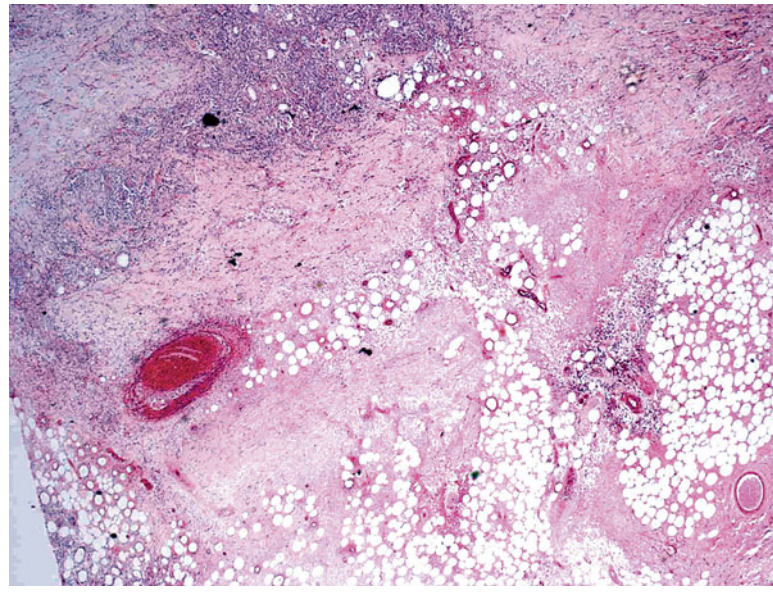

Fig. 10.43 Extranodal NK/T-cell lymphoma, nasal type. Angiodestructive growth pattern and occlusion of the blood vessel lumens by lymphoid cells are common but not evident in all cases

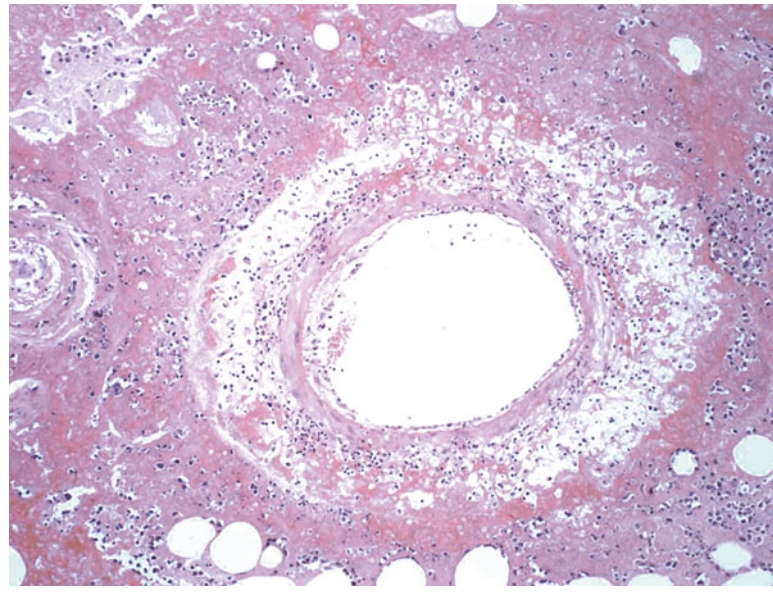

Fig. 10.44 Extranodal NK/T-cell lymphoma, nasal type. Vascular occlusion can cause ischemic necrosis of both tumor cells and normal tissue

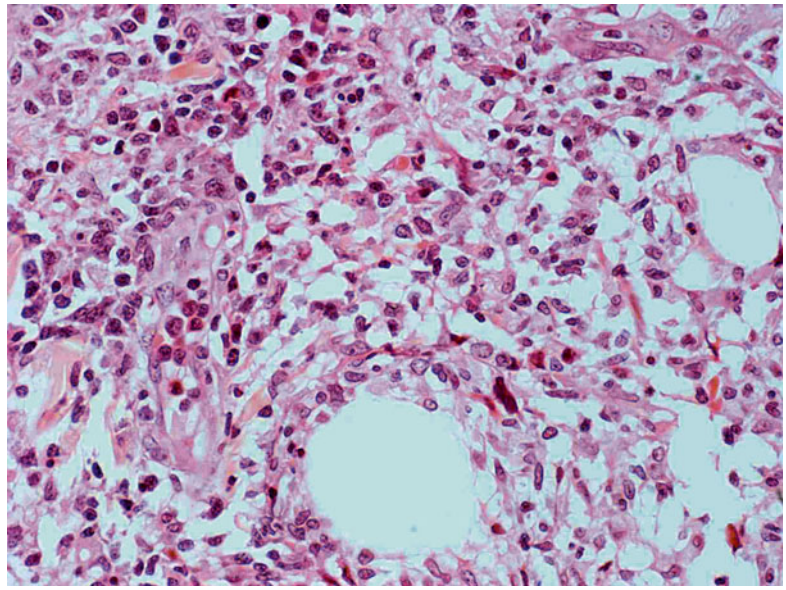

Fig. 10.45 Polymorphous infiltrate admixed with inflammatory cells, with the malignant cells composed of a mixture of normal-appearing small lymphocytes and atypical lymphoid cells of varying size with irregular nuclei, moderately dense granular chromatin, and pale to clear to finely granular cytoplasm with high mitotic activity

Cytomorphology

These cases feature polymorphous infiltrate admixed with inflammatory cells, with the malignant cells composed of a mixture of normal-appearing small lymphocytes and atypical lymphoid cells of varying size with irregular nuclei, moderately dense granular chromatin, and pale to clear to finely granular cytoplasm with high mitotic activity (Fig. 10.45) (Chan et al. 1989, 1997). The cytological spectrum of extranodal NK/T-cell lymphoma "nasal type" is very broad ranging from bland cytology (Fig. 10.46) to large atypical cells with necrosis (Fig. 10.47). In most cases, the lymphoma is composed of medium-sized cells with irregular nuclei, granular cytoplasm, and frequent mitosis (Pagano et al. 2006).

Immunophenotype

The neoplastic cells are usually positive for CD2, CD7, CD45RO, CD43, cytoplasmic CD3ε (cd3 epsilon cytoplasmic portion), CD56, and cytotoxic granule proteins (TIA-1, granzyme B, and perforin) (Chan et al. 1989, 1997; Pagano et al. 2006). They are usually negative for surface CD3, CD4, and CD8, but some that may lack CD56 antigens may still be classified as extranodal NK/T cells, nasal-type lymphoma, if they also express cytotoxic markers and EBV (Chan et al. 1989, 1997; Swerdlow et al. 2008; Pagano et al. 2006). CD4+ and CD7+ immunophenotypes have also been described (Chan et al. 1989, 1997; Pagano et al. 2006; Bekkenk et al. 2004). EBV is almost always (94 %) positive (Chan et al. 1989, 1997; Pagano et al. 2006; Bekkenk et al. 2004; Cheung et al. 1998, 2003). EBV positivity is helpful since it is rare in other cutaneous lymphomas and similar-looking extranasal or nasal-type CD3+ CD56 – lymphomas lacking EBV may be a type of PTCL-u or other neoplasms. EBER in situ hybridization is the most consistent test for the presence of EBV. CD30+ expression has been suggested to be of good prognostic parameter via p21 expression and increased apoptosis (Hubinger et al. 2001; Mraz-Gernhard et al. 2001).

Expression of killer cell inhibitor receptors via KIR immunophenotype or molecular RT-PCR techniques have been used to determine clonality

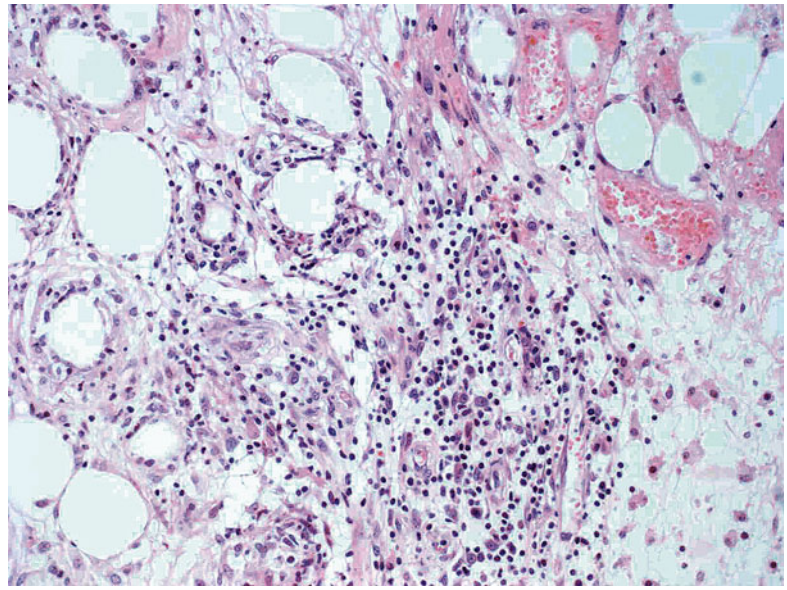

Fig. 10.46 Extranodal NK/T-cell lymphoma, nasal type. The cytological spectrum of extranodal NK/T-cell lymphoma "nasal type" is very broad ranging from bland cytology below

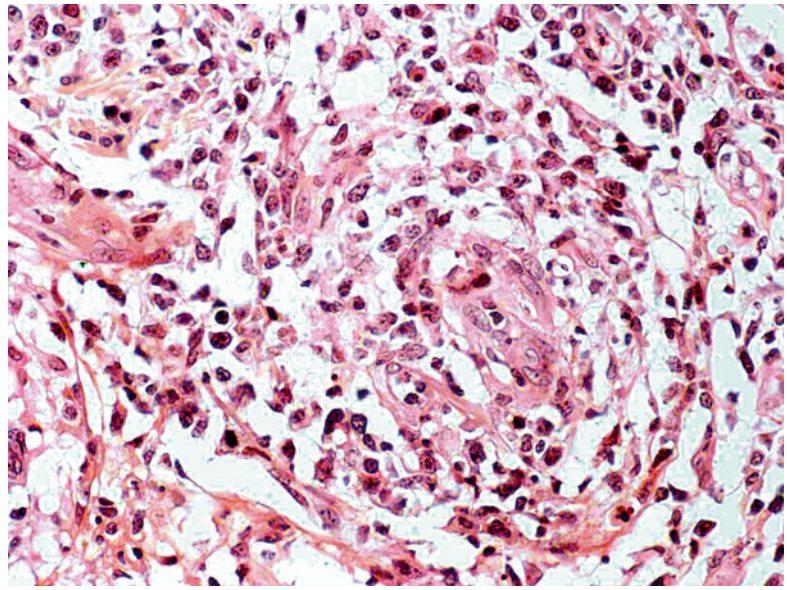

Fig. 10.47 Extranodal NK/T-cell lymphoma, nasal type, also showing medium-large atypical cells

or oligoclonality of true NK-cell lymphomas and other cytotoxic cell lymphomas (Dukers et al. 2001; Kamarashev et al. 2001; Lin et al. 2001; Urosevic et al. 2004).

Cytogenetics and Molecular Findings

TCR genes are germ line since NK cells do not have rearrangement of TCR genes (Chan et al. 1989, 1997; Bekkenk et al. 2004; Siu et al. 1999).

Table 10.4 Summary of NK/T-cell lymphoma, nasal type, extranasal (cutaneous) NKTL, and aggressive NK/T-cell leukemia/lymphoma

	Nasal (aerodigestive) NK/T	Extranasal (cutaneous) NKTL	NK/T-cell leukemia/ lymphoma
Epidemiology	Asia, Central America, South America, and Mexico; men are affected more than women; occurs most often in the fifth decade of life	Similar to EN-NK/T-NT	Asia; men and women affected equally; median age of onset of 42 years
Sites frequently involved	Aerodigestive tract can disseminate to the skin, soft tissue, gastrointestinal tract, testes, and rarely bone marrow	Skin torso but also extremities, salivary gland, and viscera and has overlap with aggressive NK when BM is involved	Bone marrow, blood, liver, spleen, skin rarely involved
Immunophenotype	EBV+, CD16–, CD56+-, cytoplasmic CD3; CD7–, surface CD3–; CD4, CD8, CD57, and TCR βF1 or δγ are usually negative; cytotoxic proteins are positive; no clonal TCR gene rearrangement	EBV+, CD16– cytotoxic phenotype similar to nasal-type TCR βF1 or δγ are usually negative; cytotoxic proteins are positive; no clonal TCR gene rearrangement	EBV+,CD16+ ;no clonal TCR gene rearrangement
Prognosis	Median survival of advanced disease 12 months (40 % alive 5 years)	Most die within 6 months of diagnosis (17 % alive 5 years)	Most die within a few weeks of diagnosis

Deletions of chromosomes 6 (q16–q27) and 13 (q14–q34) are common karyotypic findings (Siu et al. 1999). Mutations of k-*ras* have been described, and p53 is overexpressed in many patients (Hongyo et al. 2005; Hoshida et al. 2003; Kurniawan et al. 2006). In both cutaneous and non-cutaneous cases, both disease-free and overall survival have been poor, perhaps related to the presence of multidrug resistance genes (Suzuki et al. 2010a).

Clinical Behavior

The single most important prognostic factor in cutaneous form of extranodal NK/T-cell lymphoma, nasal type, is extracutaneous involvement to the lymph node, viscera, or bone marrow. Those patients with extracutaneous disease had a median survival of 7.6 months compared with 44.9 months for those with disease limited to the skin (Mraz-Gernhard et al. 2001).

In a more encompassing review of these cases, the 5-year overall survival ranged from 17 to 40 % (meta-analysis of European, Asian, South American reported cases) (Pagano et al. 2006), and at this juncture, the prognosis appears better when compared with the original reported skin and extra-skin series of Asian patients who had median survival of 3.5 months (Chan et al. 1997) and a small series of three cases of primary cutaneous NK-cell lymphoma with a reported 0 % 5-year survival (Fink-Puches et al. 2002). Nonetheless, patients with tumors associated with aggressive NK-cell leukemia have the worst outcome, with a median survival of 6 weeks (Chan et al. 1997).

Differential Diagnosis

In the previous classifications, these cases were classified among cutaneous CD56+ neoplasm, blastic NK, or PTCL-u or CD30-negative cutaneous large T-cell lymphoma, so these cases present a differential matrix, especially when these tumors express CD56. Lack of EBV and a non-germ line T-cell receptor gene rearrangement result appear to be the crucial commonality in the above cases.

When confronted with an EBV + lymphoma, however, with immunohistologic features of NK/T-cell type, it is helpful to differentiate between the different clinical variants of extranodal NK/T-cell lymphoma, nasal type, such (primary cutaneous) as extranasal NK/T-cell lymphoma or the aggressive natural killer (NK) cell leukemia. See Table 10.4.

Although not absolute, skin involvement favors extranasal NK/T-cell lymphoma, while bone marrow, blood, and disseminated visceral disease favor aggressive natural killer (NK) cell

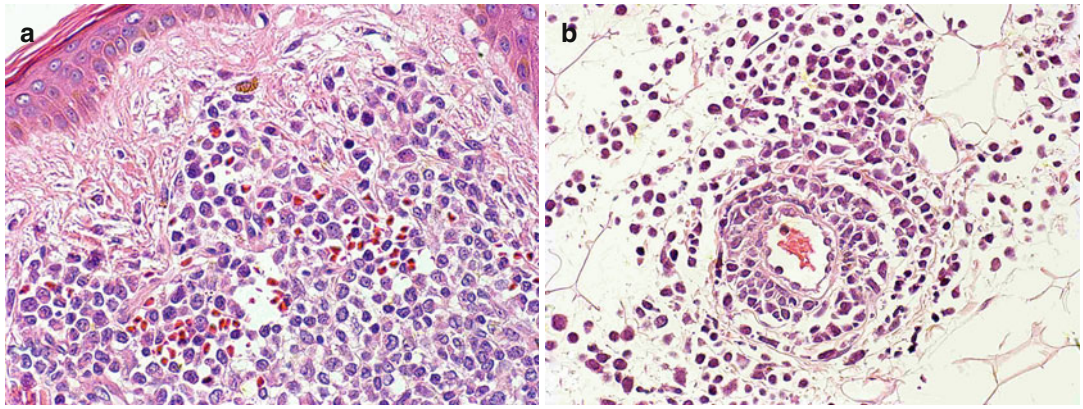

Fig. 10.48 Plasmacytoid dendritic cell neoplasm is derived from marrow precursor dendritic cells and not a true natural killer cell blast. (**a**) Blastic cells with fine nuclear chromatin. (**b**) Angiotropic blasts in single file targetoid pattern, a common arrangement of blasts in leukemia involving the skin

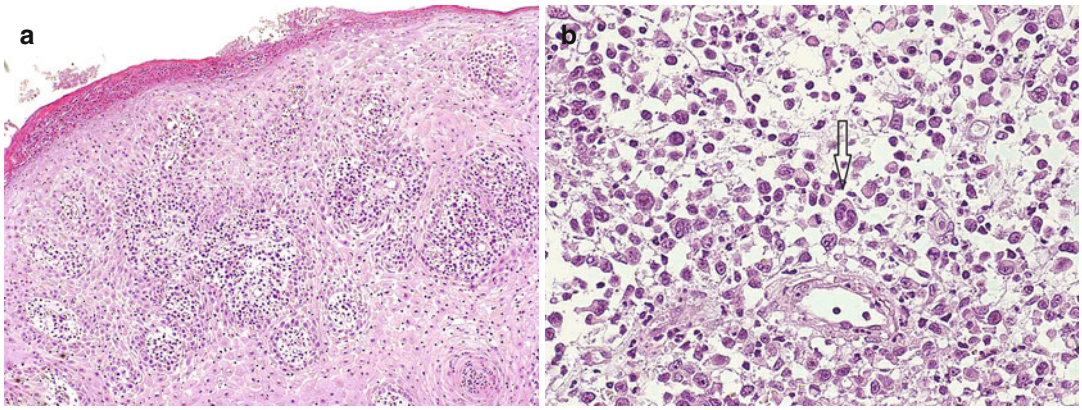

Fig. 10.49 Cutaneous adult T-cell leukemia/lymphoma (cATLL) showing epidermotropism. Tumor cells are medium to large size with nuclear pleomorphism and Reed-Sternberg-like narrow

leukemia. All of these cases may involve the aerodigestive tracts and therefore belong to the umbrella of extranodal NK/T-cell lymphoma, nasal type.

These above diseases are currently separated from the previous category of extranodal "blastic-NK" cell types which are not lymphoid in origin but derived from precursor plasmacytoid dendritic cells (also called "hematodermic neoplasm" because of common involvement of skin and marrow). The skin involvement of blast is recognized by the immature cells with blastic finely dispersed chromatin and the single file pattern often seen in leukemic skin involvement (Fig. 10.48a, b) (please see Chap. 16 for discussion of plasmacytoid dendritic cell neoplasm).

Cutaneous Adult T-Cell Leukemia/Lymphoma

This entity will be discussed in more detail in Chap. 6 since occasional cases may present in a tumor nodular pattern, but cases are largely epidermotropic. A short description is provided here.

The tumor cells may show occasional deep dermal atypical cerebriform to large pleomorphic/immunoblastic cells, especially in cases with deep dermal tumor nodules (Fig. 10.49). The tumor cells have a T regulatory phenotype – FoxP3+, CD4+, and CD25+ (Fig. 10.50). This explains their ability to suppress local immunity and the propensity of ATLL patients to be

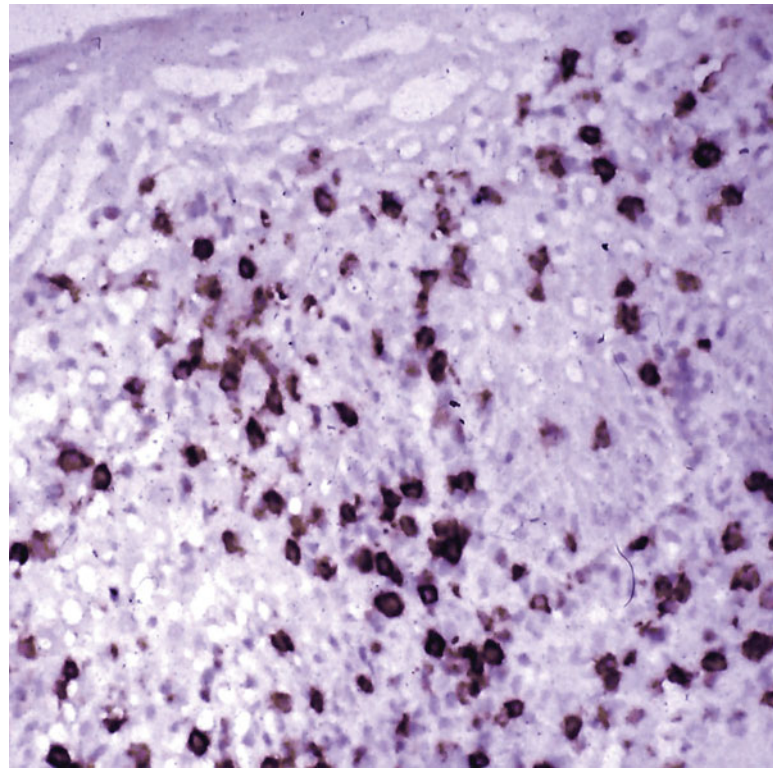

Fig. 10.50 CD25+ T helper cells in most cells are typical of cATLL

extraordinarily susceptible to opportunistic infection. Serum levels of IL-10 and TGF-beta1 are increased (Tokura, oral abstract #40, 2nd World Congress of Cutaneous Lymphomas, Feb 6–10, 2014).

Differential Diagnosis

MF is the principal differential diagnosis.

References

Adachi Y, Horio T. Chronic actinic dermatitis in a patient with adult T-cell leukemia. Photodermatol Photoimmunol Photomed. 2008;24(3):147–9.

Adams JD. Localized cutaneous pseudolymphoma associated with phenytoin therapy: a case report. Australas J Dermatol. 1981;22(1):28–9.

Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, Robson A, Calonje E, Stefanato CM, Wain EM, Wilkins B, Fields PA, Dean A, Webb K, Scarisbrick J, Morris S, Whittaker SJ. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010;28(31):4730–9.

Agostinelli C, Piccaluga PP, Went P, Rossi M, Gazzola A, Righi S, Sista T, Campidelli C, Zinzani PL, Falini B, Pileri SA. Peripheral T cell lymphoma, not otherwise specified: the stuff of genes, dreams and therapies. J Clin Pathol. 2008;61(11):1160–7.

Aguilera P, Mascaro Jr JM, Martinez A, Esteve J, Puig S, Campo E, Estrach T. Cutaneous gamma/delta T-cell lymphoma: a histopathologic mimicker of lupus erythematosus profundus (lupus panniculitis). J Am Acad Dermatol. 2007;56(4):643–7.

Aladily TN, Nathwani BN, Miranda RN, Kansal R, Yin CC, Protzel R, Takowsky GS, Medeiros LJ. Extranodal NK/T-cell lymphoma, nasal type, arising in association with saline breast implant: expanding the spectrum of breast implant-associated lymphomas. Am J Surg Pathol. 2012;36(11):1729–34.

Albrecht J, Fine LA, Piette W. Drug-associated lymphoma and pseudolymphoma: recognition and management. Dermatol Clin. 2007;25(2):233–44, vii.

Alekshun TJ, Rezania D, Ayala E, Cualing H, Sokol L. Skeletal muscle peripheral T-cell lymphoma. J Clin Oncol. 2008;26(3):501–3.

Alibert JLM. Tableau de plan fongoide: description des mala- dies de la peau observee a l'hopital St. Louis, et exposition des meilleures methods suivies pour leur traitement. Paris: Bar rior 1'Aine et Files; 1806.

Ansai S, Maeda K, Yamakawa M, Matsuda M, Saitoh S, Suwa S, Saitoh H, Ohtsuka M, Iwatsuki K. CD56-positive (nasal-type T/NK cell) lymphoma arising on the skin. Report of two cases and review of the literature. J Cutan Pathol. 1997;24(8):468–76.

Arai E, Okubo H, Tsuchida T, Kitamura K, Katayama I. Pseudolymphomatous folliculitis: a clinicopathologic study of 15 cases of cutaneous pseudolymphoma with follicular invasion. Am J Surg Pathol. 1999;23(11): 1313–9.

Arnulf B, Copie-Bergman C, fau-Larue MH, Lavergne-Slove A, Bosq J, Wechsler J, Wassef M, Matuchansky C, Epardeau B, Stern M, Bagot M, Reyes F, Gaulard P. Nonhepatosplenic gammadelta T-cell lymphoma: a subset of cytotoxic lymphomas with mucosal or skin localization. Blood. 1998;91(5):1723–31.

Arulogun SO, Prince HM, Ng J, Lade S, Ryan GF, Blewitt O, McCormack C. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood. 2008;112(8):3082–7.

Assaf C, Gellrich S, Whittaker S, Robson A, Cerroni L, Massone C, Kerl H, Rose C, Chott A, Chimenti S, Hallermann C, Petrella T, Wechsler J, Bagot M, Hummel M, Bullani-Kerl K, Bekkenk MW, Kempf W, Meijer CJ, Willemze R, Sterry W. CD56-positive haematological neoplasms of the skin: a multicentre study of the Cutaneous Lymphoma Project Group of the European Organisation for Research and Treatment of Cancer. J Clin Pathol. 2007;60(9):981–9.

Attygalle AD, Chuang SS, Diss TC, Du MQ, Isaacson PG, Dogan A. Distinguishing angioimmunoblastic T-cell lymphoma from peripheral T-cell lymphoma, unspecified, using morphology, immunophenotype and molecular genetics. Histopathology. 2007;50(4): 498–508.

Attygalle AD, Diss TC, Munson P, Isaacson PG, Du MQ, Dogan A. CD10 expression in extranodal dissemination of angioimmunoblastic T-cell lymphoma. Am J Surg Pathol. 2004;28(1):54–61.

az-Cascajo C. Strong immunoexpression of the monoclonal antibody CD-30 in lymphocytic infiltrates of the skin not by itself evidence for diagnosing malignant lymphoma. Am J Dermatopathol. 2001;23(1):79–80.

Baatz M, Zimmermann J, Blackmore CG. Automated analysis and detailed quantification of biomedical images using definiens cognition network technology. Comb Chem High Throughput Screen. 2009;12(9): 908–16.

Bakels V, van Oostveen JW, Van Der Putte SC, Meijer CJ, Willemze R. Immunophenotyping and gene rearrangement analysis provide additional criteria to differentiate between cutaneous T-cell lymphomas and pseudo-T-cell lymphomas. Am J Pathol. 1997;150(6): 1941–9.

Ballabio E, Mitchell T, van Kester MS, Taylor S, Dunlop HM, Chi J, Tosi I, Vermeer MH, Tramonti D, Saunders NJ, Boultwood J, Wainscoat JS, Pezzella F, Whittaker SJ, Tensen CP, Hatton CS, Lawrie CH. MicroRNA expression in Sezary syndrome: identification, function, and diagnostic potential. Blood. 2010;116(7): 1105–13.

Barberio E, Thomas L, Skowron F, Balme B, Dalle S. Transformed mycosis fungoides: clinicopathological features and outcome. Br J Dermatol. 2007;157(2): 284–9.

Barr-Nea L, Sandbank M, Ishay J. Pseudolymphoma of skin induced by oriental hornet (Vespa orientalis) venom. Experientia. 1976;32(12):1564–5.

Batinac T, Zamolo G, Jonjic N, Gruber F, Nacinovic A, Seili-Bekafigo I, Coklo M. Angioimmunoblastic lymphadenopathy with dysproteinemia following doxycycline administration. Tumori. 2003;89(1): 91–5.

Batista DA, Vonderheid EC, Hawkins A, Morsberger L, Long P, Murphy KM, Griffin CA. Multicolor fluorescence in situ hybridization (SKY) in mycosis fungoides and Sezary syndrome: search for recurrent chromosome abnormalities. Genes Chromosom Cancer. 2006;45(4):383–91.

Battistella M, Beylot-Barry M, Bachelez H, Rivet J, Vergier B, Bagot M. Primary cutaneous follicular helper T-cell lymphoma: a new subtype of cutaneous T-cell lymphoma reported in a series of 5 cases. Arch Dermatol. 2012;148(7):832–9.

Bayerl MG, Hennessy J, Ehmann WC, Bagg A, Rosamilia L, Clarke LE. Multiple cutaneous monoclonal B-cell proliferations as harbingers of systemic angioimmunoblastic T-cell lymphoma. J Cutan Pathol. 2010;37(7):777–86.

Bekkenk MW, Geelen FA, van Voorst Vader PC, Heule F, Geerts ML, van Vloten WA, Meijer CJ, Willemze R. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood. 2000;95(12):3653–61.

Bekkenk MW, Jansen PM, Meijer CJ, Willemze R. CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. Ann Oncol. 2004;15(7):1097–108.

Bekkenk MW, Kluin PM, Jansen PM, Meijer CJ, Willemze R. Lymphomatoid papulosis with a natural killer-cell phenotype. Br J Dermatol. 2001;145(2): 318–22.

Bekkenk MW, Vermeer MH, Jansen PM, van Marion AM, Canninga-van Dijk MR, Kluin PM, Geerts ML, Meijer CJ, Willemze R. Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. Blood. 2003;102(6): 2213–9.

Bekkenk MW, Willemze R. CD56-positive 'natural killer'/T-cell lymphoma. Ned Tijdschr Geneeskd. 2001;145(31):1524–5.

Beljaards RC, Meijer CJ, Van Der Putte SC, Hollema H, Geerts ML, Bezemer PD, Willemze R. Primary cutaneous T-cell lymphoma: clinicopathological features and prognostic parameters of 35 cases other than mycosis fungoides and CD30-positive large cell lymphoma. J Pathol. 1994;172(1):53–60.

Beltraminelli H, Leinweber B, Kerl H, Cerroni L. Primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma: a cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance? A study of 136 cases. Am J Dermatopathol. 2009;31(4):317–22.

Beltraminelli H, Mullegger R, Cerroni L. Indolent CD8+ lymphoid proliferation of the ear: a phenotypic variant of the small-medium pleomorphic cutaneous T-cell lymphoma? J Cutan Pathol. 2010;37(1):81–4.

Bendelac A, Lesavre P, Boitard C, O'Connor NT, Laure F, Laroche L, Teillac D, de Prost Y, Bach JF. Cutaneous pheomorphic T cell lymphoma. Immunologic, virologic, and T-cell receptor gene rearrangement studies in one European case with initial pseudolymphoma presentation. J Am Acad Dermatol. 1986;15(4 Pt 1):657–64.

Benner MF, Ballabio E, van Kester MS, Saunders NJ, Vermeer MH, Willemze R, Lawrie CH, Tensen CP. Primary cutaneous anaplastic large cell lymphoma shows a distinct miRNA expression profile and reveals differences from tumor-stage mycosis fungoides. Exp Dermatol. 2012a;21(8):632–4.

Benner MF, Jansen PM, Meijer CJ, Willemze R. Diagnostic and prognostic evaluation of phenotypic markers TRAF1, MUM1, BCL2 and CD15 in cutaneous CD30-positive lymphoproliferative disorders. Br J Dermatol. 2009;161(1):121–7.

Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood. 2012b;119(7):1643–9.

Berger E, Altiner A, Chu J, Patel R, Sanders S, Latkowski JA. Mycosis fungoides stage IB progressing to cutaneous tumors. Dermatol Online J. 2011;17(10):5.

Berger R, Baranger L, Bernheim A, Valensi F, Flandrin G. Cytogenetics of T-cell malignant lymphoma. Report of 17 cases and review of the chromosomal breakpoints. Cancer Genet Cytogenet. 1988;36(1):123–30.

Bergman R. Pseudolymphoma and cutaneous lymphoma: facts and controversies. Clin Dermatol. 2010;28(5): 568–74.

Berlingeri-Ramos AC, De JG, Sanchez JL, Gonzalez JR. Disease evolution of patients with mycosis fungoides–a report of 30 cases. P R Health Sci J. 2007;26(2):151–4.

Bernstein H, Shupack J, Ackerman B. Cutaneous pseudolymphoma resulting from antigen injections. Arch Dermatol. 1974;110(5):756–7.

Bernstein JE, Soltani K, Lorincz AL. Cutaneous manifestations of angioimmunoblastic lymphadenopathy. J Am Acad Dermatol. 1979;1(3):227–32.

Berti E, Tomasini D, Vermeer MH, Meijer CJ, Alessi E, Willemze R. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. Am J Pathol. 1999;155(2):483–92.

Bignon YJ, Souteyrand P. Genotyping of cutaneous T-cell lymphomas and pseudolymphomas. Curr Probl Dermatol. 1990;19:114–23.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother. 2007;56(5):739–45.

Blazejak T, Holzle E. Phenothiazine-induced pseudolymphoma. Hautarzt. 1990;41(3):161–3.

Bluestone JA, Khattri R, Sciammas R, Sperling AI. TCR gamma delta cells: a specialized T-cell subset in the immune system. Annu Rev Cell Dev Biol. 1995;11:307–53.

Bluestone JA, Matis LA. Are TCR alpha beta cells and TCR gamma delta cells that different? Res Immunol. 1990;141(7):606–10.

Blumental G, Okun MR, Ponitch JA. Pseudolymphomatous reaction to tattoos. Report of three cases. J Am Acad Dermatol. 1982;6(4 Pt 1):485–8.

Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15(4):250–7.

Boehncke WH, Gerdes J, Wiese M, Kaltoft K, Sterry W. A majority of proliferating T cells in cutaneous malignant T cell lymphomas may lack the high affinity IL-2 receptor (CD25). Arch Dermatol Res. 1993;285(3): 127–30.

Boulland ML, Kanavaros P, Wechsler J, Casiraghi O, Gaulard P. Cytotoxic protein expression in natural killer cell lymphomas and in alpha beta and gamma delta peripheral T-cell lymphomas. J Pathol. 1997;183(4):432–9.

Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood. 2009;113(21):5064–73.

Brodell RT, Santa Cruz DJ. Cutaneous pseudolymphomas. Dermatol Clin. 1985;3(4):719–34.

Brodkin DE, Hobohm DW, Nigam R. Nasal-type NK/T--cell lymphoma presenting as hemophagocytic syndrome in an 11-year-old Mexican boy. J Pediatr Hematol Oncol. 2008;30(12):938–40.

Brown HA, Macon WR, Kurtin PJ, Gibson LE. Cutaneous involvement by angioimmunoblastic T-cell lymphoma with remarkable heterogeneous Epstein-Barr virus expression. J Cutan Pathol. 2001;28(8):432–8.

Burg G, Dummer R, Kempf W. Dyscrasias with "undetermined significance". Arch Dermatol. 2005;141(3):382–4.

Carreras J, Lopez-Guillermo A, Fox BC, Colomo L, Martinez A, Roncador G, Montserrat E, Campo E, Banham AH. High numbers of tumor-infiltrating FOXP3-positive regulatory T cells are associated with improved overall survival in follicular lymphoma. Blood. 2006;108(9):2957–64.

Carreras J, Lopez-Guillermo A, Roncador G, Villamor N, Colomo L, Martinez A, Hamoudi R, Howat WJ, Montserrat E, Campo E. High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. J Clin Oncol. 2009;27(9):1470–6.

Cepeda LT, Pieretti M, Chapman SF, Horenstein MG. CD30-positive atypical lymphoid cells in common non-neoplastic cutaneous infiltrates rich in neutrophils and eosinophils. Am J Surg Pathol. 2003;27(7):912–8.

Cerroni L, Gatter K, Kerl H. Skin lymphoma: the illustrated guide. 3rd ed. Hoiboken, NJ: Wiley-Blackwell; 2009.

Cerroni L, Goteri G. Differential diagnosis between cutaneous lymphoma and pseudolymphoma. Anal Quant Cytol Histol. 2003;25(4):191–8.

Cerroni L, Peris K, Torlone G, Chimenti S. Immunophenotype of lymphocytic infiltrate in mycosis fungoides at the plaque stage and at the tumor stage. A comparative study. G Ital Dermatol Venereol. 1990;125(7–8):313–7.

Cerroni L, Rieger E, Hodl S, Kerl H. Clinicopathologic and immunologic features associated with transformation of mycosis fungoides to large-cell lymphoma. Am J Surg Pathol. 1992;16(6):543–52.

Cetinozman F, Jansen PM, Willemze R. Expression of programmed death-1 in primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma, cutaneous pseudo-T-cell lymphoma, and other types of cutaneous T-cell lymphoma. Am J Surg Pathol. 2012;36(1):109–16.

Chan JK, Sin VC, Ng CS, Lau WH. Cutaneous relapse of nasal T-cell lymphoma clinically mimicking erythema multiforme. Pathology. 1989;21(3):164–8.

Chan JK, Sin VC, Wong KF, Ng CS, Tsang WY, Chan CH, Cheung MM, Lau WH. Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood. 1997;89(12):4501–13.

Chang SE, Park IJ, Huh J, Choi JH, Sung KJ, Moon KC, Koh JK. CD56 expression in a case of primary cutaneous CD30+ anaplastic large cell lymphoma. Br J Dermatol. 2000;142(4):766–70.

Cheung MM, Chan JK, Lau WH, Foo W, Chan PT, Ng CS, Ngan RK. Primary non-Hodgkin's lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients. J Clin Oncol. 1998;16(1):70–7.

Cheung MM, Chan JK, Wong KF. Natural killer cell neoplasms: a distinctive group of highly aggressive lymphomas/leukemias. Semin Hematol. 2003;40(3):221–32.

Cooke CB, Krenacs L, Stetler-Stevenson M, Greiner TC, Raffeld M, Kingma DW, Abruzzo L, Frantz C, Kaviani M, Jaffe ES. Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic gamma delta T-cell origin. Blood. 1996;88(11):4265–74.

Craig AJ, Cualing H, Thomas G, Lamerson C, Smith R. Cytophagic histiocytic panniculitis – a syndrome associated with benign and malignant panniculitis: case comparison and review of the literature. J Am Acad Dermatol. 1998;39(5 Pt 1):721–36.

Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973–2002. Arch Dermatol. 2007;143(7):854–9.

Cualing HD, Zhong E, Moscinski L. "Virtual flow cytometry" of immunostained lymphocytes on microscopic tissue slides: iHCFlow tissue cytometry. Cytometry B Clin Cytom. 2007;72(1):63–76.

de Leval L, Gaulard P. Pathology and biology of peripheral T-cell lymphomas. Histopathology. 2011;58(1):49–68.

del Rio ML, Penuelas-Rivas G, Dominguez-Perles R, Ramirez P, Parrilla P, Rodriguez-Barbosa JI. Antibody-mediated signaling through PD-1 costimulates T cells and enhances CD28-dependent proliferation. Eur J Immunol. 2005;35(12):3545–60.

Delaporte E, Catteau B, Cardon T, Flipo RM, Lecomte-Houcke M, Piette F, Delcambre B, Bergoend H. Cutaneous pseudolymphoma during treatment of rheumatoid polyarthritis with low-dose methotrexate. Ann Dermatol Venereol. 1995;122(8):521–5.

Diamandidou E, Colome-Grimmer M, Fayad L, Duvic M, Kurzrock R. Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. Blood. 1998;92(4):1150–9.

Dmitrovsky E, Matthews MJ, Bunn PA, Schechter GP, Makuch RW, Winkler CF, Eddy J, Sausville EA, Ihde DC. Cytologic transformation in cutaneous T cell lymphoma: a clinicopathologic entity associated with poor prognosis. J Clin Oncol. 1987;5(2):208–15.

Dogan A, Attygalle AD, Kyriakou C. Angioimmunoblastic T-cell lymphoma. Br J Haematol. 2003;121(5):681–91.

Droc C, Cualing HD, Kadin ME. Need for an improved molecular/genetic classification for CD30+ lymphomas involving the skin. Cancer Control. 2007;14(2):124–32.

Dukers DF, Vermeer MH, Jaspars LH, Sander CA, Flaig MJ, Vos W, Willemze R, Meijer CJ. Expression of killer cell inhibitory receptors is restricted to true NK cell lymphomas and a subset of intestinal enteropathy-type T cell lymphomas with a cytotoxic phenotype. J Clin Pathol. 2001;54(3):224–8.

Dummer R, Potoczna N, Haffner AC, Zimmermann DR, Gilardi S, Burg G. A primary cutaneous non-T, non-B CD4+, CD56+ lymphoma. Arch Dermatol. 1996;132(5):550–3.

Eckert F, Schmid U, Kaudewitz P, Burg G, Braun-Falco O. Follicular lymphoid hyperplasia of the skin with high content of Ki-1 positive lymphocytes. Am J Dermatopathol. 1989;11(4):345–52.

Edinger JT, Clark BZ, Pucevich BE, Geskin LJ, Swerdlow SH. CD30 expression and proliferative fraction in nontransformed mycosis fungoides. Am J Surg Pathol. 2009;33(12):1860–8.

Ferenczi K. Could follicular helper T-cells play a role in primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphomas? J Cutan Pathol. 2009;36(6):717–8.

Ferran M, Gallardo F, Baena V, Ferrer A, Florensa L, Pujol RM. The 'deck chair sign' in specific cutaneous involvement by angioimmunoblastic T cell lymphoma. Dermatology. 2006;213(1):50–2.

Fink-Puches R, Zenahlik P, Back B, Smolle J, Kerl H, Cerroni L. Primary cutaneous lymphomas: applicability of current classification schemes (European Organization for Research and Treatment of Cancer, World Health Organization) based on clinicopathologic features observed in a large group of patients. Blood. 2002;99(3):800–5.

Friedmann D, Wechsler J, Delfau MH, Esteve E, Farcet JP, de Muret A, Parneix-Spake A, Vaillant L, Revuz J, Bagot M. Primary cutaneous pleomorphic small T-cell lymphoma. A review of 11 cases. The French Study Group on Cutaneous Lymphomas. Arch Dermatol. 1995;131(9):1009–15.

Frizzera G, Moran EM, Rappaport H. Angioimmunoblastic lymphadenopathy. Diagnosis and clinical course. Am J Med. 1975;59(6):803–18.

Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, Morabito F, Martelli M, Brusamolino E, Iannitto E, Zaja F, Cortelazzo S, Rigacci L, Devizzi L, Todeschini G, Santini G, Brugiatelli M, Federico M. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood. 2004;103(7):2474–9.

Gallardo F, Barranco C, Toll A, Pujol RM. CD30 antigen expression in cutaneous inflammatory infiltrates of scabies: a dynamic immunophenotypic pattern that should be distinguished from lymphomatoid papulosis. J Cutan Pathol. 2002;29(6):368–73.

Gammon B, Guitart J. Intertriginous mycosis fungoides: a distinct presentation of cutaneous T-cell lymphoma that may be caused by malignant follicular helper T cells. Arch Dermatol. 2012;148(9):1040–4.

Garcia-Herrera A, Colomo L, Camos M, Carreras J, Balague O, Martinez A, Lopez-Guillermo A, Estrach T, Campo E. Primary cutaneous small/medium CD4+ T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. J Clin Oncol. 2008;26(20):3364–71.

Garcia-Herrera A, Song JY, Chuang SS, Villamor N, Colomo L, Pittaluga S, Alvaro T, Rozman M, de Anda GJ, Arrunategui AM, Fernandez E, Gonzalvo E, Estrach T, Colomer D, Raffeld M, Gaulard P, Campo E, Jaffe ES, Martinez A. Nonhepatosplenic gammadelta T-cell lymphomas represent a spectrum of aggressive cytotoxic T-cell lymphomas with a mainly extranodal presentation. Am J Surg Pathol. 2011;35(8):1214–25.

Gaulard P, Belhadj K, Reyes F. Gammadelta T-cell lymphomas. Semin Hematol. 2003;40(3):233–43.

Gaulard P, Berti E, Willemze R, Jaffe ES. Primary cutaneous peripheral T-cell lymphoma, rare subtypes. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, editors. WHO classification of tumors of hematopoietic and lymphoid tissues. 4th ed. Lyon: IARC; 2008:302–5.

Gaulard P, de Leval L. Follicular helper T cells: implications in neoplastic hematopathology. Semin Diagn Pathol. 2011;28(3):202–13.

Geraud C, Goerdt S, Klemke CD. Primary cutaneous CD8+ small/medium-sized pleomorphic T-cell lymphoma, eartype: a unique cutaneous T-cell lymphoma with a favourable prognosis. Br J Dermatol. 2011;164(2):456–8.

Girardi M. Cutaneous biology of gammadelta T cells. Adv Dermatol. 2004;20:203–15.

Gniadecki R. Neoplastic stem cells in cutaneous lymphomas: evidence and clinical implications. Arch Dermatol. 2004;140(9):1156–60.

Gniadecki R, Lukowsky A. Monoclonal T-cell dyscrasia of undetermined significance associated with recalcitrant erythroderma. Arch Dermatol. 2005;141(3):361–7.

Gniadecki R, Rossen K. Expression of T-cell activation marker CD134 (OX40) in lymphomatoid papulosis. Br J Dermatol. 2003;148(5):885–91.

Gniadecki R, Rossen K, Ralfkier E, Thomsen K, Skovgaard GL, Jonsson V. CD56+ lymphoma with skin involvement: clinicopathologic features and classification. Arch Dermatol. 2004;140(4):427–36.

Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. Cancer. 2004;101(6):1404–13.

Good DJ, Gascoyne RD. Atypical lymphoid hyperplasia mimicking lymphoma. Hematol Oncol Clin North Am. 2009;23(4):729–45.

Gormley RH, Hess SD, Anand D, Junkins-Hopkins J, Rook AH, Kim EJ. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. J Am Acad Dermatol. 2010;62(2):300–7.

Grange F, Hedelin G, Joly P, Beylot-Barry M, D'Incan M, Delaunay M, Vaillant L, Avril MF, Bosq J, Wechsler J, Dalac S, Grosieux C, Franck N, Esteve E, Michel C, Bodemer C, Vergier B, Laroche L, Bagot M. Prognostic factors in primary cutaneous lymphomas other than mycosis fungoides and the Sezary syndrome. The French Study Group on Cutaneous Lymphomas. Blood. 1999;93(11):3637–42.

Greer JP, Salhany KE, Cousar JB, Fields JP, King LE, Graber SE, Flexner JM, Stein RS, Collins RD. Clinical features associated with transformation of cerebriform T-cell lymphoma to a large cell process. Hematol Oncol. 1990;8(4):215–27.

Griesser H, Feller AC, Sterry W. T-cell receptor and immunoglobulin gene rearrangements in cutaneous T-cell-rich pseudolymphomas. J Invest Dermatol. 1990;95(3):292–5.

Grogg KL, Attygalle AD, Macon WR, Remstein ED, Kurtin PJ, Dogan A. Angioimmunoblastic T-cell lymphoma: a neoplasm of germinal-center T-helper cells? Blood. 2005;106(4):1501–2.

Grogg KL, Jung S, Erickson LA, McClure RF, Dogan A. Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior. Mod Pathol. 2008;21(6):708–15.

Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst. 2000;92(15):1240–51.

Guitart J, Magro C. Cutaneous T-cell lymphoid dyscrasia: a unifying term for idiopathic chronic dermatoses with persistent T-cell clones. Arch Dermatol. 2007;143(7): 921–32.

Guitart J, Weisenburger DD, Subtil A, Kim E, Wood G, Duvic M, Olsen E, Junkins-Hopkins J, Rosen S, Sundram U, Ivan D, Selim MA, Pincus L, Deonizio JM, Kwasny M, Kim YH. Cutaneous gammadelta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. Am J Surg Pathol. 2012;36(11):1656–65.

Habermann TM, Pittelkow MR. Cutaneous T-cell lymphoma and cutaneous B-cell lymphoma. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. Clinical Oncology. 3rd ed. New York, NY: Churchill Livingstone; 2004: 3077–108.

Hahtola S, Tuomela S, Elo L, Hakkinen T, Karenko L, Nedoszytko B, Heikkila H, Saarialho-Kere U, Roszkiewicz J, Aittokallio T, Lahesmaa R, Ranki A. Th1 response and cytotoxicity genes are down-regulated in cutaneous T-cell lymphoma. Clin Cancer Res. 2006;12(16):4812–21.

Hongyo T, Hoshida Y, Nakatsuka S, Syaifudin M, Kojya S, Yang WI, Min YH, Chan H, Kim CH, Harabuchi Y, Himi T, Inuyama M, Aozasa K, Nomura T. p53, K-ras, c-kit and beta-catenin gene mutations in sinonasal NK/T-cell lymphoma in Korea and Japan. Oncol Rep. 2005;13(2):265–71.

Hoshida Y, Hongyo T, Jia X, He Y, Hasui K, Dong Z, Luo WJ, Ham MF, Nomura T, Aozasa K. Analysis of p53, K-ras, c-kit, and beta-catenin gene mutations in sinonasal NK/T cell lymphoma in northeast district of China. Cancer Sci. 2003;94(3):297–301.

Hu S, Young KH, Konoplev SN, Medeiros LJ. Follicular T-cell lymphoma: a member of an emerging family of follicular helper T-cell derived T-cell lymphomas. Hum Pathol. 2012;43(11):1789–98.

Huang CT, Chuang SS. Angioimmunoblastic T-cell lymphoma with cutaneous involvement: a case report with subtle histologic changes and clonal T-cell proliferation. Arch Pathol Lab Med. 2004;128(10):e122–4.

Huang Y, Moreau A, Dupuis J, Streubel B, Petit B, Le Gouill S, Martin-Garcia N, Copie-Bergman C, Gaillard F, Qubaja M, Fabiani B, Roncador G, Haioun C, fau-Larue MH, Marafioti T, Chott A, Gaulard P. Peripheral T-cell lymphomas with a follicular growth pattern are derived from follicular helper T cells (TFH) and may show overlapping features with angioimmunoblastic T-cell lymphomas. Am J Surg Pathol. 2009;33(5):682–90.

Hubinger G, Muller E, Scheffrahn I, Schneider C, Hildt E, Singer BB, Sigg I, Graf J, Bergmann L. CD30-mediated cell cycle arrest associated with induced expression of p21(CIP1/WAF1) in the anaplastic large cell lymphoma cell line Karpas 299. Oncogene. 2001;20(5):590–8.

Hudak S, Hagen M, Liu Y, Catron D, Oldham E, McEvoy LM, Bowman EP. Immune surveillance and effector functions of CCR10(+) skin homing T cells. J Immunol. 2002;169(3):1189–96.

Ishida T, Inagaki H, Utsunomiya A, Takatsuka Y, Komatsu H, Iida S, Takeuchi G, Eimoto T, Nakamura S, Ueda R. CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. Clin Cancer Res. 2004;10(16):5494–500.

Ishida T, Ueda R. Immunopathogenesis of lymphoma: focus on CCR4. Cancer Sci. 2011;102(1):44–50.

Jakob T, Neuber K, Altenhoff J, Kowalzick L, Ring J. Stage-dependent expression of CD7, CD45RO, CD45RA and CD25 on CD4-positive peripheral blood T-lymphocytes in cutaneous T-cell lymphoma. Acta Derm Venereol. 1996;76(1):34–6.

Jenni D, Karpova MB, Seifert B, Golling P, Cozzio A, Kempf W, French LE, Dummer R. Primary cutaneous lymphoma: two-decade comparison in a population of 263 cases from a Swiss tertiary referral centre. Br J Dermatol. 2011;164(5):1071–7.

Jones D, Dang NH, Duvic M, Washington LT, Huh YO. Absence of CD26 expression is a useful marker for diagnosis of T-cell lymphoma in peripheral blood. Am J Clin Pathol. 2001;115(6):885–92.

Kabelitz D. Analysis of the human T-cell receptor V gamma gene usage by flow cytometry. Ann N Y Acad Sci. 1995;756:103–5.

Kabelitz D, Glatzel A, Wesch D. Antigen recognition by human gammadelta T lymphocytes. Int Arch Allergy Immunol. 2000;122(1):1–7.

Kabelitz D, He W. The multifunctionality of human Vgamma9Vdelta2 gammadelta T cells: clonal plasticity or distinct subsets?Scand. J Immunol. 2012;76(3): 213–22.

Kabelitz D, Marischen L, Oberg HH, Holtmeier W, Wesch D. Epithelial defence by gamma delta T cells. Int Arch Allergy Immunol. 2005;137(1):73–81.

Kabelitz D, Wesch D. Features and functions of gamma delta T lymphocytes: focus on chemokines and their receptors. Crit Rev Immunol. 2003;23(5–6):339–70.

Kadin ME. Cutaneous gamma delta T-cell lymphomas – how and why should they be recognized? Arch Dermatol. 2000;136(8):1052–4.

Kadin ME. Pathobiology of CD30+ cutaneous T-cell lymphomas. J Cutan Pathol. 2006;33 Suppl 1:10–7.

Kadin ME, Pavlov IY, Delgado JC, Vonderheid EC. High soluble CD30, CD25, and IL-6 may identify patients with worse survival in CD30+ cutaneous lymphomas and early mycosis fungoides. J Invest Dermatol. 2012;132(3 Pt 1):703–10.

Kamarashev J, Burg G, Mingari MC, Kempf W, Hofbauer G, Dummer R. Differential expression of cytotoxic molecules and killer cell inhibitory receptors in CD8+ and CD56+ cutaneous lymphomas. Am J Pathol. 2001;158(5):1593–8.

Kamarashev J, Theler B, Dummer R, Burg G. Mycosis fungoides–analysis of the duration of disease stages in patients who progress and the time point of high-grade transformation. Int J Dermatol. 2007;46(9):930–5.

Kantekure K, Yang Y, Raghunath P, Schaffer A, Woetmann A, Zhang Q, Odum N, Wasik M. Expression patterns of the immunosuppressive proteins PD-1/CD279 and PD-L1/CD274 at different stages of cutaneous T-cell lymphoma/mycosis fungoides. Am J Dermatopathol. 2012;34(1):126–8.

Karenko L, Hahtola S, Ranki A. Molecular cytogenetics in the study of cutaneous T-cell lymphomas (CTCL). Cytogenet Genome Res. 2007;118(2–4):353–61.

Kelley TW, Parker CJ. CD4 (+)CD25 (+)Foxp3 (+) regulatory T cells and hematologic malignancies. Front Biosci (Sch Ed). 2010;2:980–92.

Kempf W, Kazakov DV, Palmedo G, Fraitag S, Schaerer L, Kutzner H. Pityriasis lichenoides et varioliformis acuta with numerous CD30(+) cells: a variant mimicking lymphomatoid papulosis and other cutaneous lymphomas. A clinicopathologic, immunohistochemical, and molecular biological study of 13 cases. Am J Surg Pathol. 2012;36(7):1021–9.

Kempf W, Sander CA. Classification of cutaneous lymphomas – an update. Histopathology. 2010;56(1):57–70.

Kikuchi A, Sakuraoka K, Kurihara S, Akiyama M, Shimizu H, Nishikawa T. CD8+ cutaneous anaplastic large-cell lymphoma: report of two cases with immunophenotyping, T-cell-receptor gene rearrangement and electron microscopic studies. Br J Dermatol. 1992;126(4):404–8.

Kim EJ, Lin J, Junkins-Hopkins JM, Vittorio CC, Rook AH. Mycosis fungoides and sezary syndrome: an update. Curr Oncol Rep. 2006;8(5):376–86.

Kim YC, Vandersteen DP. Primary cutaneous pleomorphic small/medium-sized T-cell lymphoma in a young man. Br J Dermatol. 2001;144(4):903–5.

Koch R, Jaffe ES, Mensing C, Zeis M, Schmitz N, Sander CA. Cutaneous gamma/delta T-cell lymphoma. J Dtsch Dermatol Ges. 2009;7(12):1065–7.

Kulow BF, Cualing H, Steele P, VanHorn J, Breneman JC, Mutasim DF, Breneman DL. Progression of cutaneous B-cell pseudolymphoma to cutaneous B-cell lymphoma. J Cutan Med Surg. 2002;6(6):519–28.

Kumar S, Krenacs L, Medeiros J, Elenitoba-Johnson KS, Greiner TC, Sorbara L, Kingma DW, Raffeld M, Jaffe ES. Subcutaneous panniculitic T-cell lymphoma is a tumor of cytotoxic T lymphocytes. Hum Pathol. 1998;29(4):397–403.

Kurniawan AN, Hongyo T, Hardjolukito ES, Ham MF, Takakuwa T, Kodariah R, Hoshida Y, Nomura T, Aozasa K. Gene mutation analysis of sinonasal lymphomas in Indonesia. Oncol Rep. 2006;15(5):1257–63.

Lai P, Hsiao Y, Hsu J, Wey SJ. Early stage mycosis fungoides with focal CD30-positive large cell transformation. Dermatol Sin. 2013;31(2):73–7. doi:http://dx.doi.org/10.1016/j.dsi.2012.06.006

Landa NG, Zelickson BD, Peters MS, Muller SA, Pittelkow MR. Lymphoma versus pseudolymphoma of the skin: gene rearrangement study of 21 cases with clinicopathologic correlation. J Am Acad Dermatol. 1993;29(6):945–53.

Lanier LL. NK cell recognition. Annu Rev Immunol. 2005;23:225–74.

Lanier LL, Cwirla S, Federspiel N, Phillips JH. Human natural killer cells isolated from peripheral blood do not rearrange T cell antigen receptor beta chain genes. J Exp Med. 1986;163(1):209–14.

Leinweber B, Beltraminelli H, Kerl H, Cerroni L. Solitary small- to medium-sized pleomorphic T-cell nodules of undetermined significance: clinical, histopathological, immunohistochemical and molecular analysis of 26 cases. Dermatology. 2009;219(1):42–7.

Lin CW, Lee WH, Chang CL, Yang JY, Hsu SM. Restricted killer cell immunoglobulin-like receptor repertoire without T-cell receptor gamma rearrangement supports a true natural killer-cell lineage in a subset of sinonasal lymphomas. Am J Pathol. 2001;159(5):1671–9.

Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol. 2003;49(6):1049–58.

Lukes RJ, Collins RD. Immunologic characteristics of human malignant lymphomas. Cancer. 1974;34:1488.

Mao X, Lillington D, Scarisbrick JJ, Mitchell T, Czepulkowski B, Russell-Jones R, Young B, Whittaker SJ. Molecular cytogenetic analysis of cutaneous T-cell lymphomas: identification of common genetic alterations in Sezary syndrome and mycosis fungoides. Br J Dermatol. 2002;147(3):464–75.

Martel P, Laroche L, Courville P, Larroche C, Wechsler J, Lenormand B, Delfau MH, Bodemer C, Bagot M, Joly P. Cutaneous involvement in patients with angioimmunoblastic lymphadenopathy with dysproteinemia: a clinical, immunohistological, and molecular analysis. Arch Dermatol. 2000;136(7):881–6.

McComb ME, Telang GH, Vonderheid EC. Secondary syphilis presenting as pseudolymphoma of the skin. J Am Acad Dermatol. 2003;49(2 Suppl Case Reports): S174–6.

Mraz-Gernhard S, Natkunam Y, Hoppe RT, LeBoit P, Kohler S, Kim YH. Natural killer/natural killer-like T-cell lymphoma, CD56+, presenting in the skin: an increasingly recognized entity with an aggressive course. J Clin Oncol. 2001;19(8):2179–88.

Natkunam Y, Smoller BR, Zehnder JL, Dorfman RF, Warnke RA. Aggressive cutaneous NK and NK-like T-cell lymphomas: clinicopathologic, immunohistochemical, and molecular analyses of 12 cases. Am J Surg Pathol. 1999;23(5):571–81.

Navas IC, Ortiz-Romero PL, Villuendas R, Martinez P, Garcia C, Gomez E, Rodriguez JL, Garcia D, Vanaclocha F, Iglesias L, Piris MA, Algara P. p16(INK4a) gene alterations are frequent in lesions of mycosis fungoides. Am J Pathol. 2000;156(5): 1565–72.

Nielsen PS, Riber-Hansen R, Raundahl J, Steiniche T. Automated quantification of MART1-verified Ki67 indices by digital image analysis in melanocytic lesions. Arch Pathol Lab Med. 2012;136(6):627–34.

Nofal A, bdel-Mawla MY, Assaf M, Salah E. Primary cutaneous aggressive epidermotropic CD8(+) T-cell lymphoma: proposed diagnostic criteria and therapeutic evaluation. J Am Acad Dermatol. 2012;67(4): 748–59.

Nowell PC, Finan JB, Vonderheid EC. Clonal characteristics of cutaneous T cell lymphomas: cytogenetic evidence from blood, lymph nodes, and skin. J Invest Dermatol. 1982;78(1):69–75.

OLIVIER J. Mycosis fungoides a tumeurs d'emblee; remission during 3 1/2 years. Arch Belg Dermatol Syphiligr. 1951;7(3):131–2.

Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, Zackheim H, Duvic M, Estrach T, Lamberg S, Wood G, Dummer R, Ranki A, Burg G, Heald P, Pittelkow M, Bernengo MG, Sterry W, Laroche L, Trautinger F, Whittaker S. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110(6):1713–22.

Pagano L, Gallamini A, Trape G, Fianchi L, Mattei D, Todeschini G, Spadea A, Cinieri S, Iannitto E, Martelli M, Nosari A, Bona ED, Tosti ME, Petti MC, Falcucci P, Montanaro M, Pulsoni A, Larocca LM, Leone G. NK/T-cell lymphomas 'nasal type': an Italian multicentric retrospective survey. Ann Oncol. 2006;17(5): 794–800.

Pernet G. Drawing and photograph of a case of mycosis fungoides d'emblee. Proc R Soc Med. 1912;5(Dermatol Sect):207–8.

Petrella T, Maubec E, Cornillet-Lefebvre P, Willemze R, Pluot M, Durlach A, Marinho E, Benhamou JL, Jansen P, Robson A, Grange F. Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? Am J Surg Pathol. 2007;31(12):1887–92.

Pol-Rodriguez MM, Fox LP, Sulis ML, Miller IJ, Garzon MC. Extranodal nasal-type natural killer T-cell lymphoma in an adolescent from Bangladesh. J Am Acad Dermatol. 2006;54(5 Suppl):S192–7.

Ponti R, Fierro MT, Quaglino P, Lisa B, Paola FC, Michela O, Paolo F, Comessatti A, Novelli M, Bernengo MG. TCRgamma-chain gene rearrangement by PCR-based GeneScan: diagnostic accuracy improvement and clonal heterogeneity analysis in multiple cutaneous T-cell lymphoma samples. J Invest Dermatol. 2008;128(4):1030–8.

Ponti R, Quaglino P, Novelli M, Fierro MT, Comessatti A, Peroni A, Bonello L, Bernengo MG. T-cell receptor gamma gene rearrangement by multiplex polymerase chain reaction/heteroduplex analysis in patients with cutaneous T-cell lymphoma (mycosis fungoides/Sezary syndrome) and benign inflammatory disease: correlation with clinical, histological and immunophenotypical findings. Br J Dermatol. 2005; 153(3):565–73.

Pringle JJ. Mycosis Fungoides a Tumeurs d'Emblee. Proc R Soc Med. 1914;7(Dermatol Sect):155–8.

Quintanilla-Martinez L, Fend F, Moguel LR, Spilove L, Beaty MW, Kingma DW, Raffeld M, Jaffe ES. Peripheral T-cell lymphoma with Reed-Sternberg-like cells of B-cell phenotype and genotype associated with Epstein-Barr virus infection. Am J Surg Pathol. 1999;23(10):1233–40.

Quintanilla-Martinez L, Preffer F, Rubin D, Ferry JA, Harris NL. CD20+ T-cell lymphoma. Neoplastic transformation of a normal T-cell subset. Am J Clin Pathol. 1994;102(4):483–9.

Rezania D, Sokol L, Cualing HD. Classification and treatment of rare and aggressive types of peripheral T-cell/natural killer-cell lymphomas of the skin. Cancer Control. 2007;14(2):112–23.

Rijlaarsdam JU, Scheffer E, Meijer CJ, Willemze R. Cutaneous pseudo-T-cell lymphomas. A clinicopathologic study of 20 patients. Cancer. 1992;69(3):717–24.

Rijlaarsdam JU, Willemze R. Cutaneous pseudolymphomas: classification and differential diagnosis. Semin Dermatol. 1994;13(3):187–96.

Rizvi MA, Evens AM, Tallman MS, Nelson BP, Rosen ST. T-cell non-Hodgkin lymphoma. Blood. 2006;107(4):1255–64.

Rodriguez Pinilla SM, Roncador G, Rodriguez-Peralto JL, Mollejo M, Garcia JF, Montes-Moreno S, Camacho FI, Ortiz P, Limeres-Gonzalez MA, Torres A, Campo E, Navarro-Conde P, Piris MA. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma expresses follicular T-cell markers. Am J Surg Pathol. 2009;33(1):81–90.

Rodriguez-Pinilla SM, Ortiz-Romero PL, Monsalvez V, Tomas IE, Almagro M, Sevilla A, Camacho G, Longo MI, Pulpillo A, Az-Perez JA, Montes-Moreno S, Castro Y, Echevarria B, Trebol I, Gonzalez C, Sanchez L, Otin AP, Requena L, Rodriguez-Peralto JL, Cerroni L, Piris MA. TCR-gamma expression in primary cutaneous T-cell Lymphomas. Am J Surg Pathol. 2013;37(3):375–84.

Roullet M, Gheith SM, Mauger J, Junkins-Hopkins JM, Choi JK. Percentage of {gamma}{delta} T cells in panniculitis by paraffin immunohistochemical analysis. Am J Clin Pathol. 2009;131(6):820–6.

Rudiger T, Weisenburger DD, Anderson JR, Armitage JO, Diebold J, Maclennan KA, Nathwani BN, Ullrich F, Muller-Hermelink HK. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol. 2002;13(1):140–9.

Salhany KE, Cousar JB, Greer JP, Casey TT, Fields JP, Collins RD. Transformation of cutaneous T cell lymphoma to large cell lymphoma. A clinicopathologic and immunologic study. Am J Pathol. 1988; 132(2):265–77.

Salhany KE, Macon WR, Choi JK, Elenitsas R, Lessin SR, Felgar RE, Wilson DM, Przybylski GK, Lister J, Wasik MA, Swerdlow SH. Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotypic analysis of alpha/beta and gamma/delta subtypes. Am J Surg Pathol. 1998; 22(7):881–93.

Sallah S, Gagnon GA. Angioimmunoblastic lymphadenopathy with dysproteinemia: emphasis on pathogenesis and treatment. Acta Haematol. 1998;99(2): 57–64.

Santucci M, Pimpinelli N, Massi D, et al. Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. Cancer 2003;97:610–27.

Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol. 2004;15(10):1467–75.

Savage NM, Johnson RC, Natkunam Y. The spectrum of lymphoblastic, nodal and extranodal T-cell lymphomas: characteristic features and diagnostic dilemmas. Hum Pathol. 2012;44(4):451–71.

Savoia P, Fierro MT, Novelli M, Quaglino P, Verrone A, Geuna M, Bernengo MG. CD56-positive cutaneous lymphoma: a poorly recognized entity in the spectrum of primary cutaneous disease. Br J Dermatol. 1997;137(6):966–71.

Scarisbrick JJ, Mitchell TJ, Calonje E, Orchard G, Russell-Jones R, Whittaker SJ. Microsatellite instability is associated with hypermethylation of the hMLH1 gene and reduced gene expression in mycosis fungoides. J Invest Dermatol. 2003;121(4):894–901.

Scarisbrick JJ, Woolford AJ, Calonje E, Photiou A, Ferreira S, Orchard G, Russell-Jones R, Whittaker SJ. Frequent abnormalities of the p15 and p16 genes in mycosis fungoides and sezary syndrome. J Invest Dermatol. 2002;118(3):493–9.

Siu LL, Wong KF, Chan JK, Kwong YL. Comparative genomic hybridization analysis of natural killer cell lymphoma/leukemia. Recognition of consistent patterns of genetic alterations. Am J Pathol. 1999;155(5):1419–25.

Smithberger ES, Rezania D, Chavan RN, Lien MH, Cualing HD, Messina JL. Primary cutaneous angioimmunoblastic T-cell lymphoma histologically mimicking an inflammatory dermatosis. J Drugs Dermatol. 2010;9(7):851–5.

Smolle J, Torne R, Soyer HP, Kerl H. Immunohistochemical classification of cutaneous pseudolymphomas: delineation of distinct patterns. J Cutan Pathol. 1990;17(3):149–59.

Sterry W. Criteria for the differentiation of pseudolymphomas and malignant lymphomas of the skin. Z Hautkr. 1986;61(10):705–8.

Sterry W, Siebel A, Mielke V. HTLV-1-negative pleomorphic T-cell lymphoma of the skin: the clinicopathological correlations and natural history of 15 patients. Br J Dermatol. 1992;126(5):456–62.

Suarez-Vilela D, Izquierdo-Garcia FM. Angioimmunoblastic lymphadenopathy-like T-cell lymphoma: cutaneous clinical onset with prominent granulomatous reaction. Am J Surg Pathol. 2003;27(5): 699–700.

Suchak R, O'Connor S, McNamara C, Robson A. Indolent CD8-positive lymphoid proliferation on the face: part of the spectrum of primary cutaneous small-/medium-sized pleomorphic T-cell lymphoma or a distinct entity? J Cutan Pathol. 2010;37(9):977–81.

Summers E, Samadashwily G, Florell SR. A unique presentation of an Epstein-Barr virus-associated natural killer/T-cell lymphoproliferative disorder in a white male adolescent. Arch Dermatol. 2011;147(2):216–20.

Suzuki R, Suzumiya J, Yamaguchi M, Nakamura S, Kameoka J, Kojima H, Abe M, Kinoshita T, Yoshino T, Iwatsuki K, Kagami Y, Tsuzuki T, Kurokawa M, Ito K, Kawa K, Oshimi K. Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. Ann Oncol. 2010a;21(5):1032–40.

Suzuki SY, Ito K, Ito M, Kawai K. Prognosis of 100 Japanese patients with mycosis fungoides and Sezary syndrome. J Dermatol Sci. 2010b;57(1):37–43.

Swerdlow SJ, Campo E, Harris NL, Jaffe ES, Pileri S, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumors of haematopoieitic and lymphoid tissues, 4th ed. Lyon: IARC press; 2008.

Swick BL, Baum CL, Venkat AP, Liu V. Indolent CD8+ lymphoid proliferation of the ear: report of two cases and review of the literature. J Cutan Pathol. 2011;38(2):209–15.

Takahashi N, Miura I, Chubachi A, Miura AB, Nakamura S. A clinicopathological study of 20 patients with T/natural killer (NK)-cell lymphoma-associated hemophagocytic syndrome with special reference to nasal and nasal-type NK/T-cell lymphoma. Int J Hematol. 2001;74(3):303–8.

Tallon B, Kaddu S, Cerroni L, Kerl H, Aberer E. Pseudolymphomatous tumid lupus erythematosus of the oral mucosa. Am J Dermatopathol. 2010;32(7):704–7.

Toro JR, Beaty M, Sorbara L, Turner ML, White J, Kingma DW, Raffeld M, Jaffe ES. gamma delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. Arch Dermatol. 2000;136(8):1024–32.

Toro JR, Liewehr DJ, Pabby N, Sorbara L, Raffeld M, Steinberg SM, Jaffe ES. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood. 2003;101(9):3407–12.

Tracey L, Villuendas R, Dotor AM, Spiteri I, Ortiz P, Garcia JF, Peralto JL, Lawler M, Piris MA. Mycosis fungoides shows concurrent deregulation of multiple genes involved in the TNF signaling pathway: an expression profile study. Blood. 2003;102(3):1042–50.

Tracey L, Villuendas R, Ortiz P, Dopazo A, Spiteri I, Lombardia L, Rodriguez-Peralto JL, Fernandez-Herrera J, Hernandez A, Fraga J, Dominguez O, Herrero J, Alonso MA, Dopazo J, Piris MA. Identification of genes involved in resistance to interferon-alpha in cutaneous T-cell lymphoma. Am J Pathol. 2002;161(5):1825–37.

Tsuchiya T, Ohshima K, Karube K, Yamaguchi T, Suefuji H, Hamasaki M, Kawasaki C, Suzumiya J, Tomonaga M, Kikuchi M. Th1, Th2, and activated T-cell marker and clinical prognosis in peripheral T-cell lymphoma, unspecified: comparison with AILD, ALCL, lymphoblastic lymphoma, and ATLL. Blood. 2004;103(1):236–41.

Urosevic M, Kamarashev J, Burg G, Dummer R. Primary cutaneous CD8+ and CD56+ T-cell lymphomas express HLA-G and killer-cell inhibitory ligand, ILT2. Blood. 2004;103(5):1796–8.

Van Der Putte SC, Toonstra J, Felten PC, van Vloten WA. Solitary nonepidermotropic T cell pseudolymphoma of the skin. J Am Acad Dermatol. 1986;14(3):444–53.

van Kester MS, Ballabio E, Benner MF, Chen XH, Saunders NJ, van der Fits L, van Doorn R, Vermeer MH, Willemze R, Tensen CP, Lawrie CH. miRNA expression profiling of mycosis fungoides. Mol Oncol. 2011;5(3):273–80.

van Kester MS, Borg MK, Zoutman WH, Out-Luiting JJ, Jansen PM, Dreef EJ, Vermeer MH, van Doorn R, Willemze R, Tensen CP. A meta-analysis of gene expression data identifies a molecular signature characteristic for tumor-stage mycosis fungoides. J Invest Dermatol. 2012;132(8):2050–9.

van Kester MS, Tensen CP, Vermeer MH, Dijkman R, Mulder AA, Szuhai K, Willemze R, van Doorn R. Cutaneous anaplastic large cell lymphoma and peripheral T-cell lymphoma NOS show distinct chromosomal alterations and differential expression of chemokine receptors and apoptosis regulators. J Invest Dermatol. 2010;130(2):563–75.

van Doorn R, Van Haselen CW, van Voorst V, Geerts ML, Heule F, de Rie M, Steijlen PM, Dekker SK, van Vloten WA, Willemze R. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. Arch Dermatol. 2000;136(4):504–10.

Vergier B, de Muret A, Beylot-Barry M, Vaillant L, Ekouevi D, Chene G, Carlotti A, Franck N, Dechelotte P, Souteyrand P, Courville P, Joly P, Delaunay M, Bagot M, Grange F, Fraitag S, Bosq J, Petrella T, Durlach A, de Mascarel A, Merlio JP, Wechsler J. Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. French Study Group of Cutaneious Lymphomas. Blood. 2000;95(7):2212–8.

Von Den DP, Coors EA. Localized cutaneous small to medium-sized pleomorphic T-cell lymphoma: a report of 3 cases stable for years. J Am Acad Dermatol. 2002;46(4):531–5.

Vonderheid EC, Tam DW, Johnson WC, Van Scott EJ, Wallner PE. Prognostic significance of cytomorphology in the cutaneous T-cell lymphomas. Cancer. 1981;47(1):119–25.

Wain EM, Orchard GE, Mayou S, Atherton DJ, Misch KJ, Russell-Jones R. Mycosis fungoides with a CD56+ immunophenotype. J Am Acad Dermatol. 2005;53(1):158–63.

Wang L, Han R, Hancock WW. Programmed cell death 1 (PD-1) and its ligand PD-L1 are required for allograft tolerance. Eur J Immunol. 2007;37(10):2983–90.

Wasik MA, Vonderheid EC, Bigler RD, Marti R, Lessin SR, Polansky M, Kadin ME. Increased serum concentration of the soluble interleukin-2 receptor in cutaneous T-cell lymphoma. Clinical and prognostic implications. Arch Dermatol. 1996;132(1):42–7.

Went P, Agostinelli C, Gallamini A, Piccaluga PP, Ascani S, Sabattini E, Bacci F, Falini B, Motta T, Paulli M, Artusi T, Piccioli M, Zinzani PL, Pileri SA. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol. 2006;24(16):2472–9.

Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, az-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105(10):3768–85.

Williams VL, Torres-Cabala CA, Duvic M. Primary cutaneous small- to medium-sized CD4+ pleomorphic T-cell lymphoma: a retrospective case series and review of the provisional cutaneous lymphoma category. Am J Clin Dermatol. 2011;12(6):389–401.

Wirt DP, Grogan TM, Jolley CS, Rangel CS, Payne CM, Hansen RC, Lynch PJ, Schuchardt M. The immunoarchitecture of cutaneous pseudolymphoma. Hum Pathol. 1985;16(5):492–510.

Wolfe JT, Chooback L, Finn DT, Jaworsky C, Rook AH, Lessin SR. Large-cell transformation following detection of minimal residual disease in cutaneous T-cell lymphoma: molecular and in situ analysis of a single neoplastic T-cell clone expressing the identical T-cell receptor. J Clin Oncol. 1995;13(7):1751–7.

Wood GS. Analysis of clonality in cutaneous T cell lymphoma and associated diseases. Ann N Y Acad Sci. 2001;941:26–30.

Wood GS, Bahler DW, Hoppe RT, Warnke RA, Sklar JL, Levy R. Transformation of mycosis fungoides: T-cell receptor beta gene analysis demonstrates a common clonal origin for plaque-type mycosis fungoides and CD30+ large-cell lymphoma. J Invest Dermatol. 1993;101(3):296–300.

Wood PB, Parikh SR, Krause JR. Extranodal NK/T-cell lymphoma, nasal type. Proc (Bayl Univ Med Cent). 2011;24(3):251–4.

Wozniak MB, Tracey L, Ortiz-Romero PL, Montes S, Alvarez M, Fraga J, Fernandez HJ, Vidal S, Rodriguez-Peralto JL, Piris MA, Villuendas DR. Psoralen plus

ultraviolet A +/− interferon-alpha treatment resistance in mycosis fungoides: the role of tumour microenvironment, nuclear transcription factor-kappaB and T-cell receptor pathways. Br J Dermatol. 2009;160(1):92–102.

Yao X, Teruya-Feldstein J, Raffeld M, Sorbara L, Jaffe ES. Peripheral T-cell lymphoma with aberrant expression of CD79a and CD20: a diagnostic pitfall. Mod Pathol. 2001;14(2):105–10.

Yu JB, Blitzblau RC, Decker RH, Housman DM, Wilson LD. Analysis of primary CD30+ cutaneous lymphoproliferative disease and survival from the surveillance, epidemiology, and end results database. J Clin Oncol. 2008;26(9):1483–8.

Zhang Q, Nowak I, Vonderheid EC, Rook AH, Kadin ME, Nowell PC, Shaw LM, Wasik MA. Activation of Jak/STAT proteins involved in signal transduction pathway mediated by receptor for interleukin 2 in malignant T lymphocytes derived from cutaneous anaplastic large T-cell lymphoma and Sezary syndrome. Proc Natl Acad Sci U S A. 1996;93(17):9148–53.

Zucca E, Zinzani PL. Understanding the group of peripheral T-cell lymphomas, unspecified. Curr Hematol Rep. 2005;4(1):23–30.