Subcutaneous Pattern: Subcutaneous Lymphoproliferative Disorders

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Malignant Disorders

Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL), Alpha-Beta Type

Epidemiology

Most patients are adults. Pediatric patients comprise 20 % of cases and can be as young as 5 months of age (Huppmann et al. 2013). Females exceed males. A unique feature is the high frequency of autoimmune disease, especially systemic lupus erythematosus.

Clinical Features

Most patients have multiple skin lesions which appear as nodules ranging from 0.5 to several centimeters in diameter (Fig. 11.1). Extremities and trunk are most common sites. Lymphadenopathy is uncommon. Systemic B symptoms occur in 50 % of patients. Most common laboratory abnormalities include abnormal liver function tests and cytopenias which can result from hemophagocytic syndrome in up to 35 % of patients (Fig. 11.2) (Gonzalez et al. 1991). SPTCL patients without hemophagocytic syndrome have better survival than patients with the syndrome (5-year OS: 91 % vs. 46 %; $P<0.001$) (Willemze et al. 2008).

Autoimmune diseases, particularly systemic lupus erythematosus, are common among SPTCL patients. The distinction between SPTCL and lupus erythematosus profundus is not always clear, and some cases appear to show progression of lupus profundus to SPTCL. Magro suggested there may be a spectrum of subcutaneous T-cell dyscrasias including lupus profundus and SPTCL (Magro et al. 2001).

In a multicenter study of the French Cutaneous Lymphoma Group (GFELC), 27 patients with SPTCL diagnosed since 2000 had a median age of 31.1 year; F/M ratio was 22:5 (Michonneau et al. 2013). Five cases occurred in children of whom three were under age 3. Almost half of patients (47 %) had an autoimmune disease, and 24 % were diagnosed with another panniculitis. Three cases occurred after pregnancy and in three young children after infectious events. Hemophagocytic syndrome was present in 35 % of cases. Serum beta2-microglobulin was elevated in 83 % of cases (4.51+/−2 mg/L). Median follow-up was 20.5 months. Complete remission was reached in 74 % of cases. 69.5 % were treated with immunosuppressive agents (group 1), and 30.5 % received chemotherapy (group 2). In both groups, complete remission was 77.7 % and 37.5 % ($P=0.07$), respectively, and progression was only observed with chemotherapy (37.5 %, $P=0.02$). The study

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indicated that SPTCL in this group of French patients was often associated with autoimmunity or infections, and a good treatment response with low toxicity was encountered with immunosuppressive treatments.

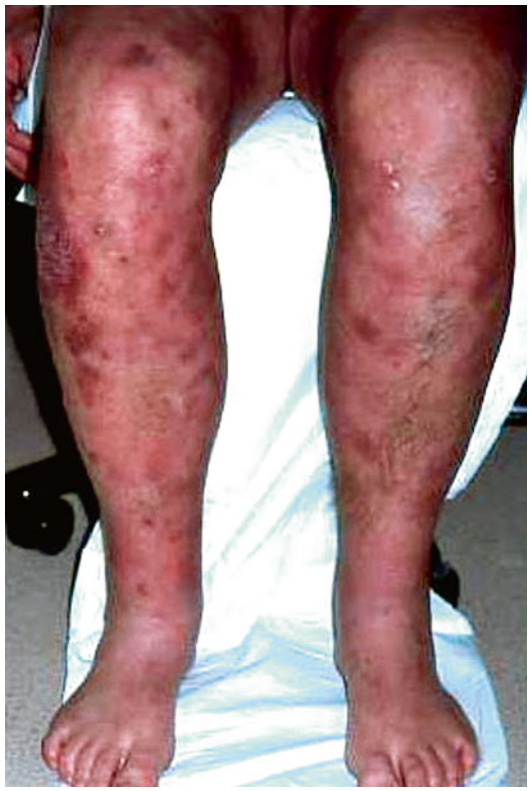

Fig. 11.1 SPTCL – multiple discrete nodular lesions of lower extremities

Histology

The pattern is distinctive and evokes an instant sight diagnosis. At low magnification, one sees a dense lymphocytic infiltration of the subcutaneous tissue and usual sparing of the dermis and epidermis (Fig. 11.3). High magnification reveals atypical lymphocytes with irregular nuclei rimming individual fat cells. Reactive histiocytes are common in areas of fat infiltration. Plasma cells which are common in lupus panniculitis are typically absent. Lymphocytes that surround individual fat cells with frequent apoptotic bodies (karyorrhexis) are seen (Fig. 11.4). Fat necrosis occurs in most cases.

Immunophenotype

Tumor cells have a mature T αβ phenotype, expressing TCRβf1. They are usually CD3+, CD8+, CD4−, CD56−, and CD30− and strongly express cytotoxic molecules (granzyme B, perforin,TIA-1) (Fig. 11.5).

Genetics

Comparative genomic hybridization studies on single cell laser-microdissected cells performed by Hahtola et al. revealed large numbers of DNA copy number changes, the most common of

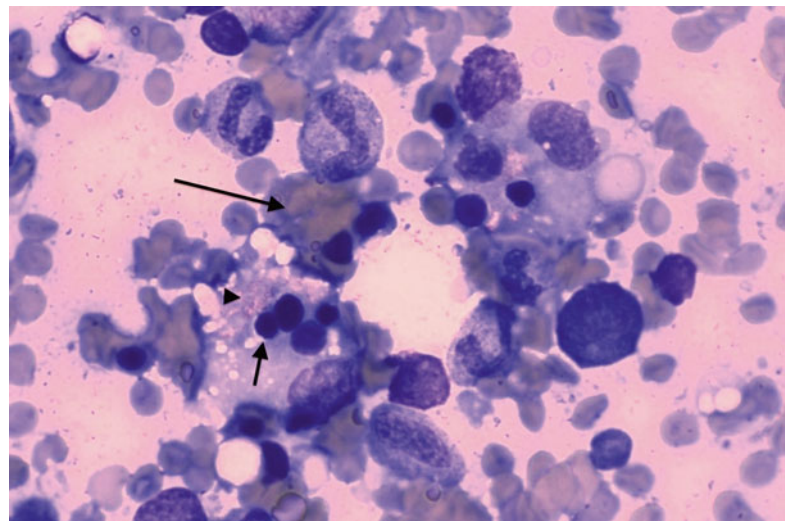

Fig. 11.2 Hemophagocytic syndrome in SPTCL – bone marrow aspirate showing histiocyte phagocytosis of nucleated erythrocytes (*arrows*)

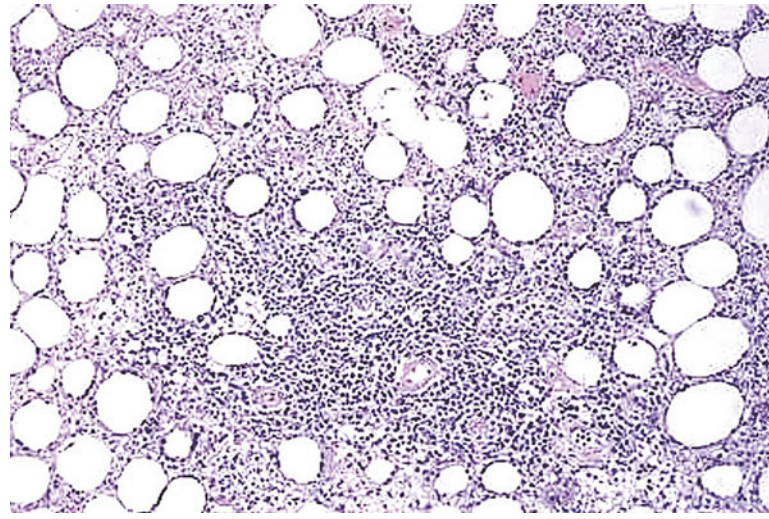

Fig. 11.3 SPTCL – dense lymphocytic infiltrate permeating subcutaneous fat

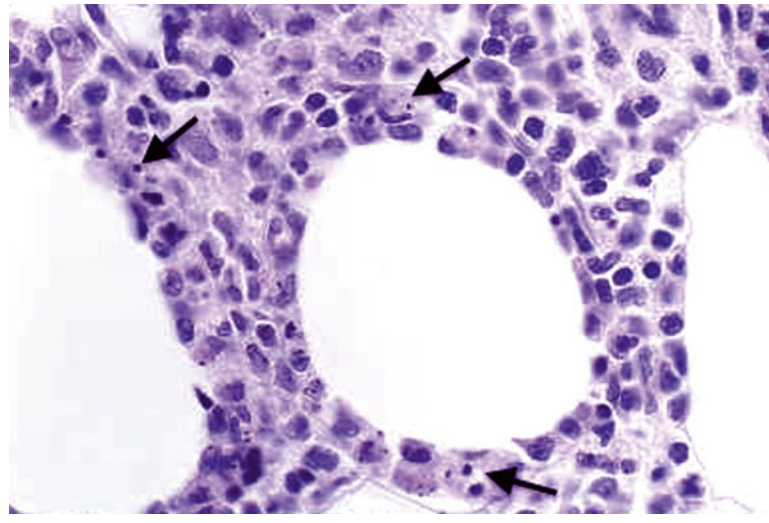

Fig. 11.4 SPTCL – lymphocytic surrounding individual fat cells. Atypical lymphocytes with irregular-shaped nuclei rim fat cells. Apoptotic bodies (karyorrhexis) are seen (*arrows*)

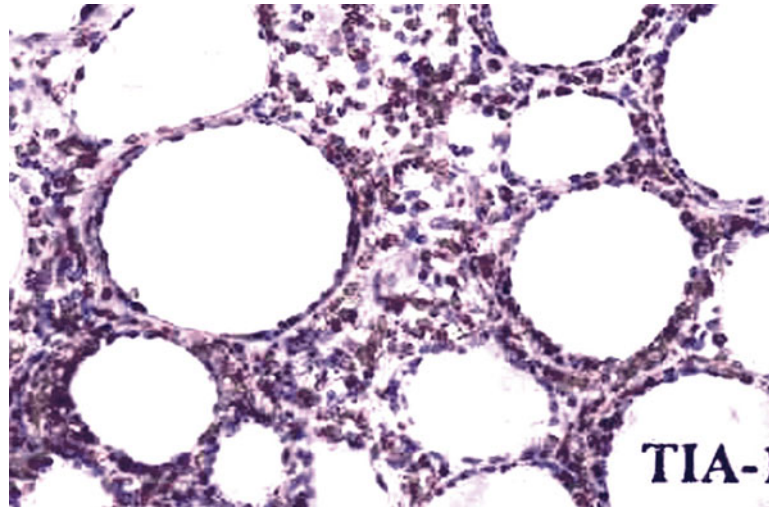

Fig. 11.5 SPTCL – tumor cells strongly express cytotoxic molecules (granzyme B, perforin, TIA-1)

which were losses of chromosomes 1 pter, 2 pter, 10 qter, 11 qter, 12 qter, 16, 19, 20, and 22 and gains of chromosomes 2q and 4q. Some of the DNA copy number aberrations in SPTCL, such as loss of 10q, 17p, and chromosome 19, overlap with those characteristic of mycosis fungoides and Sezary syndrome, whereas 5q and 10q gains are more specific for SPTCL (Hahtola et al. 2008). Analysis of tumors shows clonal rearrangement of TCR genes in most cases. No clonal TCR gene rearrangement was detected in 4 of 17 pediatric cases (Huppmann et al. 2013). Epstein-Barr viral sequences have not been detected.

Differential Diagnosis

Any other condition with a predominant lymphocytic infiltration of subcutaneous tissues can lead to a mistaken diagnosis of SPTCL. Principal differential diagnostic features are summarized in Table 11.1. The prototypic benign condition mimicking SPTCL is lupus profundus. Some cases of cytophagic histiocytic panniculitis (CHP) overlap with SPTCL and could be indistinguishable (see Chap. 4 for discussion). There may be a continuum between the non-clonal indolent CHP and fatal clonal SPTCL (Marzano et al. 2000). The most significant malignant condition that can mimic SPTCL is primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL). These differential diagnoses are discussed in the following sections.

The deep infiltrating component of CD30+ cALCL can surround individual fat cells in the manner of SPTCL (Fig. 11.6). In contrast to SPTCL, cALCL has large anaplastic CD30+ cells, and the main tumor cell infiltrate is within the dermis.

Primary Cutaneous Gamma-Delta T-Cell Lymphoma (PCGD-TCL)

Clinical Features

Most cases occur in adults. In one series of 53 patients, the median age at presentation was 61 years (range 26–91) (Guitart et al. 2012). There is no gender predilection. The most common presentation is deep plaques, followed by patches resembling psoriasis or mycosis fungoides. Lesions frequently ulcerate (Fig. 11.7). Lesions most often involve the extremities, but the trunk is also frequently affected. Lymphadenopathy has been reported in 3/42 cases and bone marrow involvement in 5/28 cases (Guitart et al. 2012). A mucosal form of gamma-delta T-cell lymphoma occurs and a mucocutaneous form of the disease has been suggested (de Wolf-Peeters and Achten 2000). Approximately one-half of patients report systemic symptoms. Progression of disease is associated with extensive ulcerating lesions and hemophagocytic syndrome (Guitart et al. 2012). PCGD-TCL is resistant to radiation and multi-agent chemotherapy. Median survival in one large patient series is 15 months (Willemze et al. 2008) and in another is 31 months (Guitart et al. 2012).

Histology

Unlike SPTCL, primary cutaneous gamma-delta T-cell lymphomas involve the dermis and epidermis as well as subcutaneous tissue (Fig. 11.8). This is the principal histopathologic difference and explains the clinical manifestation of ulcerating lesions. Most cases have a dense lymphocytic infiltrate with partial involvement of epidermal, dermal, and subcutaneous compartments. Interface changes with exocytosis of erythrocytes and necrotic keratinocytes are common (Fig. 11.9). Although extensive epidermal infiltration with pagetoid features is seen, Pautrier microabscesses do not occur. Cytologically, primary cutaneous gamma-delta T-cell lymphomas reveal medium-sized lymphocytes, some with nuclear pleomorphism with Reed-Sternberg-like appearance (Fig. 11.10).

Immunophenotype

The main feature is the expression of the γδ T-cell phenotype now disclosed with a commercially available antibody that recognizes the TCR-δ subunit of the TCR in paraffin-embedded material (Fig. 11.11) (Rodriguez-Pinilla et al. 2013). It should be noted that tumor cells in some cases of PCGD-TCL also express TCR-βf1 (Rodriguez-Pinilla et al. 2013). All cases of PCGD-TCL express CD3. One-half of cases are double nega-

Table 11.1 Principle features distinguishing subcutaneous panniculitis-like T-cell lymphoma from other entities infiltrating the subcutis

	Demographics	Clinical features	Histology	Cytology	Immunophenotype	TCR clonality	Prognosis
SPTCL	20 % children/F > M	Plaques, tumors, extremities, and trunk	Subcutaneous rimming of fat cells	Minimal pleomorphism, karyorrhexis	TCRβf1+, CD8+, cytotoxic proteins+	+	Fair to good, death associated with hemophagocytic syndrome
PCGD-TCL	Adults, M > F	Ulcerated plaques, nodules, tumors	Epidermal with interface changes, dermal; subcutaneous involvement variable	Pleomorphism of tumor cells, karyorrhexis	TCRγδ+, βf1−/+, CD3+, CD4−, CD56+/−, EBER−/+	+	Poor
NKTCL	Adults, M > F	Nodules, tumors	Angiocentric, necrosis	Variable cell size	EBER+/, CD56+	−	Poor
LP	History of lupus erythematosus (LE)	Cutaneous atrophy	Subcutaneous, germinal centers, plasma cells mucin, hyperkeratotic follicular plugging	Minimal lymphocytic atypia, clusters of plasmacytoid dendritic cells	Human myxovirus resistance protein 1	−/+	No deaths attributed to panniculitis
ILLP	No hx of LE, young male	Painless nodules in extremities	Subcutaneous panniculitis with eccrinotropism	Nuclear atypia, focal necrosis	TCRβf1+, mixed CD4/CD8 with decreased ratio	+	Persistence without progression, constitutional symptoms ominous
EN	Young women; delayed hypersensitivity to bacterial infection or drugs	Painful nodules in extremities	Predominantly septal inflammation between fat lobules	Variable numbers of neutrophils, lymphocytes, and histiocytes as well as variable numbers of necrotic adipocytes, Langhans giant cells	TCRβf1+, mixed lymphohistiocytic infiltrate	−	Etiology varied, commonly infectious, i.e., *Mycobacterium TB*

LP lupus profundus, *ILLP* indeterminate lymphocytic lobular panniculitis, *EN* erythema nodosum

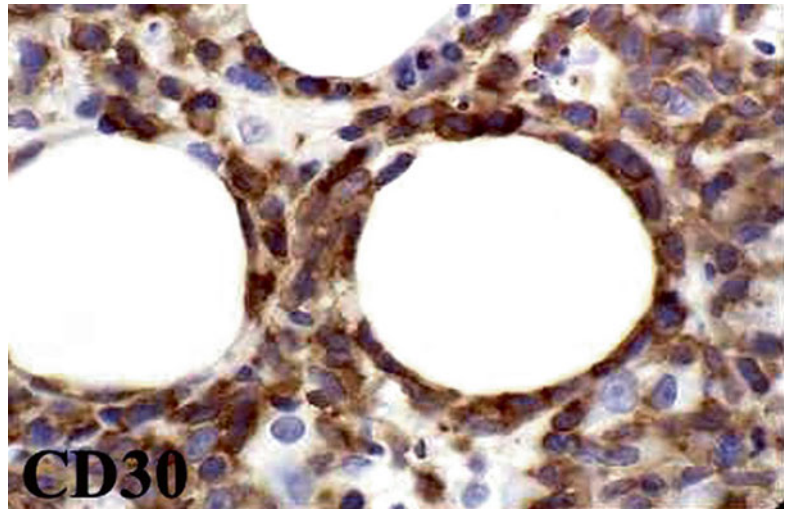

Fig. 11.6 CD30+ tumor cells in cALCL surrounding fat cells simulating SPTCL

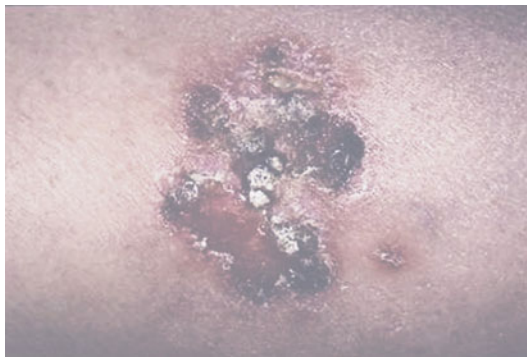

Fig. 11.7 Ulcerating lesions of primary cutaneous gamma-delta T-cell lymphoma

tive for CD4 and CD8 (Guitart et al. 2012). Cytotoxic proteins are expressed in >80 % of cases (Fig. 11.12). EBER by FISH is detected in approximately 10 %. The PCGD-TCL shows the expression of CD56 in about half the cases. The CD56 expression is similar to those of NK cells, which are effector cells together with gamma-delta T cells as part of the immediate immune response to foreign or microbial antigens (Toro et al. 2000; Garcia-Rodriguez et al. 2008; Garcia-Herrera et al. 2011).

Genetics

TCR clonality was detected in skin lesions in 96 % of cases in one large series and also in blood (9/12) and bone marrow (2/4) cases (Guitart et al. 2012).

Differential Diagnosis

The most significant differential diagnosis is SPTCL because some PCGD-TCL can have a predominantly panniculitic pattern (Guitart et al. 2012). Epidermal and dermal infiltrates support the diagnosis of PCGD-TCL. Tumor cell expression of TCR-γ is confirmatory.

The differential diagnosis of PCGD-TCL and extranodal NK/T TCL is often difficult to make (Rodriguez-Pinilla et al. 2013). Both tumors commonly express cytoplasmic CD3, CD2, and cytotoxic proteins, with variable expression of CD7 and CD56. However, most extranodal NK/T TCL are derived from NK cells and lack TCR gene rearrangements which are not characteristic of PCGD-TCL. Also extranodal NK/T TCL do not express TCR-γ. The nasal type of extranodal NK/T is EBV positive by EBER in situ hybridization.

Reactive Panniculitis Disorders

Lupus Profundus

Magro described two main groups of lymphocytic lobular panniculitis having overlapping features with SPTCL: (1) lupus erythematosus profundus (LEP) (Fig. 11.13) and (2) indeterminate lymphocytic lobular panniculitis (ILLP)

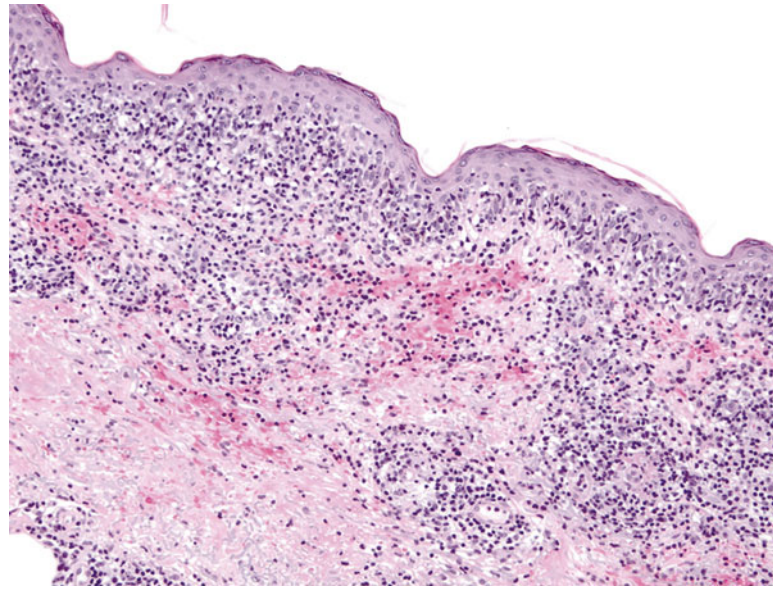

Fig. 11.8 Primary cutaneous gamma-delta T-cell lymphoma. Epidermal and dermal involvement with extravasation of erythrocytes distinguish this entity from SPTCL

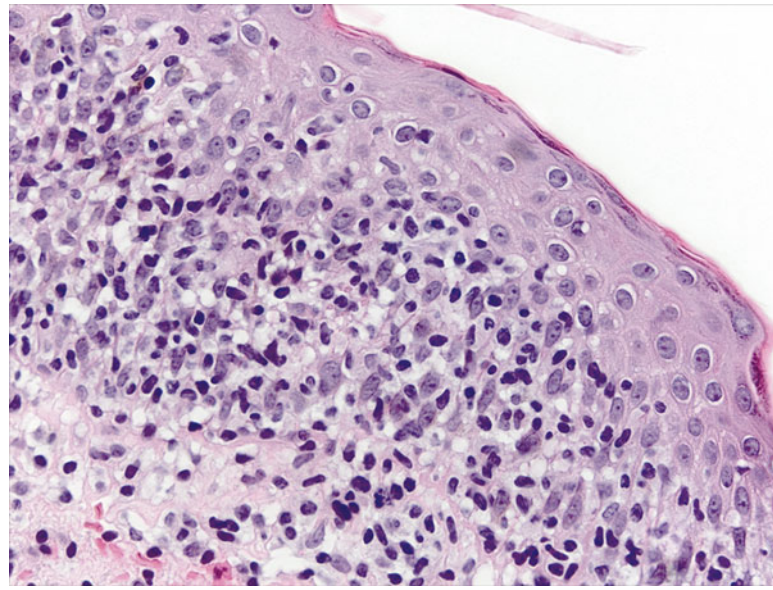

Fig. 11.9 Primary cutaneous gamma-delta T-cell lymphoma. Interface changes shown here occur in approximately one-half of cases

which is not associated with cutaneous or systemic LE (Magro et al. 2001). LEP showed histological similarities to SPTCL including dense lobular lymphocytic infiltration, but with the absence of lymphoid atypia (Fig. 11.14), histiocytes with ingested debris, eosinophilic necrosis of the fat lobule, and thrombosis. The infiltrate in ILLP had a similar cytomorphology and distribution with variable angioinvasion which was of lesser intensity and not associated with significant fat necrosis or vasculitis. Germinal centers, dermal/subcuticular mucin deposition, and an atrophy causing interface dermatitis with hyperkeratosis and follicular plugging were largely confined to the LEP group. The absence of T-cell monoclonality by gene rearrangement analysis

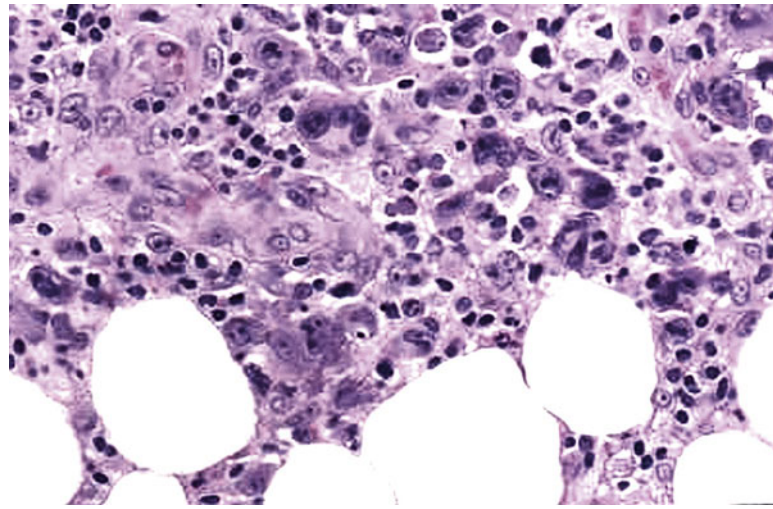

Fig. 11.10 Nuclear pleomorphism in primary cutaneous gamma-delta T-cell lymphoma

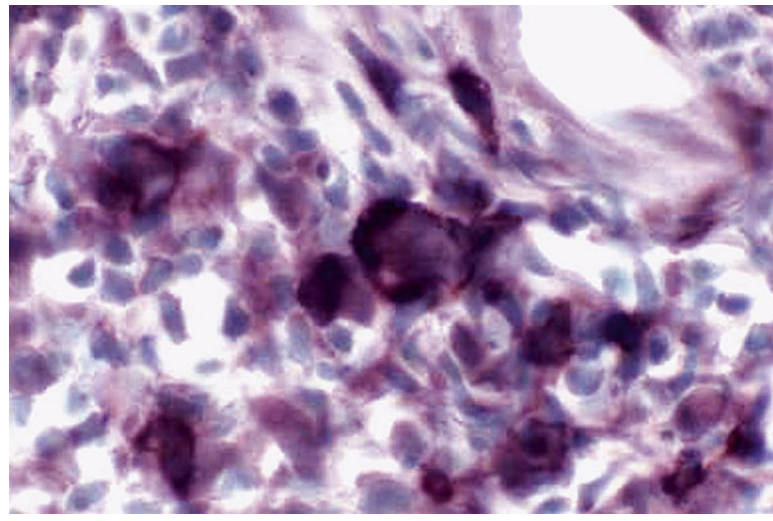

Fig. 11.11 Primary cutaneous gamma-delta T-cell lymphoma. Staining of tumor cells for TCR**δ**

strongly favors LEP (Magro et al. 2001). However, detection of T-cell clonality, whether oligoclonal or stable persistent clone, is also characteristic of ILLP, and therefore ILLP is within the spectrum of lesions in continuity with SPTCL (Magro et al. 2008).

Differential Diagnosis

Recently, Wang and Magro demonstrated the usefulness of IHC staining of human myxovirus resistance protein 1 (MxA) in the differential diagnosis of LEP from SPTCL and PCGD-TCL (Wang and Magro 2012). In SPTCL and GDTCL, MxA was primarily seen in macrophages and generally did not exceed 20 % of the infiltrate. In contrast, a significant portion of the subcutaneous infiltrate was positive for MxA in LEP, with 50 % of the infiltrate staining on average. A greater number of macrophages and lymphocytes stained with a greater intensity as well ($P < 0.001$). Moreover, endothelial cell staining was uniquely identified in LEP but not in lymphoma. Although

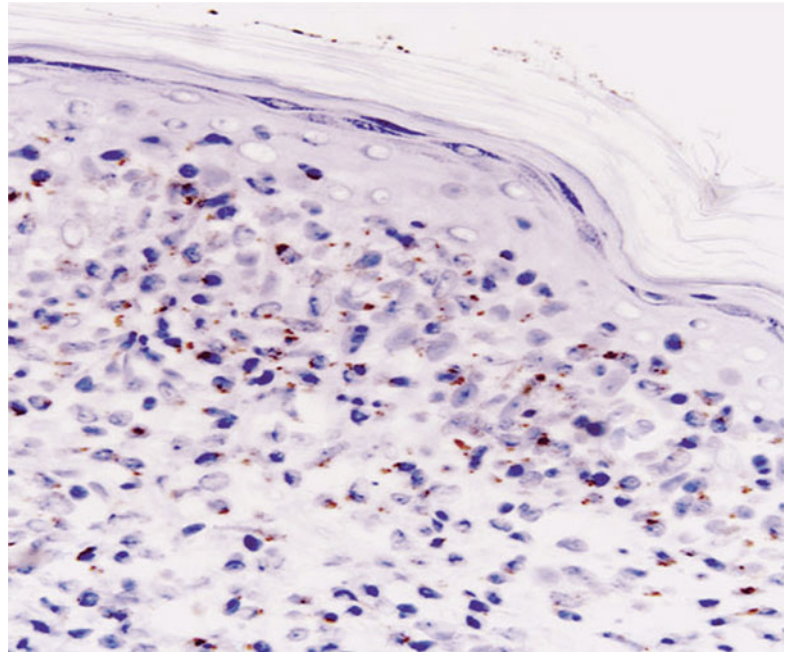

Fig. 11.12 Primary cutaneous gamma-delta T-cell lymphoma. Staining of tumor cells for cytotoxic proteins like granzyme B shown here is seen in nearly all cases

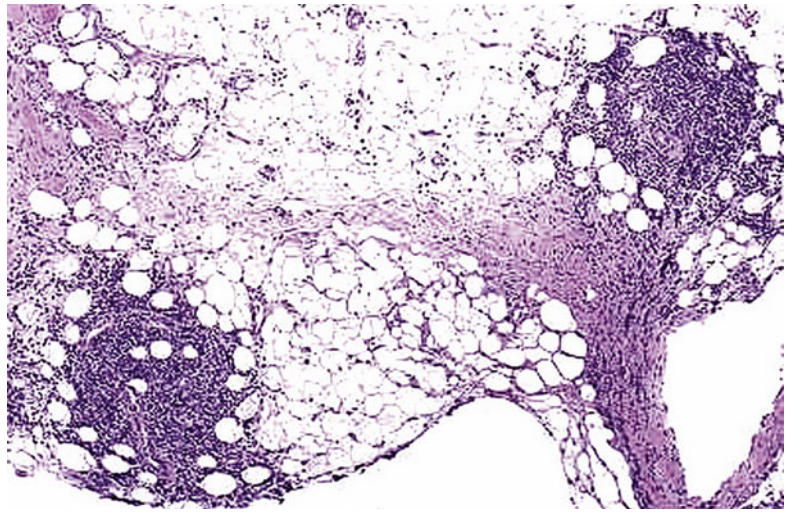

Fig. 11.13 Lupus profundus. Nodular lymphocytic infiltrates of subcutaneous fat. Rimming of fat cells by lymphocytes is not seen in this example

specificity was not 100 %, minimal staining of MxA was a predictor for SPTCL or GDTCL. Conversely, extensive staining for MxA both qualitatively and quantitatively was a feature of LEP. Endothelial staining also appeared to be specific for LEP.

Liau et al. found that the presence of clusters of plasmacytoid dendritic cells is a helpful feature for differentiating lupus panniculitis from subcutaneous panniculitis-like T-cell lymphoma. They also found that the presence of lymphoid follicles, dermal mucin deposition,

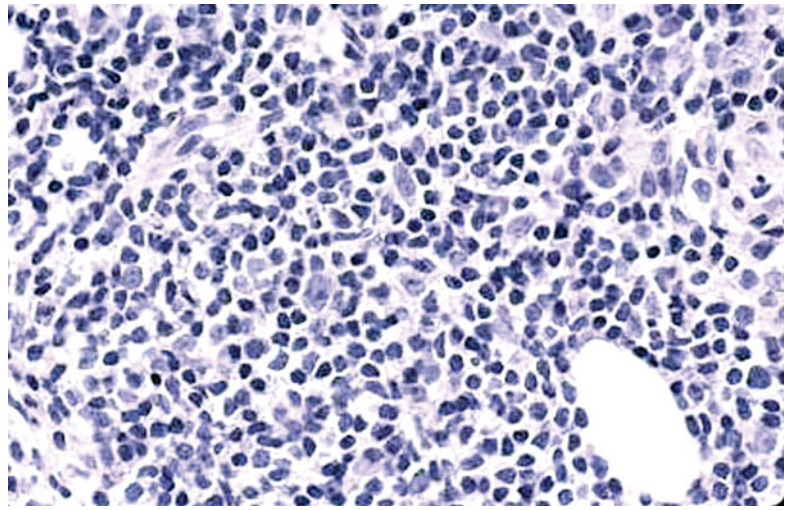

Fig. 11.14 Lupus profundus. Dense lymphocytic infiltrate without atypia

and lack of moderate to marked nuclear atypia or adipocyte rimming were more suggestive of LEP (Liau et al. 2013).

Infectious Panniculitis

Infection is the most frequent cause of panniculitis in developing countries: secondary to acute bacterial etiology such as *Staphylococcus*/*Streptococcus* infections, followed by cutaneous tuberculosis (Mert et al. 2007). Erythema nodosum (EN) is an inflammatory disease of the skin and subcutaneous tissue that presents with bilateral painful nodules in the extremities, histologically seen in the septa between the subcutaneous fat lobules (Fig. 11.15a–c). The hallmark lesions are tender, reddish nodules that present symmetrically on the extensor surfaces of the lower extremities. Erythema nodosum is considered an immunologic response to a wide variety of antigens or even associated with lymphomas (Fox and Schwartz 1992). EN is most commonly associated with cutaneous tuberculid disease instead of an active cutaneous tuberculosis (Garcia-Rodriguez et al. 2008). EN is also described in association with nodular vasculitis (erythema induratum) as it is one of the many manifestations of cutaneous tuberculosis (Losada-Lopez et al. 2012). Hence, the diagnosis of an infectious-disease-associated panniculitis vis-a-vis tumor panniculitis is more frequent in the developing world than in developed countries (Mechai et al. 2011). Detection of TB-associated EN is additionally facilitated by molecular PCR methods in cutaneous lesions (Chen et al. 2013).

Although most EN are secondary to infections, including tuberculosis (Bohn et al. 1997), EN is associated with a wide range of disorders, some (Pileckyte and Griniute 2003) systemic diseases such as sarcoidosis (Pileckyte and Griniute 2003), Behcet disease, or inflammatory bowel diseases but also secondary to some drugs, mainly estrogen-progestins, salicylic acid, minocycline, and sulfamidic acid.

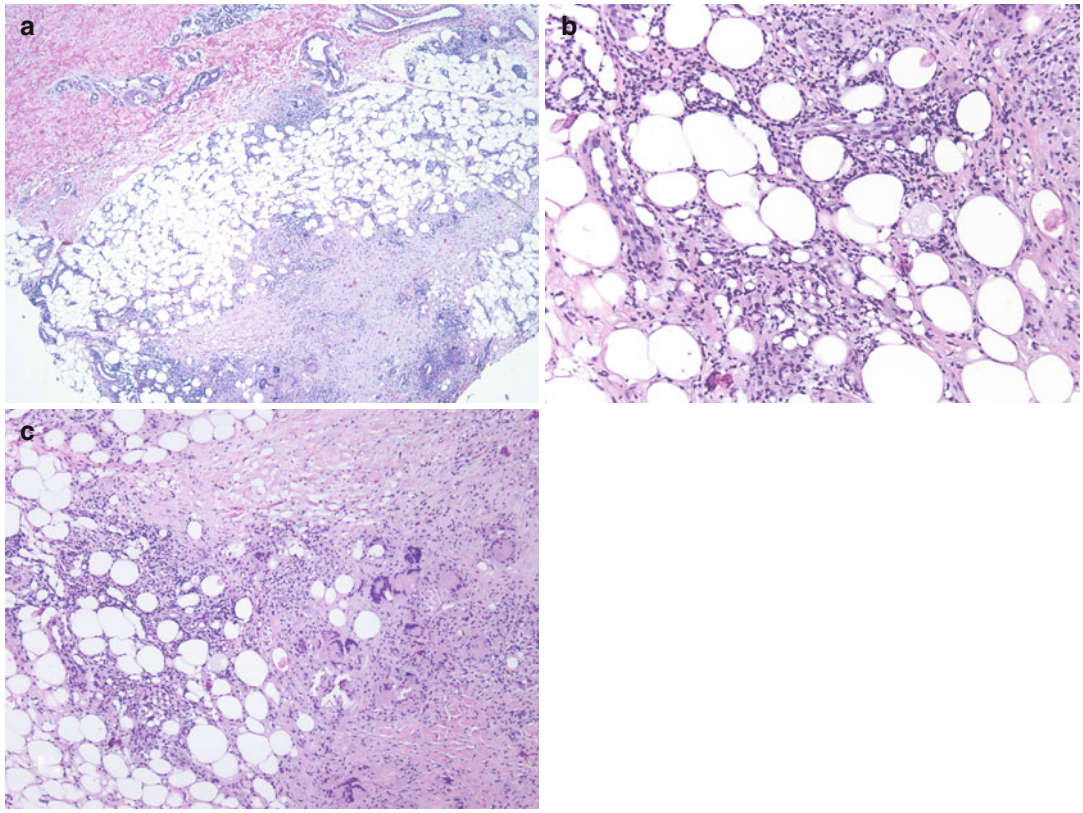

Fig. 11.15 Erythema nodosum. (**a**) Septal lobular panniculitis with fibrosis and Langhans giant cells in fibrotic areas. (**b**) Panniculitis with increased vessels and histiocytes. (**c**) Panniculitis with poorly formed granuloma on the right side with multinucleated Langhans-type giant cells typical of *Mycobacteria*

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