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Cutaneous lymphomas with a panniculitic presentation

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ABSTRACT

Subcutaneous panniculitis-like T-cell lymphoma and primary cutaneous gamma/delta T-cell lymphoma are the two most common types of cutaneous T-cell lymphoma presenting with panniculitis-like lesions. In this article the characteristic clinical, histological and immunophenotypical features of these conditions are reviewed and criteria to differentiate these tumors from other benign and malignant lymphoproliferations presenting with panniculitis-like lesions are discussed.

Introduction

In 1991, Gonzalez et al. described a new type of T-cell lymphoma with clinicopathologic features simulating a panniculitis, which was subsequently named subcutaneous panniculitis-like T-cell lymphoma (SPTL).[1] SPTCL was initially defined as a cytotoxic T-cell lymphoma with either an α/β or a γ/δ T-cell phenotype, which preferentially infiltrates the subcutaneous tissue, is often complicated by a hemophagocytic syndrome (HPS), has an aggressive clinical course and should therefore be treated with aggressive multi-agent chemotherapy.[2] However, more recent studies showed clinical, histological and immunophenotypical differences between SPTCL with an α/β T-cell phenotype and SPTCL with a γ/δ T-cell phenotype, suggesting that these may represent different entities (see Table 1).[3–5] In recent classifications the term SPTCL is only used for cases with an α/β T-cell phenotype, while cases expressing the γ/δ T-cell receptor are reclassified as primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL).[6,7] Differentiation between SPTCL and PCGD-TCL is important, since both conditions have a different prognosis and require a different therapeutic approach. In addition, both conditions should be differentiated from other types of malignant lymphoma with preferential subcutaneous involvement and from other forms of lobular panniculitis, in particular lupus panniculitis.

Subcutaneous panniculitis-like T-cell lymphoma

SPTCL is a rare type of lymphoma accounting for $<1\%$ of all cutaneous T-cell lymphomas (CTCL). It is slightly more common in females than in males and may affect both children and adults.[6,8] In a series of 63 SPTCL patients the median age at diagnosis was 36 years (range: 9–79 years) and 12 of 63 patients (19%) were 20 years or younger.[5] SPTCL may be preceded for many years by a seemingly benign panniculitis.[9,10]

Clinical features

Clinically, patients present with solitary, but more commonly multiple nodules or deeply seated plaques with a diameter varying between 1 and 20 cm. The skin lesions usually do not show ulceration and mainly involve the legs, the arms and the trunk and less commonly the face. After regression they may leave areas of lipoatrophy (Fig. 1). Systemic symptoms such as fever, fatigue and weight loss, and laboratory abnormalities, including cytopenias and elevated liver function tests are common, but a frank HPS is observed in only 15–20% of patients.[1,5] Dissemination to extracutaneous sites is rare. Lymphadenopathy is usually absent. Hepatosplenomegaly may be seen, but is generally not due to lymphomatous involvement. Up to 20% of patients may have associated auto-immune disease, most commonly systemic lupus erythematosus (SLE), but also an association with (juvenile) rheumatoid arthritis, Sjögren disease and mixed connective tissue disease has been reported.[5,8,11]

Histology

Histologically, SPTCL reveals dense, nodular or diffuse subcutaneous infiltrates with a pattern resembling a lobular panniculitis. Small aggregates of non-neoplastic cells may be observed in the reticular dermis surrounding vessels and sweat glands, but the epidermis is typically uninvolved (Fig. 2A). The neoplastic cells are usually small- to medium-sized lymphoid cells with irregular and hyperchromatic nuclei. Rimming of individual fat cells by neoplastic T cells is a helpful, though not completely specific

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Table 1
Distinguishing features between PTCL and PCGD-TCL[5].

	SPTCL	PCGD-TCL
Immunophenotype	TCR-β, CD4−, CD8+, CD56−	TCR-γ/δ+, CD4−, CD8−, CD56+/−
Architecture	Subcutaneous	Subcutaneous and/or epidermal/dermal
Clinical features	Nodules and plaques; rarely ulceration; association with auto-immune disorders (20%), including reported cases of coexistence of SPTLC and lupus erythematosus	Nodules and plaques Ulceration common
HPS	Uncommon (15–20%)	Common (50%)
5-year survival	80%[a]	10–20%
Treatment	Systemic steroids and immunomodulatory agents	Systemic chemotherapy

SPTCL: subcutaneous panniculitis-like T-cell lymphoma;
PCGD-TCL: primary cutaneous γ/δ T-cell lymphoma.
HPS: hemophagocytic syndrome.

[a] 5-year survival: 91% in patients with HPS, 46% in patients with HPS.[5]

diagnostic feature, and may be present only focally (Fig. 2B). The neoplastic T-cells are admixed with small reactive lymphocytes and many histiocytes, which are frequently vacuolated because of ingested lipid material. Other inflammatory cells, including neutrophils and eosinophils as well as plasma cells and plasmacytoid dencritic cells, both common in lupus panniculitis, are generally lacking.[12,13] However, considerable proportions of plasma cells were reported in some cases of pediatric SPTCL and in SPTCL with concurrent or prior diagnosis of lupus panniculitis.[5,8] Necrosis, karyorrhexis, cytophagocytosis and fat necrosis are common findings.[4,5] The proliferation rate is usually high. In the early stages the neoplastic infiltrates may lack significant atypia and a heavy inflammatory infiltrate may predominate.[9,10]

Immunophenotype

The neoplastic cells have a mature CD3+, CD4−, CD8+ T-cell phenotype, with expression of cytotoxic proteins, including granzyme B, TIA-1 and perforin (Fig. 3A–B).[3–5,14] The neoplastic T-cells express βF1, but not TCR γ/TCRδ, and are negative for CD56, facilitating differentiation from cutaneous gamma/delta T-cell lymphoma (Fig. 3C).[5,15] Loss of pan-T-cell markers, such as CD2, CD5 and CD7, may occur.[5] CD30 is rarely, if ever, expressed. The proliferation rate is usually high with characteristic rimming of MIB-1+ cells around adipocytes (Fig. 3D).

Genetics

The neoplastic cells show rearrangement of T-cell receptor genes, and are negative for Epstein-Barr viral sequences.[4,5] Different clonal T-cell populations in the original biopsy and a biopsy of a recurrent lesion seven years later have been reported.[8] No specific cytogenetic features have yet been reported.

Differential diagnosis

The differential diagnosis of SPTCL includes PCGD-TCL, other types of CTCL which occasionally present with subcutaneous involvement and lupus panniculitis. Both SPTCL and PCGD-TCL may present with nodular skin lesions with panniculitis-like features with rimming of fat cells. In contrast to SPTCL, PCGD-TCL with panniculitis-like features commonly involve not only the subcutis, but also the dermis and/or epidermis, either in the same or in other biopsies, and may show ulceration.[5,15,16] Angiocentricity and

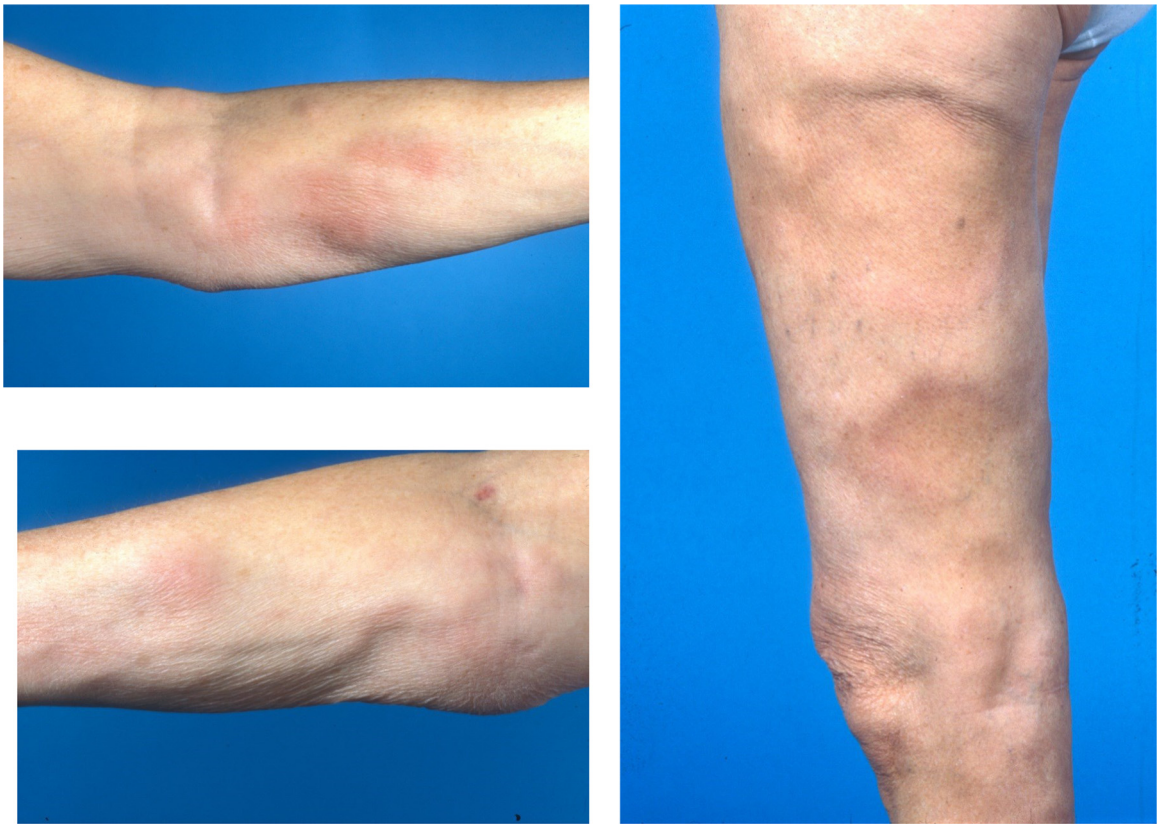

Fig. 1. Subcutaneous panniculitis-like T-cell lymphoma. A-B: Nodular lesion on both arms next to areas of lipoatrophy. C: large areas of lipoatrophy on the right leg after regression of the skin lesions.