

Leukaemia Section

Review

Subcutaneous panniculitis-like T-cell lymphoma

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Abstract

Review on Subcutaneous panniculitis-like T-cell lymphoma, with data on clinics and the genes possibly involved.

KEYWORDS

Subcutaneous panniculitis-like T-cell lymphoma; NAV3; IDO1; IFNG; CXCR3; CCL5; ARID1B; SMARCA4; CHD4; MTOR; TSC1

Clinics and pathology

Disease

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a lymphoma derived from cytotoxic $\alpha\beta$ T cells that preferentially involves subcutaneous tissue (Gonzalez, Medeiros et al. 1991; Salhany, Macon et al. 1998; Parveen and Thompson 2009). The definition of SPTCL was revised in the 2008 World Health Organization (WHO) classification to exclude cases of γ/δ T-cell origin; these latter cases are now classified as primary cutaneous T-cell γ/δ lymphoma (Harris, Swerdlow et al. 2008).

Etiology

No specific etiologic factor has been identified for SPTCL. Autoimmune diseases occur in approximately 20% of patients and some cases show overlapping histologic features with subcutaneous lupus (Marzano, Berti et al. 2000). The lesions have

been associated with rheumatoid arthritis (Levy, George et al. 1997), inflammatory bowel disease (Hoque, Child et al. 2003), and Sjögren syndrome (Yokota, Akiyama et al. 2009). Lesions occurring following transplantation also have been described; however, a clear association with Epstein-Barr virus or other infectious agents has not been identified (Salhany, Macon et al. 1998; Go and Wester 2004; Bregman, Yeane et al. 2005).

Epidemiology

SPTCL represents less than 1% of all non-Hodgkin lymphomas. It affects both children and adults with a median age of onset of 35 years. It is slightly more common in women but no racial or ethnic predisposition has been reported (Kumar, Krenacs et al. 1998; Weenig, Ng et al. 2001; Willemze, Jansen et al. 2008).

Clinics

Patients with SPTCL typically present with solitary or multiple painless subcutaneous nodules or plaques. The lesions are most commonly located on the lower extremities but the upper extremities and trunk may also be involved. The lesions may be small or measure several centimeters. The nodules may become necrotic but ulceration is rare (Willemze, Jansen et al. 2008; Parveen and Thompson 2009). Systemic symptoms, including fever, fatigue, and weight loss are reported in approximately half of cases while hemophagocytic

syndrome is seen in 15-20% of cases (Marzano, Alessi et al. 1997).

Pathology

SPTCL is characterized by a dense subcutaneous infiltrate of small to medium-sized lymphoid cells. The infiltrate involves the fat lobules, usually with relative sparing of septa. Typically, there is minimal involvement of the overlying epidermis and dermis. The adipocytes characteristically show rimming by neoplastic lymphocytes. Macrophages and vacuolated histiocytes with associated fat necrosis and karyorrhectic debris are commonly present (Parveen and Thompson 2009). Erythrophagocytosis by histiocytes is occasionally seen (Gonzalez, Medeiros et al. 1991; Salhany, Macon et al. 1998; Willemze, Jansen et al. 2008).

By immunohistochemistry, the tumor cells have a mature alpha-beta cytotoxic T-cell phenotype and are characteristically positive for CD3 and CD8 and negative for CD4. The cytotoxic proteins granzyme B, TIA-1, and perforin are usually present (Kumar, Krenacs et al. 1998). Rarely, there is co-expression of CD4 and CD8 while the absence of both CD4 and CD8 should prompt consideration of a γ/δ T-cell lymphoma (Santucci, Pimpinelli et al. 2003; Kong, Dai et al. 2008).

In situ hybridization for Epstein-Barr virus-encoded RNA (EBER) is negative in almost all cases (Salhany, Macon et al. 1998).

Treatment

Multi-agent chemotherapy has traditionally been used for the treatment of SPTCL but more recent studies suggest that conservative immunosuppressive agents such as cyclosporine, steroids or chlorambucil may be as effective and should be considered in patients without associated hemophagocytic syndrome (Tsukamoto, Katsunobu et al. 2006). Local radiation therapy has been used effectively in patients presenting with a solitary lesion (Willemze, Jansen et al. 2008). For patients with more aggressive disease, anthracycline-based combination chemotherapeutic regimens with or without stem cell transplantation are frequently used (Go and Wester 2004).

Prognosis

SPTCL generally is a clinically indolent disease with a waxing and waning course. The 5-year disease-

specific survival is around 80% (Gonzalez, Medeiros et al. 1991; Salhany, Macon et al. 1998). In most patients the disease remains confined to the subcutaneous tissue, and spread to lymph nodes and internal organs is rare. Patients who develop hemophagocytic syndrome generally have a poor outcome (Aronson, West et al. 1985; Gonzalez, Medeiros et al. 1991). Most previous reports of SPTCL with a rapidly fatal course in the absence of hemophagocytic syndrome are probably attributable to inclusion of γ/δ T-cell lymphomas, which have a much worse prognosis, in the previous classification of SPTCL (Toro, Liewehr et al. 2003).

Genetics

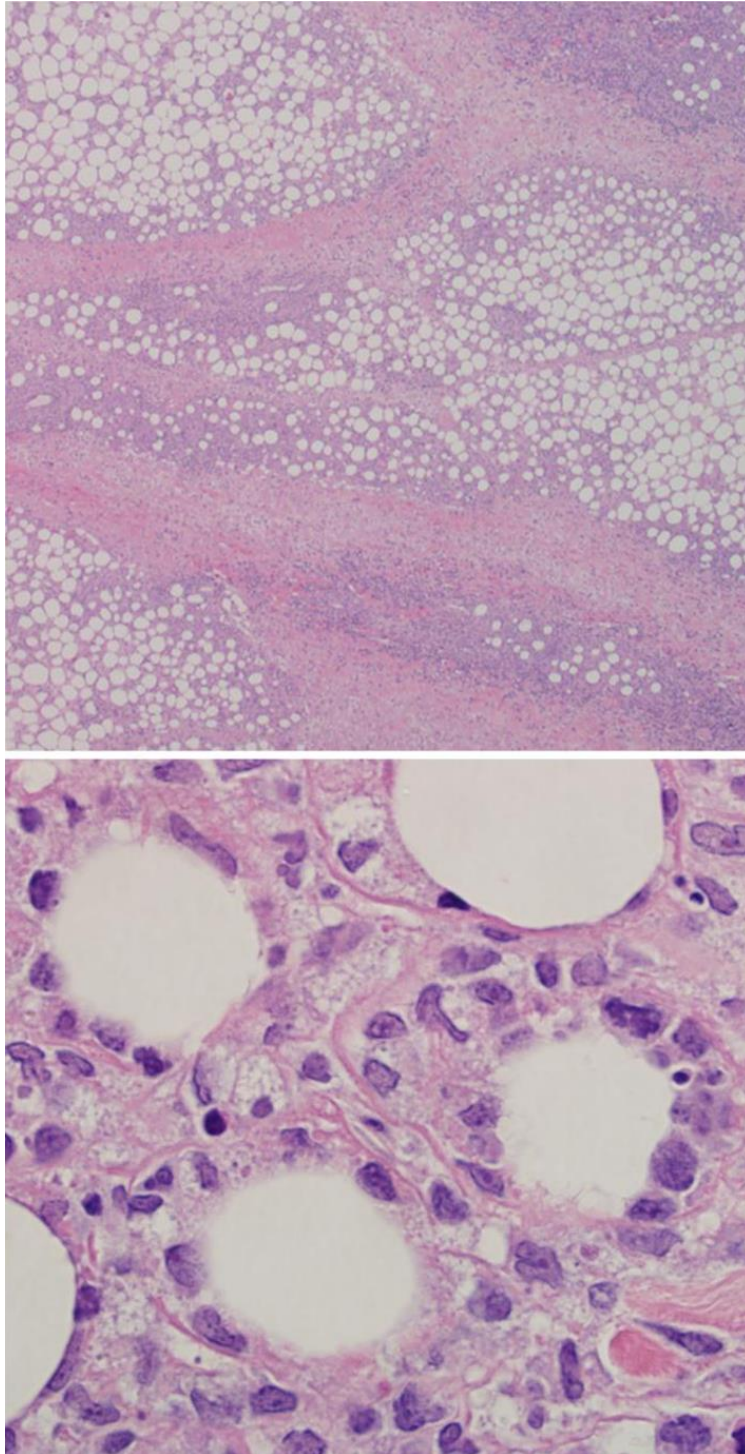
Note

Polymerase chain reaction (PCR) analysis of SPTCL has shown clonal rearrangements of the TCR β , γ , and α genes without evidence of clonal immunoglobulin gene rearrangements (Ghobrial, Weenig et al. 2005; Willemze, Jansen et al. 2008; Kong, Dai et al. 2009).

Deletion of NAV3 (neuron navigator 3) gene has been identified in approximately 50% of cases by fluorescence in situ hybridization (FISH) and loss of heterozygosity (LOH) assays (Hahtola, Burghart et al. 2008).

Gene expression microarray and quantitative PCR analysis have shown upregulated expression of indoleamine 2,3-dioxygenase (IDO1), an immunotolerance-inducing gene, along with upregulation of Th1 type cytokines, most notably IFNG, CXCR3, and CCL5. Over-expression of these genes may contribute to the formation of an immunosuppressive microenvironment, favorable for the neoplastic T-cells

A recent next-generation sequencing study has identified recurrent mutations in epigenetic modifiers and the PI3K/AKT/mTOR pathway in SPTCL, with mutations in ARID1B, SMARCA4, CHD4, MTOR, and TSC1 each observed in 3/18 cases (Li, Lu et al. 2017).



Subcutaneous panniculitis-like T-cell lymphoma. At low power (top), the tumor can be seen infiltrating the fat lobules. At high power (bottom), cytologically atypical tumor cells can be seen "rimming" the fat spaces.

Cytogenetics

Cytogenetics morphological

Relatively few cases have been analyzed by conventional cytogenetics and no consistent abnormalities have been identified.

Cytogenetics molecular

Several DNA copy number abnormalities have been identified by comparative genomic hybridization (CGH), including losses of chromosomes 1p, 2p, 2q, 5p, 7p, 9q, 10q, 11q, 12q, 16, 17q, 19, 20, and 22, and gains of chromosomes 2q, 4q, 5q, 6q, 13q. Some of these changes overlapped those seen in other cutaneous T-cell lymphomas, whereas alterations of

chromosomes 5q and 13q appeared unique to SPTCL (Hahtola, Burghart et al. 2008).

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