Subcutaneous panniculitis-like T-cell lymphoma responsive to combination therapy with methotrexate and corticosteroids

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Abstract

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare condition that falls underneath the umbrella of primary cutaneous T-cell lymphomas (CTCLs). Subcutaneous panniculitis-like T-cell lymphoma can be very difficult to diagnose as it may mimic other subtypes of CTCL, such as γ/δ T-cell lymphoma (TCL), or other forms of panniculitis. Confirmation of diagnosis often requires immunohistochemical analysis and is essential for proper prognosis and therapeutic management. Herein, we present a case of SPTCL that mimicked lupus panniculitis and was successfully treated with prednisone taper and methotrexate.

Keywords: lymphoma, cutaneous T-cell lymphoma, methotrexate, corticosteroids

Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare form of non-Hodgkin lymphoma further categorized as a subtype of primary cutaneous T-cell lymphoma (CTCL). Subcutaneous panniculitis-like T-cell lymphoma accounts for less than 1% of all CTCL cases [1]. Subcutaneous panniculitis-like T-cell lymphoma can be challenging to diagnose as it may mimic other CTCL subtypes or forms of panniculitis. In this case, we present a woman diagnosed with SPTCL that mimicked lupus panniculitis and was subsequently successfully treated with prednisone taper and methotrexate.

Case Synopsis

A woman in her 60s presented with a three-year history of recurrent fevers, night sweats, fatigue, myalgias, arthalgias, and widespread painful subcutaneous nodules of unknown origin necessitating multiple hospital admissions. Needle biopsy of a nodule during a previous hospitalization revealed fat necrosis with a lymphocytic infiltrate. CT scan of the chest, abdomen, and pelvis were unremarkable. Bone marrow evaluation was negative for malignancy. She received several courses of antibiotics and corticosteroids, leading to resolution of the nodules, several with atrophy. On presentation, she denied any additional past medical history or recent travel. Her review of symptoms was negative for malar rash, discoid lupus erythematosus lesions, photosensitivity, Raynaud phenomenon, miscarriages, thrombotic events, seizures, psychosis, chest pain, shortness of breath, pain with deep breathing, swollen joints, and renal disease. Family history was significant for rheumatoid arthritis, systemic lupus erythematosus, and juvenile idiopathic arthritis.

On examination, she was ill-appearing and febrile to 38.5C. Tender erythematous to violaceous subcutaneous nodules were present on the bilateral upper and lower extremities, breasts, and thighs, admixed with depressed plaques (**Figure 1A, C**). Laboratory tests revealed elevated inflammatory markers, with an ESR of 70 mm/hr, CRP of 129.4mg/L and ferritin of 999ng/mL. Complete blood count

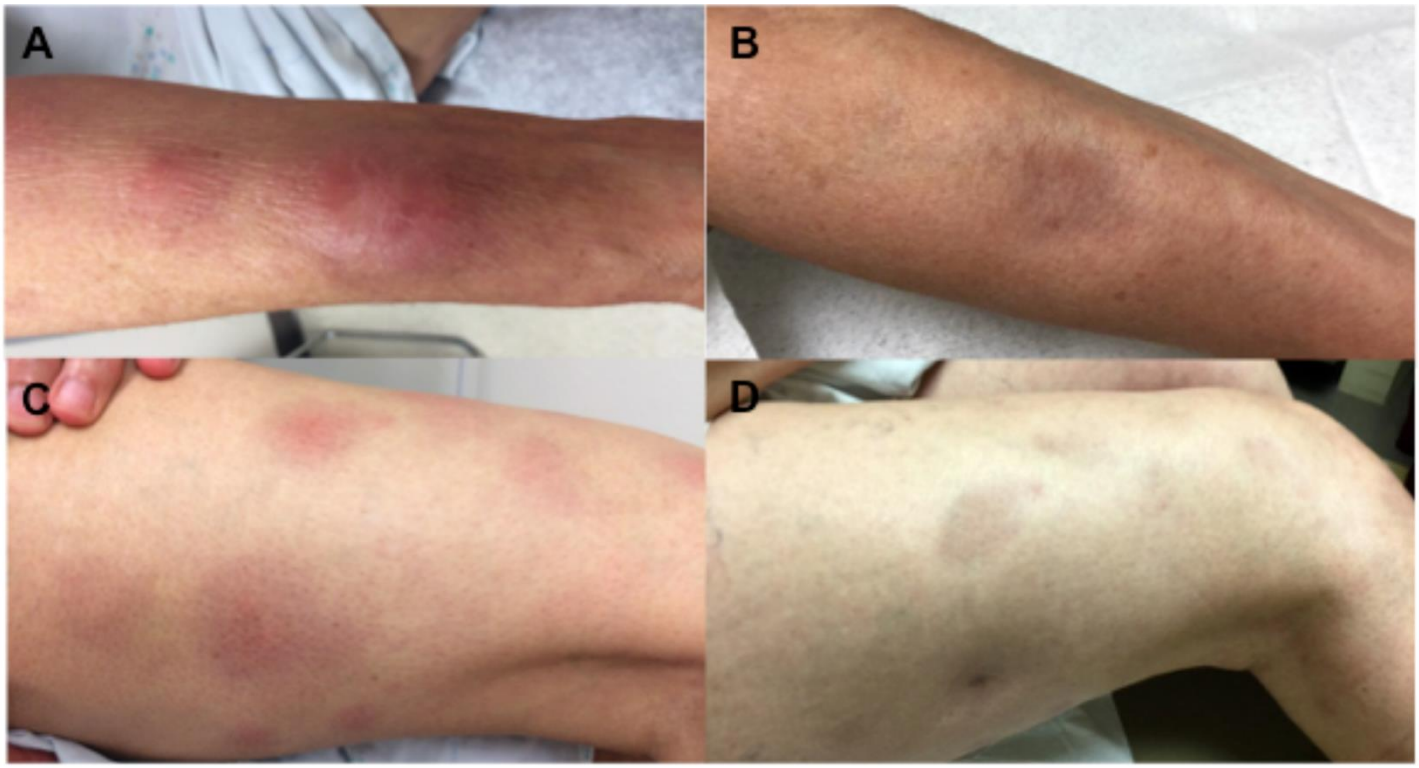

Figure 1. *Clinical photos. Forearm subcutaneous nodule before (**A**) and after (**B**) treatment with prednisone and methotrexate. Similarly, right upper leg depressed plaques before (**C**) and after (**D**) treatment.*

revealed a normocytic anemia and lymphopenia. Comprehensive metabolic panel revealed albumin of 3.2g/dL and AST of 51 U/L. Antinuclear antibody (ANA) by ELISA was positive and ANA by indirect fluorescence negative. Amylase and lipase were both normal. HIV was negative.

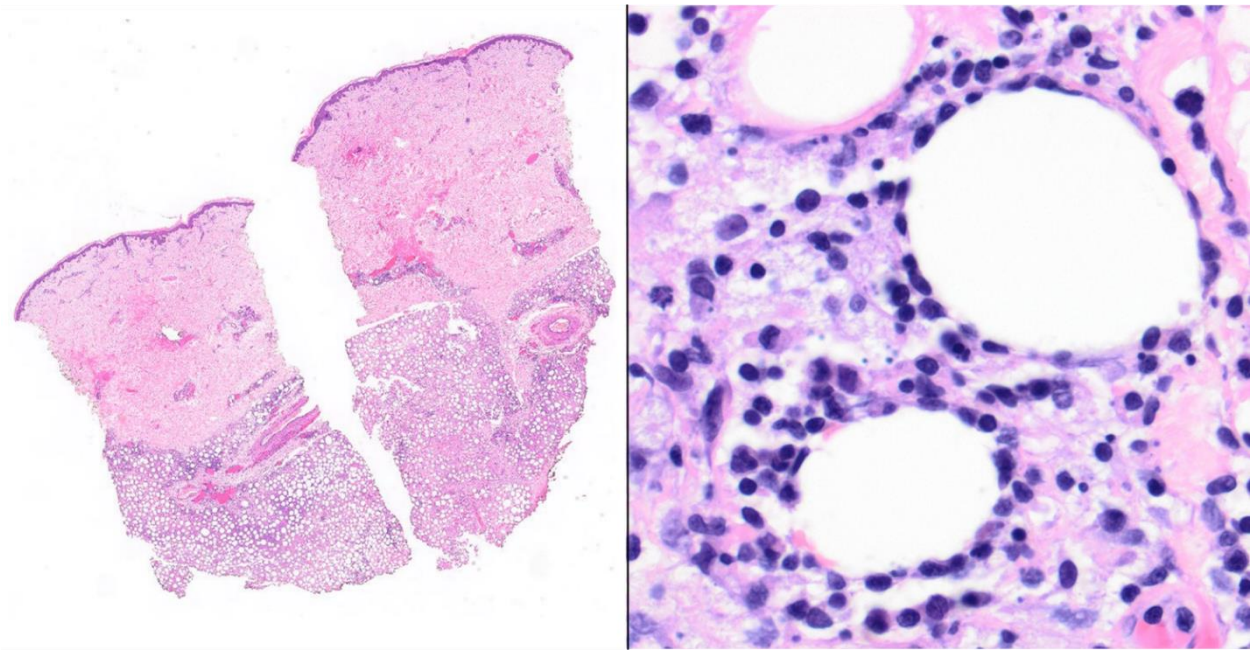

Figure 2. *Histopathologic findings. Low magnification demonstrates an atypical lymphohistiocytic infiltrate largely restricted to the subcutaneous tissue. H&E, 0.5×. At higher magnification, a population of atypical lymphocytes with condensed chromatin are noted both rimming adipocytes and present interstitially. H&E, 400×.*

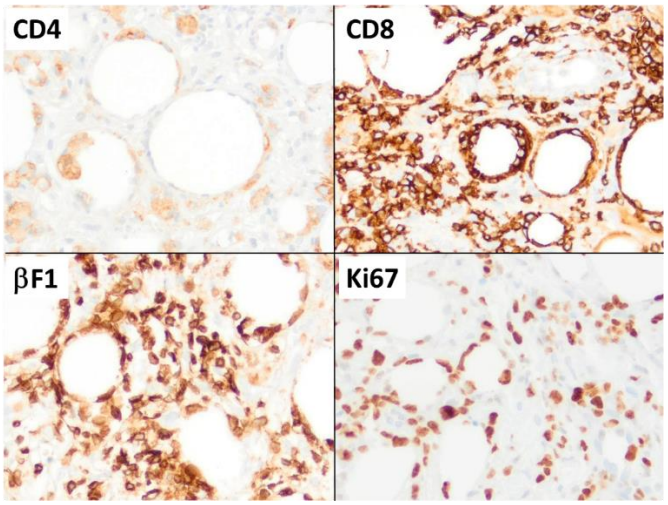

Figure 3. *Immunohistochemistry. The atypical lymphocytes are positive for CD8 and TCR alpha beta (BF1). CD4 highlights background histiocytes. Ki67 shows a high proliferative index. All immunohistochemistry shown at 200×.*

Punch biopsy was performed and demonstrated a subcutaneous infiltrate of atypical small to medium-sized lymphocytes in association with extensive fat necrosis. Adipocyte rimming by atypical lymphocytes was prominent (**Figure 2**). Mitotic figures and karyorrhectic debris were easily identified. The dermis revealed a superficial and deep lymphocytic infiltrate and subtle interface basal vacuolar change. Immunohistochemistry was negative for Epstein-Barr virus (EBV). The atypical lymphocytes expressed CD2, CD3, CD5 (dim), CD7, CD8, and βF1 by immunohistochemistry (**Figure 3**). Reproducible clonal amplifications were identified on T-cell gene rearrangement PCR studies using BIOMED-2 *TCRG* and *TCRB* primers (**Figure 4**). Subsequent PET/CT scan demonstrated uptake in areas of cutaneous disease, without visceral or solid organ involvement.

Initial differential diagnosis included Sweet syndrome, lupus panniculitis, leprosy, and leukemia/lymphoma. Based on the patient's indolent disease course, histological findings, α/β immunophenotype, and monoclonal T-cell population, a diagnosis of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was made.

The patient was started on prednisone at 1mg/kg/day. After one month on prednisone, the nodules remained unchanged but there were no new lesions. Methotrexate 15mg weekly was added. She demonstrated clinical improvement after one month on methotrexate and tapering prednisone, with cessation of fevers and reduction of erythema and tenderness of nodules (**Figure 1B, D**). Over the next 3 months, she was able to taper off prednisone and achieve remission on methotrexate mono-therapy. She has remained in clinical remission on methotrexate monotherapy for 21 months.

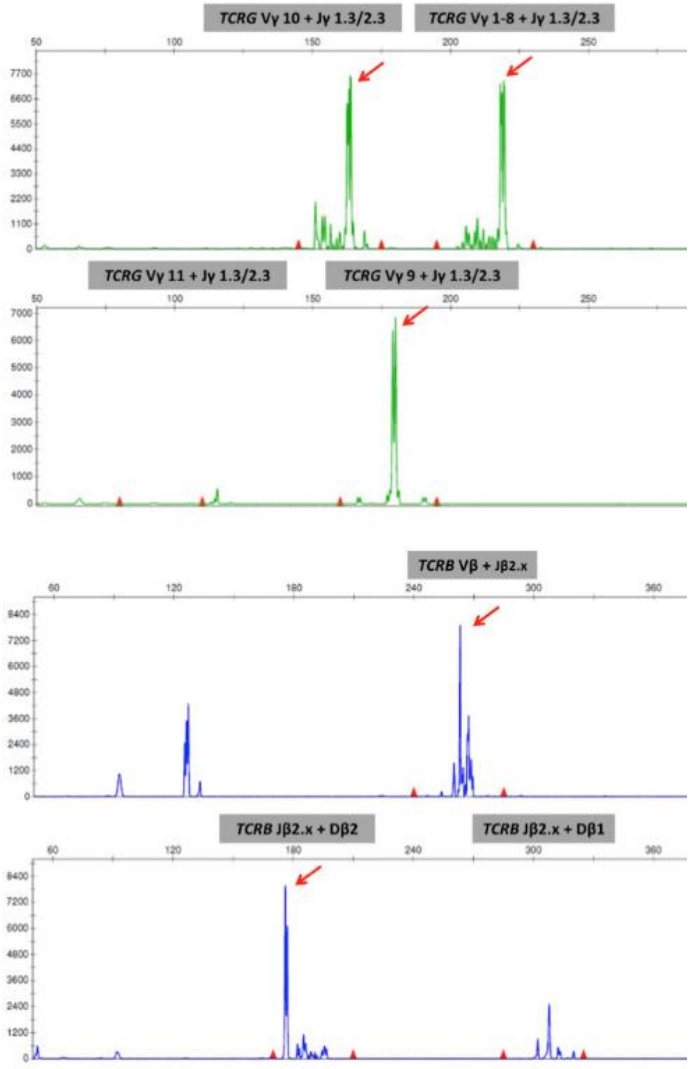

Figure 4. *T-cell clonality studies. T-cell receptor clonality studies were performed by polymerase chain reaction using BIOMED-2 primer sets. Monoclonal peaks are indicated by red arrows for each TCRG and TCRB primer set, confirming the presence of a monoclonal T-cell population.*

Case Discussion

Original classification systems defined SPTCL as a primary cutaneous lymphoma involving the subcutaneous fat. WHO-EORTC classification now separates SPTCL from the histologic mimic, primary cutaneous γ/δ T-cell lymphoma (TCL), based on the T-cell receptor expressed and the clinical course. Although SPTCL is limited to the subcutis and often indolent, γ/δ TCL can invade the dermis and epidermis and frequently has a more aggressive clinical course [1, 2].

SPTCL can affect all ages, though classically presents in younger adults with approximately 20% of affected individuals under the age of 20 [1]. Sexes are affected equally. Erythematous subcutaneous nodules and/or plaques typically develop on the legs but can be located anywhere on the body. Lesions may be painless or painful. Ulceration of nodules is rare. Presentation may include systemic B-symptoms. An uncommon though very serious complication of SPTCL is hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH). Hemophagocytic lymphohistiocytosis can be primary (genetic) or secondary (acquired), with the most frequent secondary causes of HLH including infection (EBV) and malignancy (lymphoma). Hemophagocytic lymphohistiocytosis often presents with fever, hepatosplenomegaly, rashes, cytopenias, and elevated ferritin and progresses to multi-organ failure [3]. Hemophagocytic lymphohistiocytosis is more frequently seen with γ/δ+ TCL than SPTCL and has high associated mortality [1].

The diagnosis of SPTCL can be challenging as it mimics other forms of panniculitis. In this patient, her age, sex, positive ANA, lesion distribution, resolution with depressed plaques, and family history of autoimmune disorders all favored lupus panniculitis (LEP). Subcutaneous panniculitis-like T-cell lymphoma and LEP are difficult to distinguish as they can have overlapping clinical and histological features. Histologically, SPTCL demonstrates a lobular pattern of subcutaneous infiltration by atypical T-cells. Although there may be deep dermal spillover, the superficial dermis and epidermis are not involved. Adipocyte rimming by T-cells is a helpful diagnostic tool although not specific to SPTCL. Fat necrosis, cytophagocytosis, and karyorrhexis may be present and if extensive may obscure the neoplastic infiltrate. Immunohisto-chemical analysis is required to confirm the diagnosis. T-cells of SPTCL are βF1+/CD3+/CD4-/CD8+/CD56- and express several cytotoxic proteins such as granzyme A, perforin, and TIA-1 [1]. T-cell receptor gene rearrangement PCR studies to assess for clonality may be helpful, with clonality being universal in SPTCL and rare in LEP [5]. Ki-67 proliferation index >20% or Ki-67 "hotspots" are highly suggestive of SPTCL (Figure. 3), [4]. Clusters of plasmacytoid dendritic cells and increased staining with myxovirus resistance protein 1 (MxA) favor LEP [5, 6]. Given the clinical and histologic overlap, there is some debate whether SPTCL and LEP are distinct entities or instead reside on a continuum of a single disease [7]. Distinction of γ/δ TCL and SPTCL from LEP is critical owing to the association of HPS with γ/δ TCL and SPTCL; HPS is most commonly associated with γ/δ TCL [4].

Conclusion

Treatment for SPTCL traditionally consisted of anthracycline-based chemotherapies and radiation, with severe disease treated with CHOP or CHOP-like regimens. However, γ/δ TCL and SPTCL are now recognized as two separate diseases with different clinical courses. Subcutaneous panniculitis-like T-cell lymphoma is now treated with a combination of corticosteroids and methotrexate or methotrexate monotherapy [6, 7]. γ/δ TCL often requires traditional chemotherapy [1]. Response to treatment is characterized by reduction in erythema, resolution of systemic symptoms, the absence of new lesions, and an improvement in subcutaneous nodules and plaques marked by healing with atrophy and/or depression. Five-year survival for SPTCL is approximately 80%. Recurrent disease may be treated with repeat courses of prednisone and methotrexate or methotrexate monotherapy [7].

Further workup for SPTCL includes imaging to ensure disease is limited to the skin, or if systemic involvement is present, to stage progression. Imaging may also help differentiate SPTCL from disease mimics.

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