BRIEF ARTICLES

Subcutaneous panniculitis-like T-Cell lymphoma: A mixed diagnostic approach to diagnosing a vague clinical picture

Callie R Hill, BS,[1] Apphia Wang, MD[1] Boni E Elewski, MD[1], Peter G Pavlidakey, MD[1]

[1]Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL

ABSTRACT

Subcutaneous panniculitis-like T-Cell lymphoma (SPTCL) is a rare subtype of cutaneous T-cell lymphoma, and it has been associated with a range of clinical symptoms from mild to severe. Most commonly, this disease is described as following a slowly progressing course, associated with vague constitutional symptoms and good prognosis. This case report describes the clinical presentation and findings of SPTCL in a 31 year old female and describes the challenges of recognizing and properly diagnosing this disease. SPTCL has been described as a mimicker of other, more common and nonmalignant diseases of the skin, such as lupus panniculitis. This report highlights a variety of specific tests including immunohistochemical and immunoperoxidase staining, as well as genotypic analysis of T-cell receptors, that were effective in combination in isolating this diagnosis. Moreover, choice of treatment for these patients can be challenging, as an array of interventions have been described in past cases to treat SPTCL. This report recognizes the efficacy of a treatment course that included a six-cycle course of combined chemotherapy (vincristine, doxurubicine, cyclophosphamide, and prednisone, also known as CHOP) followed by weekly methotrexate and PET scan surveillance for two years. With both initial and maintenance therapy, this patient showed excellence response evidenced by a progressive decrease in metabolic activity of malignant lesions, lack of new lesions, and remaining without symptoms. While this disease is rare, it is important to include SPTCL in the differential when considering patients with a panniculitic picture.

INTRODUCTION

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare disease, accounting for less than 1% of non-Hodgkin's lymphomas, that is characterized by infiltration of T-cells in the subcutaneous adipose tissue typically without lymph node involvement.[1, 2] It was first described in 1991, and was later accepted as a distinct disease by the World Health Organization in 2001.[3, 4] SPTCL classically follows an indolent clinical course with good prognosis.[4] Associated symptoms are commonly constitutional and nonspecific, including fever, weight loss, and fatigue. However, more severe symptoms, including central nervous system involvement and hemophagocytic syndrome, have also been reported and associated with poorer prognosis.[5, 6] Physical exam findings typically reveal multiple subcutaneous nodules or plaques, most commonly located on the trunk or extremities, that can be associated with other features such as pain, erythema, warmth, and induration.[5, 7] SPTCL

can be difficult to discern from more common skin conditions including cellulitis, psoriasis, benign panniculitis, and other soft tissue inflammatory conditions.[7] To make this challenging diagnosis, clinicians employ an assortment of specific tests that go beyond histopathological findings and exploit the immunophenotypic and genotypic qualities of T-cell receptors in the subcutaneous tissue. [6] Treatment approaches for SPTCL are also quite variable and patient-specific, often taking into consideration factors of local versus diffuse disease, pathologic features, and severity of symptoms.[8]

CASE REPORT

A 31-year-old African American female presented with a two-year history of tender, enlarging subcutaneous nodules of her right breast and arm. She reported them as initially dime-sized and painless, but became progressively tender as they grew in size. She denied history of fever, weight loss, rashes, patchy alopecia, photosensitivity, Raynaud's phenomenon, xerostomia, nasal or oral ulcers, dysphagia, muscle weakness, or thrombotic events. She denied history of local trauma, chronic pancreatitis, recent travel, sick contacts, or animal bites when nodules first appeared. Physical exam was performed and significant for a warm, indurated subcutaneous mass measuring 4 cm and localized to the outer upper quadrant of the right breast. Similar areas of induration were noted along the dorsal aspect of the right upper arm (Fig 1), and the inner upper quadrant of the left breast.

Complete blood count, metabolic panel, and rheumatologic labs were drawn. Investigators found a leukopenia of 3.90× 10^9/L (Normal range, 4.5 - 11.0 × 10^9/L) and mildly elevated RNP/Sm: 25 units (Normal < 20 units). Serologic workup was negative for lupus anticoagulant and rheumatologic labs: ANA, Scl, anti-DNA, anti-Sm, ANCA, MPO, ACE, and beta-glycoprotein. Chest X-ray was unremarkable.

Punch biopsy from a right chest nodule showed an atypical panniculitic infiltrate most consistent with subcutaneous panniculitis-like T-cell lymphoma (Fig 2). A CD123 immunostain highlighted diffuse numbers of plastacytoid dendritic cells. Immunohistochemical staining of CD8+ was notable for neoplastic cells rimming numerous adipocytes. A TCR beta F1 also highlighted neoplastic cells. Immunoperoxidase staining of Ki-67 also appreciated high numbers of lymphocytes rimming adipocytes (Fig 3).

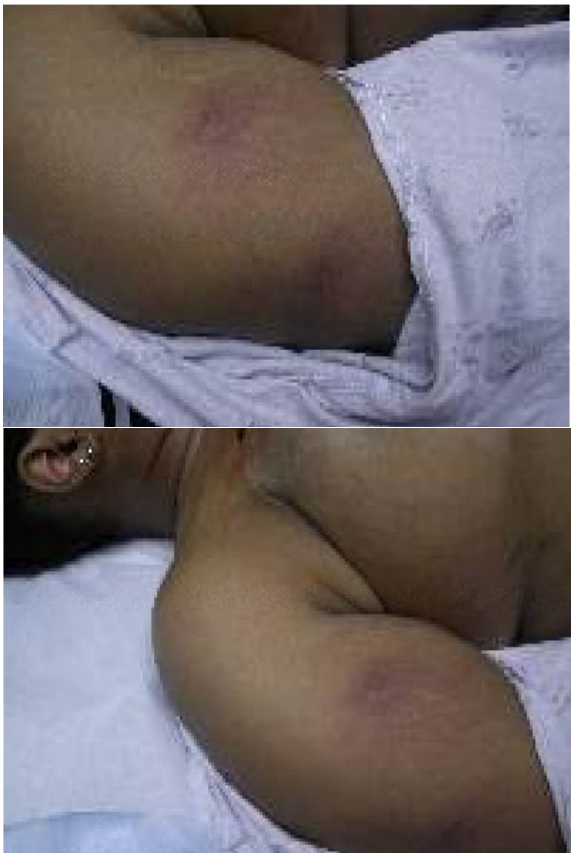


Figure 1: 3-4 cm indurated, erythematous plaque of the right proximal arm.

In addition, genotypic analysis of T-cell receptor (TCR) gene rearrangement by PCR assay was positive for clonal peaks (Fig 4). Examination of the clinical picture, in conjunction with histopathological evidence, immunohistochemical staining, and genotypic analysis led to the diagnosis of subcutaneous panniculitis-like T-cell lymphoma.

Initial staging with whole body PET/CT showed a large FDG cutaneous and subcutaneous lesion of the right breast with extension into the pectoralis major muscle and another intensely hypermetabolic lesion of the right arm consistent with active lymphoma. In addition, hypermetabolic adenopathy of the right axilla and left external iliac and inguinal nodes was shown. The patient was started on a combination therapy of vincristine, doxurubicine, cyclophosphamide, and prednisone, also commonly known as CHOP. The patient completed six cycles of CHOP therapy and was started on weekly maintenance therapy with methotrexate. PET imaging in the following two years showed an interval decrease in hypermetabolic activity of the existing subcutaneous masses and without occurrence of new lesions.

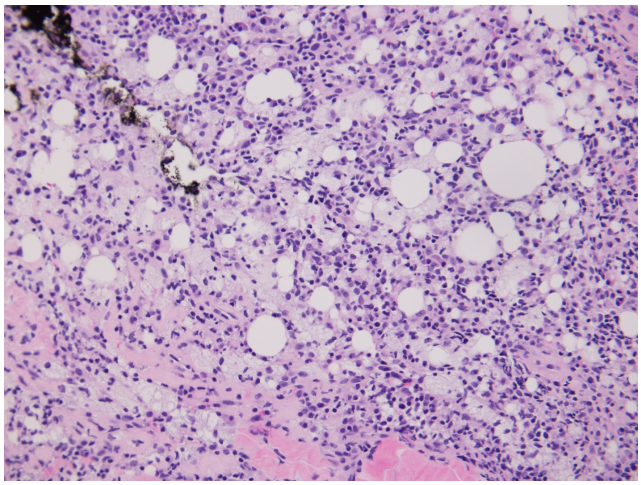


Figure 2: Histopathological Findings: Skin, right chest, punch biopsy: Atypical panniculitic infiltrate consistent with subcutaneous panniculitis-like T-cell lymphoma.

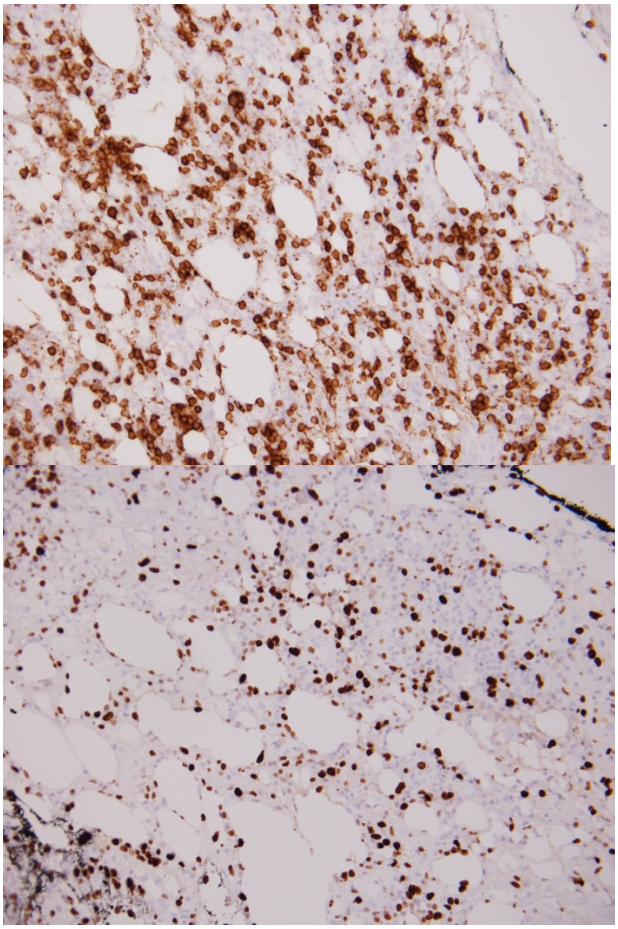
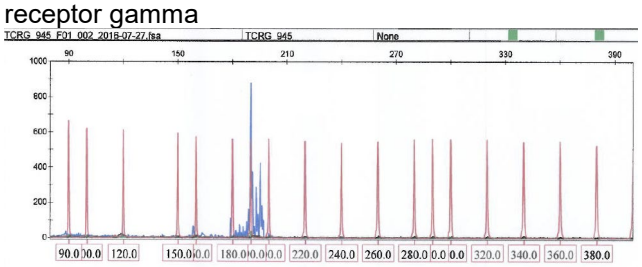


Figure 3: Targeted Ki-67 study highlighting high numbers of lymphocytes *(top)* and CD8 staining showing neoplastic cells *(bottom)* reaming numerous adipocytes.

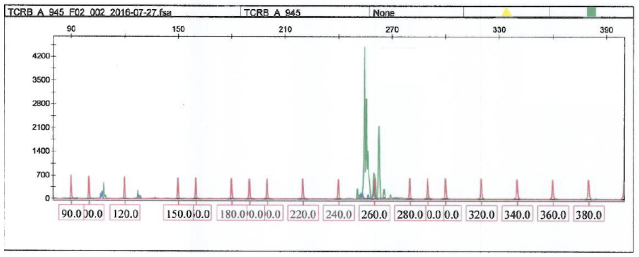
DISCUSSION

SPTCL is a rare disease that typically follows an indolent clinical course, first described by Gonzalez and colleagues in 1991.[3, 9] The World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classifies SPTCL as an indolent subtype of cutaneous T-cell lymphoma (CTCL).[10] Using data from 1476 patients registered by Dutch and Austrian Cutaneous Lymphoma Groups, SPTCL was found to have a frequency and 5-year survival of 1% and 82%, respectively.[10] This disease is easily misdiagnosed due to its strong histological and clinical resemblance

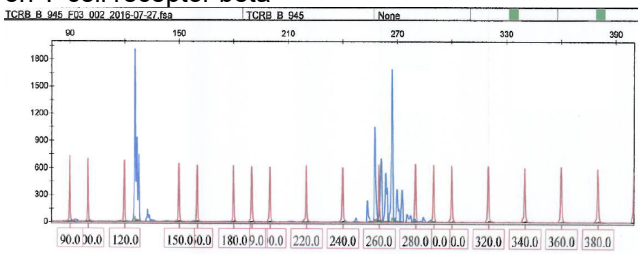
Figure 4 (A-C): T-cell gene rearrangement showing clonal peaks with intensity consistent with clonal neoplasms.
A: Clonal peaks migrating at 190 bases on T-cell receptor gamma



B: Clonal peaks at 254 bases (Vbeta + Jbeta, tube A)



C: Clonal peak at 278 bases (Dbeta + Jbeta, tube C) on T-cell receptor beta



to nonmalignant panniculitis, such as lupus panniculitis.[11, 12]

SPTCL is a cytotoxic T-cell lymphoma derived from α/β T-cells within subcutaneous tissue and commonly CD8+ and CD56-.[10, 13-16] This is an important distinction, as cases of CTCL with ϒ/δ T-cell phenotype typically represent a more aggressive clinical course with distinctly different immunophenotypical and histological characteristics. Therefore, SPTCL has been reserved for cases with α/β phenotypes, whereas ϒ/δ phenotypes are now classified as primary cutaneous ϒ/δ T-cell lymphomas.[10] The mechanism by which tumor cells migrate to subcutaneous tissue in SPTCL is not understood; however, the pathology of SPTCL may be related to chemokine receptors on tumor cells. One group recognized the expression of CCR4 and CCR5 on neoplastic T-lymphocytes of a patient with SPTCL. Furthermore, these receptors were proposed to play a role in promoting the recruitment, migration, and expansion of malignant lymphocytes in the subcutaneous tissue.[16]

This disease is most common in young adults, with an increased predominance in women.[14] Patients typically present with multiple subcutaneous nodules or plaques, with the most common locations being the extremities or trunk.[11, 17] Unique to this patient's case is the occurrence of nodules on the breast. The spectrum of associated clinical symptoms is otherwise nonspecific in SPTCL. Interestingly, while not reported in this patient, fever of unknown origin is a common symptom reported to precede the diagnosis of SPTCL.[18] Weight loss and fatigue may herald a more rapidly progressive syndrome; however, involvement extending beyond cutaneous tissue is still rare.[19] Facial swelling has also been reported in some cases.[20, 21] In addition, hemophagocytosis (HPS), pancytopenia, coagulopathy, and hepatosplenomegaly have been reported on rare instances of SPTCL. HPS is a result of T cell overproduction of cytokines (interferon-ϒ, IL-2, IL-6, IL-12, IL-18 and tumor necrosis factor-alpha) and is associated with poorer prognosis. [8, 15, 22, 23]

Radiologic imaging has been used in the initial work-up and detection of disseminated SPTCL. In similar case reports describing SPTCL diagnosed in breast tissue, radiologic findings have ranged from ill-defined hyperdensity to calcifications suggestive of fat necrosis. Seo et al described a patient with similar presenting features of subcutaneous breast nodule and

mammographic findings of increased opacity without calcifications or architectural distortion. This patient was also initially diagnosed with lupus panniculitis.[17] Architectural distortion and asymmetrical density with "flakelike" calcifications suggesting fat necrosis has also been described [24]. Radiologic imaging has not only been used to detect disseminated or extracutaneous SPTCL, but also to determine treatment response.[2] As seen in this case, PET/CT whole body initial staging showed FDG hypermetabolic areas of the breast and upper arm consistent with active lymphoma. There has been a reported case of SPTCL in which fluorine-18 fluorodeoxyglucose (F-18 FDG) PET/CT showed enhancing subcutaneous nodules with an infiltrative pattern throughout the body and following three cycles of CHOP therapy, a total remission of metabolically active lesions in repeat F-18 FDG PET/CT of their patient was demonstrated.[1]

Biopsy for histopathological interpretation is commonly performed as a first step in diagnosis. A predominant infiltrate of small, hyperchromatic cells with irregularly shaped nuclei are characteristic, as well as neoplastic cells rimming adipocytes are typically seen.[19, 20] T-cells of this disease characteristically have immunohistochemical phenotype of CD3+, CD4-, CD8+, CD56-, and TCR+.[2] As seen in this patient, diagnostic testing showing CD8+ and Ki-67 was useful in identifying neoplastic cells rimming adipocytes.[8] This feature was described in the original case of SPTCL by Gonzalez and colleagues.[3] One study recognized this phenomenon in 16 cases of SPTCL, noting it to be a helpful diagnostic tool in identifying the disease. However, while helpful, this finding is not specific to SPTCL, as it can be found in other cases of lobular panniculitis, as well as primary and secondary cutaneous lymphomas.[12] First interpretation of the biopsy from our patient was read as mixed septal and lobular panniculitis, prompting an initial diagnosis of lupus panniculitis. Still, with histopathology alone, our clinicians were unable to firmly rule out T-cell lymphoma. For this reason, more precise tests were warranted.

The finding of diffuse numbers of plastacytoid dendritic cells with immunohistochemical staining for CD123 in our patient was notable, as this phenomenon has been observed in both SPTCL and lupus erythematous profundus (LEP). One study found an overlap of both SPTCL characteristics of lymphocytes rimming adipocytes as well as other areas of B-cell nodules arranged peripherally to fat lobules resembling LEP histopathology. Therefore, as in this patient, LEP is a potential mimic for SPTCL. Another hypothesis suggests LEP and SPTCL could be two ends of one disease spectrum.[25] T-cell receptor gene rearrangement analysis, as applied in this case, has shown significance in the diagnosis of malignant lymphomas.[10, 26, 27] While this study is useful in detecting clonal T-cell populations in patients with T-cell lymphomas, they can also be seen in other benign conditions such as PLEVA, lichen sclerosis, lichen planus, and some pseudolymphomas. Therefore, it is important to recognize the use of these tests in conjunction with clinical and histologic findings when arriving at a diagnosis of SPTCL.[10]

Standardized therapy guidelines have yet to be established for this disease. This patient showed an excellent response to six cycles of CHOP therapy evidence by decreased hypermetabolic activity on PET surveillance. She continued to show improvement and remain asymptomatic with weekly methotrexate maintenance over the following two years. A wide variety of therapies have been used in the treatment of SPTCL,

including radiotherapy, CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone), auto/allo-stem cell transplant, cyclosporine, high dose steroids, as well as other derivations of chemotherapy regimens.[8, 14] Therefore, when determining therapy for these patients, consideration of factors such as extent of disease, severity of symptoms, pathologic features, and response to past treatments is important. In the few case reports describing breast involvement of SPTCL, treatment regimens including CHOP and local radiotherapy have been found to induce remission.[17] Cyclosporine alone has also been reported to successfully treat SPTCL with long term remission.[20, 28] Another group found cyclosporine, when added to CHOP therapy in a relapsed patient, to be efficacious in inducing long term remission.[5] The primary mechanism of action of this drug is to decrease expression of cytokines.[14] Other clinicians have shown the effectiveness of cyclosporine in treating relapsed SPTCL that was refractory to anthracycline based chemotherapy, but question its efficacy as first line treatment.[26, 28] Another consideration, in patients with severe systemic symptoms, is to combine cyclosporine with high dose steroids.[20] One group noted complete clinical remission with monotherapy of corticosteroids in a pregnant patient.[29] Therefore, when considering therapy, risks and benefits of certain therapies should be weighed for each patient.

When considering recurrent or refractory disease, a wide variety of salvage chemotherapies and treatment modalities have been explored. In regards to CHOP therapy, one group found gemcitabine, cisplatin, and methylprednisolone (GEM-P) to be efficacious in a patient refractory to CHOP.[8] The effectiveness of stem cell transplation in patients with refractory or recurring SPTCL has been reported in several cases.[15, 30, 31]

CONCLUSION

As this case demonstrates, the clinical presentation, diagnostic approaches, and therapies for SPTCL are not straightforward. It is important that SPTCL is ruled out when considering other non-malignant, panniculitis-like pictures. Careful attention to histopathological evidence should be combined with approaches such as immunohistochemical staining and genotypic studies to further distinguish this disease. A large-volume patient study is warranted to determine standardized approaches to therapy as it relates to extent of disease, pathologic features, and history of relapse. Moreover, a small number of case reports have found value in FDG-CT/PET imaging to identify distribution, morphological patterns, metabolic activity, and treatment response of SPTCL. Therefore, use of this imaging modality could be helpful in both the pre- and post- treatment setting of patients with SPTCL, as well as in determining the need for maintenance therapy.

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Corresponding Author:
Callie Hill
UAB School of Medicine
Birmingham, AL
Callier@uab.edu

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