Subcutaneous Panniculitis-Like T-Cell Lymphoma With Bone Marrow Involvement

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ABSTRACT

Objectives: To describe a rare case of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with morphologic and immunophenotypic evidence of bone marrow involvement.

Methods: Biopsy specimens of skin and subcutis and bone marrow were examined using H&E-stained sections. Immunohistochemical studies for CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD56, and granzyme B were reviewed. In addition, T-cell receptor γ gene rearrangement studies were performed. In addition, T-cell receptor γ gene rearrangement studies were performed.

Results: A bone marrow core biopsy demonstrated several lymphohistiocytic aggregates containing atypical, cytotoxic T cells that rimmed adipocytes and were associated with karyorrhexis. These T cells were morphologically and immunophenotypically identical to a concurrent SPTCL, expressing CD2, CD3, CD7, CD8, and granzyme B but with diminished CD5 expression.

Conclusions: SPTCL may rarely involve the bone marrow. Bone marrow infiltrates show a similar morphologic and immunophenotypic appearance to those in the subcutaneous fibroadipose tissue, including rimming of adipocytes by neoplastic lymphocytes.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare lymphoma, accounting for less than 1% of all non-Hodgkin lymphomas.¹,² It shows a broad age range but frequently affects younger patients (median age, 35 years), and it is associated with autoimmune disease in approximately 20% of patients.¹,³-⁶ Histologically, lymphomatous infiltrates involve fat lobules with relative sparing of the septae and of the overlying dermis and epidermis.¹-³ The cytology of these cells can vary, but nuclei are typically irregular and hyperchromatic.²,⁴,⁷-⁹ Classically, these cells form a rim around individual adipocytes,²,⁴,⁷-⁹ a finding that is sensitive but not specific for this lymphoma.²,¹⁰ The neoplastic cells have an αβ cytotoxic T-cell phenotype with expression of CD3, CD8, T-cell receptor (TCR) βF1, and cytotoxic markers, the latter including granzyme B, perforin, and T-cell intracellular antigen.²,³,⁴,⁷ There is often loss of pan–T-cell markers, most commonly CD5.³ Expression of CD56 is typically absent, and a γδ T-cell phenotype excludes the diagnosis.¹-⁴,⁹ Reactive histiocytes, often with ingested lipid, are frequently seen, but plasma cells and other inflammatory cells, which are common in reactive conditions such as lupus panniculitis, are usually absent.³,⁴,⁷ Necrosis and karyorrhexis are often identified.²-⁵,⁷,⁹ Angioinvasion and angiodestruction may be seen but are more frequent in primary cutaneous γδ T-cell lymphoma.³,⁴ Clinically, patients typically present with multiple subcutaneous nodules, most often on the extremities and trunk but also including the face.³,⁴,⁹,¹¹ Larger lesions may become necrotic and may rarely ulcerate.³,⁹ Resolution of lesions may leave behind lipoatrophy.³ Up to 60% of patients may have systemic symptoms, and 15% to 20% of patients develop
hemophagocytic syndrome. Many patients have cytopenias and elevated liver enzymes. Notably, lymphadenopathy and hepatosplenomegaly have been reported in some patients (approximately 8%). In contrast to primary cutaneous γδ T-cell lymphoma, the 5-year median survival of SPTCL is approximately 80%, although patients with hemophagocytic lymphohistiocytosis (HLH) have a much poorer prognosis (5-year overall survival of approximately 50%). Morphologic bone marrow involvement by the neoplastic cells of SPTCL has only recently been described in three patients. Previous bone marrow examination in patients with SPTCL has been significant only for hemophagocytosis. Autopsies performed on five patients with SPTCL and fatal hemophagocytic syndrome showed no evidence of dissemination to nontumoral sites; lymph nodes, liver, and bone marrow revealed evidence only of hemophagocytosis. We describe a case of SPTCL with clear bone marrow involvement based on the presence of a subcutaneous lymphoma with morphologic and immunophenotypic features diagnostic of SPTCL and an identical, concurrent bone marrow infiltrate.

Case Report

Clinical Presentation

A 28-year-old woman with no significant medical history presented to her primary care physician with fevers, cervical and axillary lymphadenopathy, left facial swelling, an oral ulcer, and tender, erythematous nodules on her arms. She was initially thought to have an infectious process but did not respond to multiple antibiotics. In addition, an extensive workup for infectious disease, including blood cultures and serologies for Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, and hepatitis, was negative. An autoimmune process was also considered, but antinuclear and antineutrophil cytoplasmic antibodies were negative. Moreover, the patient showed no improvement with prednisone. Over the next 2 months, she continued to have fevers and developed chills. In addition, her cutaneous lesions increased in size and number, spreading to involve her arms, legs, back, and face. These lesions included nodules and thin plaques, some of which showed superficial erosions.

Eventually, the patient presented to another hospital, where laboratory studies revealed profound pancytopenia with a WBC count of less than 100/μL (reference range, 4,000-10,000/μL), a hemoglobin of 6.9 g/dL (reference range, 12.0-16.0 g/dL), and a platelet count of 19,000/μL (reference range, 150,000-400,000/μL). Fibrinogen was low at 84 mg/dL (reference range, 150-450 mg/dL), and lactate dehydrogenase was elevated at 1,493 IU/L (reference range, 120-240 IU/L). Ferritin was markedly increased at 13,900 ng/mL (reference range, 6-155 ng/mL). Triglycerides were also high at 230 mg/dL (reference range, 1-150 mg/dL). Soluble CD25 (soluble IL-2R) was eventually found to be greater than 6,500 U/mL (reference range, <970 U/mL). Natural killer-cell activity testing was not performed. A computed tomography scan confirmed the cervical and axillary lymphadenopathy found on physical examination and also identified splenomegaly.
Bone marrow biopsy and skin punch biopsy specimens were obtained, and the patient was transferred to our institution. On the basis of the presence of fever, splenomegaly, cytopenias, hypofibrinogenemia, elevated ferritin, and elevated soluble CD25, the patient met criteria for the diagnosis of HLH [Table II].

Materials and Methods

Immunohistochemistry

Formalin-fixed, paraffin-embedded (FFPE) tissue blocks were cut in 4-µm–thick sections and processed for immunohistochemistry using Cell Conditioning 1 (Ventana Medical Systems, Tucson, AZ). Antibodies against the following antigens were used: CD2 (AB75; 1:40; Leica, Buffalo Grove, IL), CD3 (SG-V6; predilute; Ventana Medical Systems), CD4 (SP35; 1/20; Leica), CD5 (SP19; predilute; Ventana Medical Systems), CD7 (SP94; predilute; Ventana Medical Systems), CD8 (SP57; predilute; Ventana Medical Systems), CD20 (L26; predilute; Ventana Medical Systems), CD56 (123CC3.D5; predilute; Cell Marque, Rocklin, CA), granyme B (polyclonal; predilute; Cell Marqué), TCR-βF1 (8A3; 1:20; Endogen, Rockford, IL), and Ki-67 (30-9; predilute; Ventana Medical Systems). Staining was performed using the BenchMark ULTRA automated immunostainer (Ventana Medical Systems). The chromogen used was 0.05% diaminobenzidine tetrahydrochloride (Dako), and the counterstain was Harris hematoxylin.

In Situ Hybridization

FFPE tissue blocks were cut in 4-µm–thick sections and processed for in situ using Cell Conditioning 2 (Ventana Medical Systems). Sections were hybridized using DNP-labeled probe targeting Epstein-Barr virus–encoded RNA 1 (predilute; Ventana Medical Systems). Sections were hybridized using DNP-labeled probe targeting Epstein-Barr virus–encoded RNA 1 (predilute; Ventana Medical Systems). Sections were hybridized using DNP-labeled probe targeting Epstein-Barr virus–encoded RNA 1 (predilute; Ventana Medical Systems). Sections were hybridized using DNP-labeled probe targeting Epstein-Barr virus–encoded RNA 1 (predilute; Ventana Medical Systems). Sections were hybridized using DNP-labeled probe targeting Epstein-Barr virus–encoded RNA 1 (predilute; Ventana Medical Systems).

Molecular Studies

Multiplex polymerase chain reaction of TCRβ and TCRγ was performed at an outside laboratory based on the BIOMED-2 strategy using DNA extracted from FFPE tissue.14

Results

Morphologic Findings

A punch biopsy specimen from the right side of the back Image 2 demonstrated a deep dermal and subcutaneous infiltrate of lymphoid cells with prominent rimming of adipocytes. These lymphocytes were cytologically atypical with nuclear enlargement and hyperchromasia, mild nuclear contour irregularities, and variably prominent nucleoli. The infiltrate was associated with abundant karyorrhectic debris. In addition, there were numerous histiocytes, including some hemophagocytic cells. Focal fat necrosis was apparent. The overlying epidermis showed mild lichenoid interface dermatitis with vacuolar degeneration of the basal layer, occasional necrotic keratinocytes, and focal epidermal necrosis. There was no evidence of basement membrane thickening, dermal mucin, hyalinosis of fat lobules, follicular plugging, increased plasma cells, clustered CD20-positive B cells, or reactive lymphoid follicles to suggest lupus panniculitis. In addition, angioinvasion and angiodestruction by the neoplastic lymphocytes were not identified.

A concomitant bone marrow biopsy and aspirate were performed. The biopsy specimen demonstrated several lymphohistiocytic aggregates occupying approximately 5% of the marrow space and containing atypical mononuclear cells rimming bone marrow adipocytes (Image 3) Image 4. As in the skin, karyorrhexis was also present. The bone marrow aspirate contained scattered macrophages with obvious erythrophagocytosis as well as cytophagocytosis of platelets and occasional lymphocytes.

Immunohistochemistry

Immunohistochemical studies on the skin biopsy specimen Image 5 demonstrated that the atypical lymphoid cells were positive for CD2, CD3, CD7, CD8, granyme B, and TCR-βF1 and were negative for CD4, CD56, and CD30. In situ hybridization for EBV RNA (EBER) was also negative. CD5 appeared diminished to absent in a major subset of cells. A Ki-67 immunohistochemical study marked many rimming lymphocytes, indicating a high proliferation index in these cells.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Diagnostic Criteria for Lymphohistiocytosis*</th>
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<tr>
<td><strong>Clinical Features</strong></td>
<td><strong>Laboratory Features</strong></td>
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<tr>
<td>Fever</td>
<td>Cytopenias of at least two lineages in the peripheral blood</td>
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<td>Splenomegaly</td>
<td>Hemoglobin &lt;90 g/L</td>
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<td>Platelets &lt;100 × 10⁹/L</td>
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<td></td>
<td>Neutrophils &lt;1.0 × 10⁹/L</td>
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<td></td>
<td>Hypertriglyceridemia and/or hypofibrinogenemia</td>
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<td></td>
<td>Fasting triglycerides &gt;265 mg/dL</td>
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<td>Fibrinogen ≤1.5 g/L</td>
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<td>Hemophagocytosis in bone marrow, spleen, or lymph nodes</td>
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<td>Low/absent natural killer–cell activity</td>
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<td></td>
<td>Hyperferritinemia (&gt;500 mg/L)</td>
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<td></td>
<td>High soluble interleukin 2 receptor (sCD25) (&gt;2,400 U/mL)</td>
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*Adapted from Henter et al18 and Jordan et al.19 Five of eight features are required for diagnosis.
Image 21 Morphologic findings in the cutaneous punch biopsy specimen from the right upper back. A, Subcutaneous infiltrate with sparing of the dermis and epidermis (H&E, ×20). B, Subcutaneous infiltrate involving fat lobules with relative sparing of septae (H&E, ×20). C, Cytologically atypical lymphocytes with enlarged, hyperchromatic, and irregular nuclei (H&E, ×400). D, Atypical lymphoid cells rimming adipocytes with adjacent karyorrhectic debris (H&E, ×400). E, Histiocytes with erythrophagocytosis and fat necrosis (H&E, ×1,000). F, Epidermis with patchy vacuolar interface change (H&E, ×400).
Immunohistochemical studies performed on the bone marrow core biopsy specimen revealed an increase in CD3-positive T lymphocytes arranged as singly scattered interstitial cells, as well as collections of T cells that rimmed individual fat spaces within ill-defined lymphohistiocytic aggregates. As in the skin, atypical lymphocytes were positive for CD2, CD3, CD7, CD8, and granzyme B. They were negative for CD4 and showed diminished CD5 expression. Cytogenetic studies on the bone marrow revealed a normal female karyotype.

Flow Cytometry
Flow cytometric analysis of the bone marrow aspirate, performed by an outside institution, reportedly did not demonstrate an aberrant T-cell population or other evidence of a lymphoproliferative disorder, possibly reflecting the limited marrow involvement. Listmode files were unavailable for analysis.

Molecular Studies
TCRγ gene rearrangement studies performed on DNA extracted from FFPE tissue from the punch biopsy specimen demonstrated a clonal rearrangement. The bone marrow aspirate clot section did not contain sufficient tissue for a similar study. The bone marrow biopsy specimen yielded an indeterminate result due to poor amplification.

Follow-up
The patient was diagnosed with subcutaneous panniculitis-like T-cell lymphoma with bone marrow involvement and associated HLH. She was treated with high-dose corticosteroids and etoposide, followed by cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone chemotherapy once the diagnosis of lymphoma was formally established. She achieved a good clinical and radiologic remission after six cycles of chemotherapy, although foci of residual subcutaneous fludeoxyglucose (18F-FDG) uptake were observed by positron emission tomography–computed tomography (PET-CT). Unfortunately, HLH and biopsy-proven relapse of the lymphoma occurred within months. A PET-CT from this time of relapse demonstrated interval development of innumerable 18F-FDG avid subcutaneous nodules as well as development of 18F-FDG avidity within mediastinal and retroperitoneal lymph nodes and within the left iliopsoas muscle. The patient was treated with gemcitabine-oxaliplatin salvage chemotherapy with no response, bexarotene and dexamethasone with a transient partial clinical response but subsequent progression, pralatrexate with no response, etoposide, methylprednisolone, high-dose cytarabine, and cisplatin chemotherapy, leading to a complete clinical and radiologic response. Following initiation of chemotherapy, four bone marrow biopsies were performed over the next 10 months, but none showed definitive evidence of marrow involvement by lymphoma. The patient underwent an allogeneic hematopoietic cell transplant from a matched unrelated donor 10 months after her initial diagnosis, using myeloablative cyclophosphamide and total-body irradiation as a conditioning regimen. She remains in complete remission 16 months after transplantation and is left with extensive lipoatrophy.

Discussion
The morphologic and immunophenotypic features seen in the cutaneous punch biopsy specimen described above are typical of SPTCL. In particular, the biopsy specimen showed a subcutaneous infiltrate involving fat...
lobules with sparing of the septae and overlying dermis and epidermis. Neoplastic lymphocytes were cytologically atypical with enlarged, hyperchromatic nuclei and irregular nuclear contours. The lymphoma cells rimmed individual fat cells, a feature characteristic of SPTCL. Furthermore, the immunophenotype of these cells was consistent with SPTCL, showing an αβ cytotoxic T-cell phenotype with expression of CD3, TCR-βF1, CD8, and granzyme B, without CD4. As expected, neoplastic cells were negative for CD56 and EBER. A TCRγ gene rearrangement study performed on this biopsy specimen confirmed a clonal T-cell process.

The most unusual feature of this case is the presence of bone marrow involvement by neoplastic cells. Reactive lymphohistiocytic aggregates can be seen in a variety of contexts. However, the bone marrow in this case demonstrated cytologically atypical, cytotoxic T cells with definite rimming of individual fat cells and an immunophenotype identical to that observed in neoplastic cells in the skin, including lack of expression of CD5. An identical TCR rearrangement would have provided another important piece of evidence. Unfortunately, molecular studies attempted on the bone marrow biopsy specimen were unsuccessful with poor amplification. Nonetheless, we consider the morphologic and immunophenotypic features to be sufficient for the diagnosis of SPTCL with bone marrow involvement. Of note, no other patients with SPTCL have had a bone marrow biopsy performed at our institution.

Morphologic and immunophenotypic evidence of bone marrow involvement by SPTCL has only recently been described in three patients. All patients had concurrent skin lesions meeting current diagnostic criteria for SPTCL. Bone marrow biopsy specimens showed focal involvement by cytologically atypical lymphocytes that expressed CD3 and CD8 and rimmed individual adipocytes. Similar to the case
presented here, flow cytometry did not show an abnormal T-cell population, and no clonal TCR gene rearrangement was identified. In addition to histopathologic evidence of bone marrow involvement by SPTCL, there have also been reports describing genetic evidence of systemic disease. SPTCL has been transferred from a donor to a recipient via allogeneic hematopoietic cell transplant. Notably, the SPTCL that developed several years after transplant in both donor and recipient demonstrated an identical T-cell clone that was also identified in the pretransplant peripheral blood of the donor and the posttransplant peripheral blood and bone marrow of the recipient. In addition, another reported case of SPTCL showed an identical T-cell clone in the skin and peripheral blood. Interestingly, five of the seven patients with morphologic or genetic evidence of systemic SPTCL, including the case presented here, were diagnosed with or suspected of having hemophagocytic syndrome. Six of seven patients had B-type symptoms. Three patients experienced a recurrence of their disease, and four patients died of their disease, the latter including all patients with genetic evidence of systemic lymphoma. Although the number of cases and follow-up are extremely limited, these findings suggest that patients with bone marrow involvement may have a worse prognosis.

The rimming of individual adipocytes in the subcutis and bone marrow suggests that this lymphoma has a peculiar tropism for adipocytes. A recent study hypothesized that adipotropism in SPTCL is mediated by the adipocyte receptor CCR5 and the lymphocyte-associated ligand CCL5. This study showed that lymphomas characteristically involving the subcutaneous fat, including SPTCL and primary cutaneous γδ T-cell lymphoma, were significantly more likely to express CCL5 than lupus panniculitis, and CCL5 expression was particularly increased in the lymphocytes rimming adipocytes. Furthermore, the study showed there were fewer CCL5-positive lymphocytes in a variety
of primary cutaneous and systemic T-cell lymphomas involving the skin that did not involve the subcutaneous fibroadipose tissue.\textsuperscript{17}

Notably, the lymphomatous infiltrate at each site in this case was accompanied by histiocytic hyperplasia with cytophagocytosis. In fact, the clinical and laboratory findings in this case, with fever, splenomegaly, cytopenias, hypofibrinogenemia, hyperferritinemia, and elevated soluble CD25, fulfilled diagnostic criteria for HLH.\textsuperscript{18,19} Since the lymphomatous infiltrates in the bone marrow were not extensive, the profound cytopenias are best attributed to HLH.

In summary, the case described herein is the fourth reported case of SPTCL with morphologic and immunophenotypic evidence of bone marrow involvement. Atypical lymphocytes with diminished CD5 expression were seen rimming individual adipocytes in both the subcutis and bone marrow. SPTCL is a rare lymphoma characterized by multiple subcutaneous nodules containing neoplastic αβ cytotoxic T cells. This lymphoma is occasionally associated with systemic symptoms and even frank hemophagocytic syndrome, as seen in this case. However, to our knowledge, morphologic bone marrow involvement by neoplastic cells has never been described until now. The presence of these cells within the marrow may result from the tropism of this lymphoma for adipocytes. In this case, the patient’s subcutaneous lymphoma and hemophagocytic syndrome responded to frontline chemotherapy but showed rapid recurrence, necessitating multiple lines of salvage treatment to eventually achieve a second remission. Allogeneic hematopoietic cell transplantation was subsequently used to achieve durable clinical remission.

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\begin{figure}[h]
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\caption{Immunohistochemical findings in bone marrow core biopsy specimen. As in skin biopsy specimen, atypical lymphocytes express CD8 (A) and granzyme B (B), with lack of expression of CD5 (C) (\times400).}
\end{figure}
Image 7: Three-dimensional maximum intensity projection images from fludeoxyglucose positron emission tomography–computed tomography demonstrate recurrence following six cycles of cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone chemotherapy with innumerable cutaneous and subcutaneous hypermetabolic lesions scattered throughout the entire body. Additional hypermetabolic foci are present in the anterior mediastinum and retroperitoneum.

References