

Subcutaneous Panniculitic T-cell Lymphoma Presenting With Anasarca in a Patient With Known Chronic Lymphocytic Leukemia

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PRACTICE POINTS

- Subcutaneous panniculitic T-cell lymphoma (SPTCL) is a rare type of cutaneous T-cell lymphoma that may be complicated by fatal hemophagocytic syndrome.
- Patients typically present with deep-seated plaques or nodules that may be masked by localized edema.
- A biopsy is necessary to diagnose SPTCL, as well as to assess the degree of cellular atypia, fat necrosis, karyorrhexis, cytophagia, and angioinvasion to distinguish it from other panniculitides.
- In patients with a known hematologic malignancy, a secondary malignancy must be considered in the differential diagnosis of paraneoplastic edema.

To the Editor:

Subcutaneous panniculitic T-cell lymphoma (SPTCL) is a rare cutaneous T-cell lymphoma that was first described in 1991¹ and comprises less than 1% of all non-Hodgkin lymphomas (NHLs). It most commonly occurs in young adults, with a median patient age of 36 years and a slight female predominance.² Patients typically present with skin nodules or deep-seated plaques involving the legs, arms, and/or trunk. Presentation on the face is less common.^{2,3} Paraneoplastic edema has been reported in several cases of SPTCL with facial and periorbital swelling.⁴⁻⁹

Diagnosis of SPTCL is achieved via analysis of a deep tissue skin biopsy and close clinicopathologic correlation. Histopathology demonstrates lobular panniculitis with

an atypical lymphoid infiltrate in the subcutaneous tissue with predominantly CD8⁺ T cells without overlying epidermotropism or interface dermatitis.³ The degree of cellular atypia, fat necrosis, karyorrhexis, cytophagia, and lack of angioinvasion can help to distinguish SPTCL from other panniculitides.^{2,3}

The prognosis of SPTCL is good, with a 5-year survival rate of 82%, and many patients are able to achieve remission.² However, SPTCL can progress to a fatal hemophagocytic syndrome, which has been reported in 17% of cases, making early diagnosis and treatment of this malignancy imperative.^{1,2} Treatment varies depending on the progression and extent of disease and can include the use of steroids, multidrug chemotherapy regimens, radiotherapy, and stem cell transplant in refractory cases.^{2-4,10,11}

Subcutaneous panniculitic T-cell lymphoma with edema has been reported in a 2-year-old child.¹² We present a case of SPTCL in an adult patient with known stage IV chronic lymphocytic leukemia (CLL) who also had full-body edema.

A 60-year-old woman with a 7-year history of stage IV CLL presented with anasarca of 3 months' duration. At the time of presentation to dermatology, physical examination revealed erythematous tender nodules on the arms and legs. She had no other medical conditions and was undergoing treatment with ibrutinib for the CLL. The patient reported profound fatigue but no fever, chills, night sweats, cough, or dyspnea. The swelling had begun initially in the legs and progressively worsened to involve the arms, face, and body. She was hospitalized and treated with intravenous steroids and antihistamines, which led

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to minor improvement in the swelling. The patient's preliminary diagnosis of erythema nodosum was thought to be related to the CLL or ibrutinib; therefore, treatment subsequently was discontinued and she was discharged from the hospital.

The swelling continued to worsen over the following 3 months, and the patient gained approximately 25 pounds. She presented to our office again with severe periorbital, facial, and lip edema as well as diffuse edema of the torso, arms, and legs (Figure 1). Erythematous tender subcutaneous nodules were noted on the right proximal thigh, left lateral calf, and forearms. She was again hospitalized, and extensive evaluation was performed to exclude other causes of anasarca, including a complete blood cell count; comprehensive metabolic profile; hepatitis panels; HIV test; C3 and C4, complement CH50, C1 esterase inhibitor, IgE, and angiotensin-converting enzyme levels; urine protein to creatinine ratio; computed tomography of the chest, abdomen, and pelvis; and allergy evaluation. The analyses failed to reveal the cause of the anasarca.

During hospitalization, the patient underwent a lymph node biopsy, bone marrow biopsy, and a 6-mm punch biopsy of the right thigh nodule. The lymph node and bone marrow biopsy results were consistent with the

known diagnosis of CLL, and the patient was started on intravenous chemotherapy with bendamustine. The skin biopsy demonstrated a predominant T-cell infiltrate consistent with a lobular panniculitis with variable amounts of adipocytes rimmed by lymphocytes, nuclear debris, and

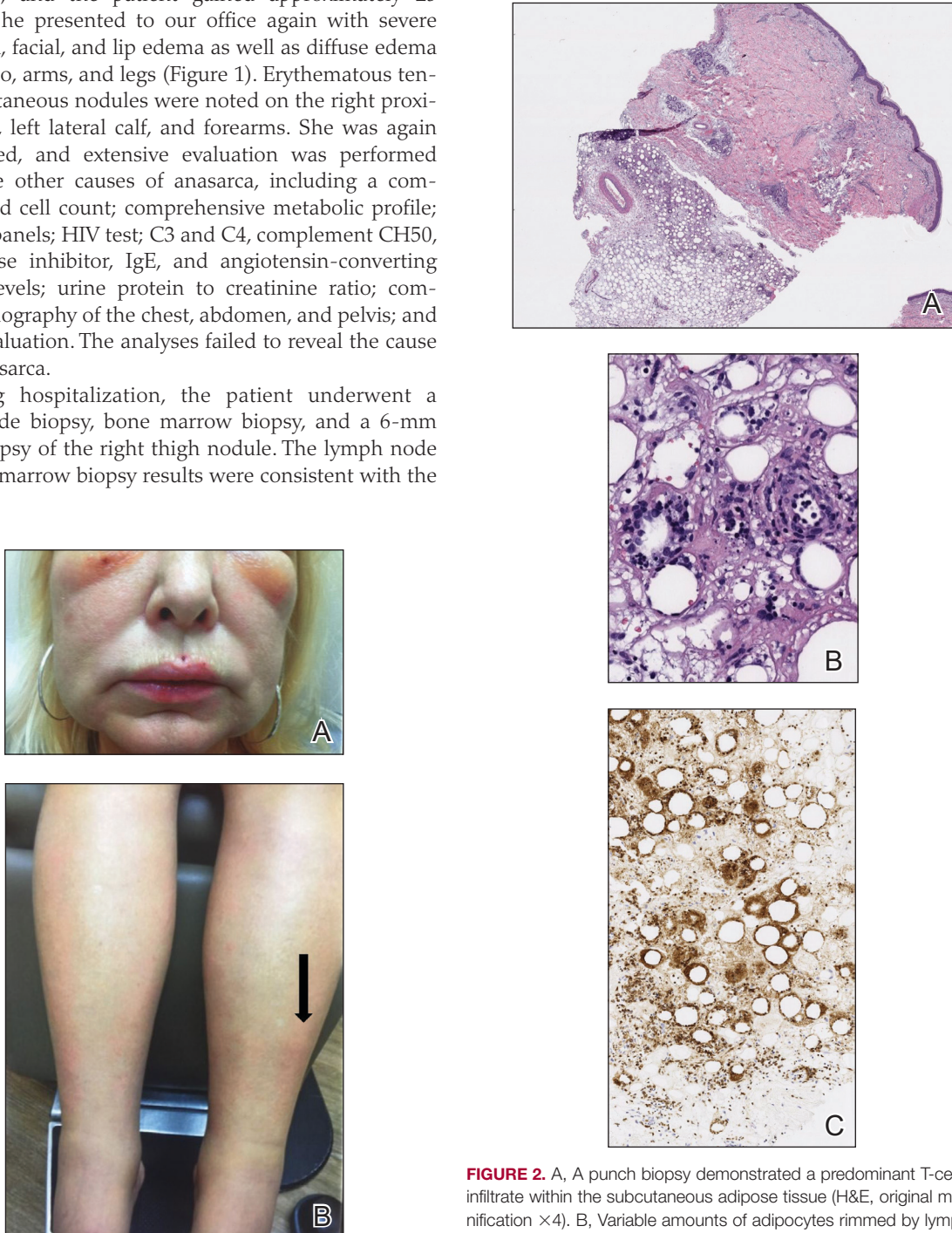


FIGURE 1. A, A 60-year-old woman with periorbital, facial, and lip edema. B, The lower extremities also showed edema, erythema, and a left lateral subcutaneous nodule (arrow).

FIGURE 2. A, A punch biopsy demonstrated a predominant T-cell infiltrate within the subcutaneous adipose tissue (H&E, original magnification $\times 4$). B, Variable amounts of adipocytes rimmed by lymphocytes, nuclear debris, and karyorrhexis were shown on high power (H&E, original magnification $\times 200$). C, An immunostain for T-cell receptor $\beta 1$ highlighted lymphocytes surrounding adipocytes (original magnification $\times 40$).

karyorrhexis (Figure 2). CD3⁺, CD8⁺, and CD4⁻ T cells were positive for T-cell receptor (TCR) β F1 and negative for TCR- γ with strong expression of cytotoxic markers including granzyme B, perforin, and T-cell intracytoplasmic antigen 1. Rare CD56⁺ cells also were noted. The biopsy did not demonstrate any notable interface dermatitis, epidermotropism, or angioinvasion. T-cell receptor gene rearrangement studies did not show clonality for γ - or β -chain probes. Subcutaneous panniculitic T-cell lymphoma was diagnosed, making this case unique with the presentation of anasarca. This case also is noteworthy due to the rare diagnosis of the secondary malignancy of SPTCL in a patient with known CLL. The patient opted to pursue hospice and comfort measures due to the effects of persistent pancytopenia and the progression of CLL. She died 2 months later.

Clinical courses of SPTCL vary based on the TCR phenotype and immunophenotypic characteristics of the tumor cells. The TCR- $\alpha\beta$ phenotype, as described in this case, typically is CD4⁻, CD8⁺, and CD56⁻ and leads to a more indolent disease course. Lymphomas with the TCR- $\gamma\delta$ phenotype typically are CD4⁻, CD8⁻, and CD56⁺; they often are associated with hemophagocytic syndrome and thus a worse prognosis. In 2009, the World Health Organization–European Organization for Research and Treatment of Cancer classification of primary cutaneous lymphomas restricted the category of SPTCL to the TCR- $\alpha\beta$ phenotype due to the stark differences between the 2 types. The TCR- $\gamma\delta$ phenotype was given its own diagnostic category—primary cutaneous $\gamma\delta$ T-cell lymphoma.³

Patients with SPTCL commonly present with nodular skin lesions or deep-seated plaques on the legs, arms, and/or trunk; presentation on the face is rare.^{2,3} Fever, chills, night sweats, and/or weight loss were present in approximately 50% of recorded cases. Underlying autoimmune disease was present in 12 of 63 (19%) patients in a 2008 study.² Facial and periorbital swelling with SPTCL has been reported.⁴⁻⁹ The presentation of anasarca, as seen in our adult patient, has been reported in a 2-year-old child.¹² Anasarca as a presenting symptom of NHL is a rare phenomenon proposed to be induced by malignant cells secreting a cytokine that causes a vascular leak syndrome.¹³ Specifically, tumor necrosis factor α was found to be elevated in at least 2 patients with NHL presenting with anasarca in a prior study. Tumor necrosis factor α is known to cause increased capillary permeability, vascular leakage, and development of edema.¹³ In retrospect, obtaining cytokine levels in our patient would have been useful to support or refute tumor necrosis factor α as a possible cause of anasarca in the setting of NHL. This case continues to highlight that a diagnosis of SPTCL and analysis of a skin biopsy should be considered in cases of sudden unremitting facial and/or body swelling that cannot be explained by other more common causes.

Subcutaneous panniculitic T-cell lymphoma can be diagnosed and distinguished from other panniculitides

via analysis of a deep tissue skin biopsy. Multiple biopsies may be required to ensure an adequate sample is obtained.⁴ Histopathology displays an atypical lymphoid infiltrate with a predominant presence of T cells. Neoplastic cells show CD3⁺, CD8⁺, and CD4⁻ T cells, which strongly express cytotoxic proteins such as granzyme B, T-cell intracellular antigen 1, and perforin.³ The degree of cellular atypia, fat necrosis, karyorrhexis, and cytophagia, as well as the lack of angioinvasion, interface dermatitis, and epidermotropism help to distinguish SPTCL from other panniculitides.^{2,3} According to a previous study, clonal TCR gene rearrangement was identified in 50% to 80% of cases, but the absence of this clonal rearrangement does not exclude the diagnosis.¹⁴

This case also highlights the occurrence of secondary malignancies in patients with CLL, an NHL that is classified as a low-grade lymphoproliferative malignancy with clonal expansion of B cells.¹⁵ Secondary CTCLs in patients with CLL are rare, but they have been previously described. In 2017, Chang et al¹⁶ identified 12 patients with CLL who subsequently developed CTCL between 1992 and 2008. Of the 12 patients, 7 developed mycosis fungoides, 3 had CTCL not otherwise specified, 1 had mature T-cell lymphoma not otherwise specified, and 1 had primary cutaneous CD30⁺ T-cell lymphoma.¹⁶ The proliferation of 2 separate lymphocytic lineages is rare, but this study demonstrated an increased risk for CTCL to develop in patients with CLL. One possible explanation is that malignant cells come from a common stem cell progenitor or from genetic events. They occur secondary to carcinogens, viruses, or cytokines from T-cell or B-cell clones; they evolve due to treatment of the preexisting lymphoproliferative disease; or they occur simply by coincidence. The behavior of the CTCL may be more aggressive in patients with CLL due to immunosuppression, which may have contributed to the extreme presentation in our patient.¹⁶ Subcutaneous panniculitic T-cell lymphoma also has been reported in a patient with CLL that was thought to be associated with prior rituximab treatment.¹⁷

Treatment of SPTCL depends on the severity and course of the disease. In patients with more indolent disease, systemic steroids have been the most frequently used initial treatment.^{2,3,10} However, the disease often will progress after steroid tapering and require further intervention. Localized lesions may be treated with radiation alone or in combination with other systemic therapies.^{3,10} In refractory, aggressive, or relapsing cases, polychemotherapeutic regimens have proven to produce long-term remission in 30% of patients, with an overall response rate of 50%.¹⁰ These regimens most commonly have included cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like treatment (EPOCH regimen [etoposide, prednisone, oncovin, cyclophosphamide, and doxorubicin hydrochloride]).^{3,10} A stem cell transplant can be considered in patients with recurrent and refractory disease, and it also has been shown to

induce remission.^{4,17} In patients with a good response to therapy, the disease often can be controlled for long periods of time, with an estimated 5-year survival rate of 80%.¹⁵

This case highlights the diagnostic challenges and variable presentations of SPTCL. Dermatologists, oncologists, and dermatopathologists should be aware of this condition and consider it in the differential diagnosis of a patient with a hematologic malignancy and unremitting facial and/or body swelling without any other cause. The possibility of a secondary hematologic cancer in a patient with CLL also must be taken into consideration. Early diagnosis and treatment can minimize morbidity and induce remission in most patients.

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