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A Rare Case of Subcutaneous Panniculitis-Like T Cell Lymphoma with Hemophagocytic Lymphohistiocytosis Mimicking Cellulitis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 48-year-old
Final Diagnosis: Hemophagocytic Lymphohistiocytosis • subcutaneous panniculitis-like T cell lymphoma
Symptoms: Chills • erythema • fever • night sweats • subcutaneous nodules
Medication: —
Clinical Procedure: Autologous stem cell transplantation • chemotherapy
Specialty: Dermatology • Hematology • Infectious Diseases • Medicine, General and Internal • Oncology • Pathology • Transplantology

Objective: Rare disease

Background: Subcutaneous panniculitis-like T cell lymphoma and primary cutaneous γδ T cell lymphoma are rare forms of non-Hodgkin lymphoma presenting as skin nodules or plaques.

Case Report: Here, we present a case of a 48-year-old man with multiple subcutaneous, tender, erythematous nodules on his right thigh and left arm. Multiple courses of antibiotics were administered with no significant improvement in the patient's lesions. The skin biopsy report showed CD3/CD8 lymphocytic rimming of the adipocytes and the patient was diagnosed with subcutaneous panniculitis-like T cell lymphoma. A subsequent bone marrow biopsy showed hemophagocytic lymphohistiocytosis. The patient underwent treatment with the cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone, and etoposide chemotherapy regimen and received an autologous peripheral blood stem cell transplant.

Conclusions: Nodular skin lesions can result from a variety of noninfectious causes in addition to bacterial and fungal infections. This case highlights the importance of early biopsy of skin lesions that do not respond to standard therapy to establish an accurate diagnosis and start timely treatment to prevent poor outcomes.

MeSH Keywords: Biopsy • Cellulitis • Hematopoietic Stem Cell Transplantation • Lymphohistiocytosis, Hemophagocytic • Lymphoma, Non-Hodgkin • Lymphoma, T-Cell, Cutaneous

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/927142

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Background

Subcutaneous panniculitis-like T cell lymphoma (SPTCL) and primary cutaneous γδ T cell lymphoma (PCGD-TCL) are rare skin lymphomas characterized by infiltration of the subcutaneous tissues with cytotoxic T cells without associated lymph node involvement [1,2]. They are diseases of young adults, with a median age at diagnosis 30–40 years. There is a female preponderance and it accounts for less than 1% of non-Hodgkin lymphoma cases [3]. Patients usually present with multiple, painless subcutaneous plaques or nodules mostly on the trunk and extremities. Some nodules can regress without treatment and newer ones can develop at different sites [1]. It can be accompanied by systemic symptoms of fevers, chills, night sweats, weight loss, and myalgias [4]. The differential diagnosis includes eczema, psoriasis, dermatitis, cellulitis, or lupus erythematosus panniculitis (LEP) [3]. Up to 20% of patients have an associated autoimmune disease such as systemic lupus erythematosus [5]. In addition, there is rarely any systemic involvement [6]. However, there have been cases reported in the literature in which panniculitis-like T cell lymphoma was found outside the subcutaneous tissue. These cases are typically found in the mesentery and are more aggressive, not responsive to multiagent chemotherapy, and carry a poorer prognosis [7–9].

The World Health Organization (WHO) has reclassified SPTCL into 2 different phenotypes. Currently, SPTCL is reserved for αβ T cell phenotype: CD8+, CD4–, and CD56–. SPTCL has a good prognosis and can be treated with immunosuppressive medication. On the other hand, PCGD-TCL is CD4–, CD8–, CD56+ and has a poor prognosis. Both phenotypes express granzyme B, perforin, and TIA1 [7].

Panniculitis-like T cell lymphoma can be associated with hemophagocytic lymphohistiocytosis (HLH) in 15–25% of cases [5]. HLH is a severe systemic inflammatory response due to the overproduction of cytokines produced by activated T cells and histiocytes [2,10]. HLH can be triggered by neoplastic and nonneoplastic agents such as viruses and rheumatic diseases. Histopathologic findings include a widespread accumulation of lymphocytes and mature macrophages affecting the spleen, lymph nodes, bone marrow, liver, and cerebrospinal fluid [11].

Case Report

A 48-year-old man, a native of Arizona, with a history of coccidioidomycosis, hypertension, obstructive sleep apnea, and hyperlipidemia, developed a lump on the right thigh. This became progressively large, painful, and hot to touch. It was associated with fever and night sweats. He denied history of smoking, drug use, unprotected sexual encounters, or foreign travel. A

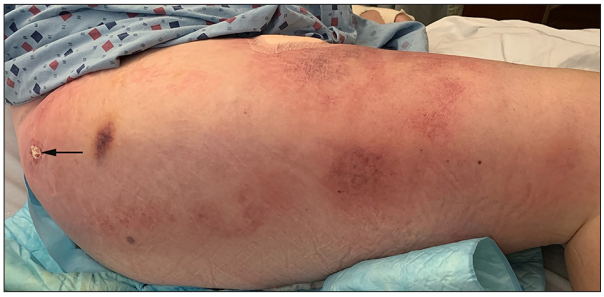

Figure 1. The right upper thigh revealed several discrete areas of induration with overlying warmth and erythema, including an ulcer at the superior lateral thigh.

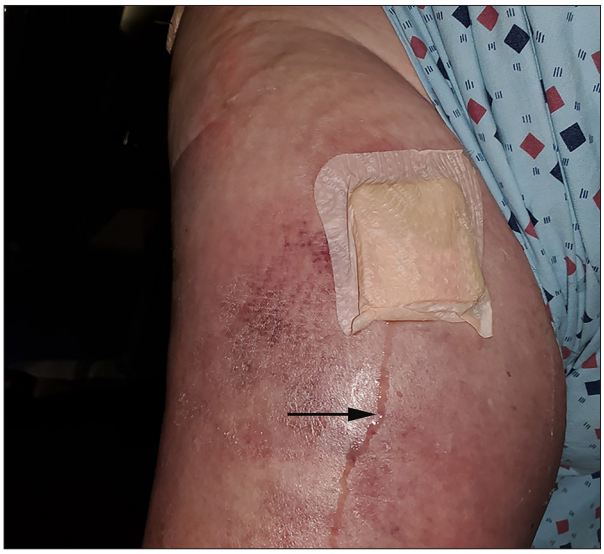

Figure 2. The left arm showed an area of induration laterally with surrounding erythema extending to the wrist, and serous drainage.

magnetic resonance image of the affected site showed subcutaneous edema. During this time, the patient was seen by an orthopedic surgeon, an oncologist, and an infectious disease specialist. A few months passed and the patient developed a similar lump on the left arm. The infectious disease physician diagnosed him with cellulitis and prescribed doxycycline and clindamycin. He ended up receiving multiple courses of oral antibiotics and steroids, without any significant improvement. Because of suspicion that this was not cellulitis, the patient was admitted to the hospital for excisional biopsy.

On admission, the patient was febrile to 39.2°C and tachycardic at 110 beats per minute. On examination, the right upper thigh revealed several discrete areas of induration with overlying warmth and erythema (**Figure 1**). The left arm showed an area of induration laterally with surrounding erythema extending to the wrist (**Figure 2**). Laboratory results showed a normal white blood cell count, anemia, and elevated transaminases. The sedimentation rate was normal and C-reactive protein

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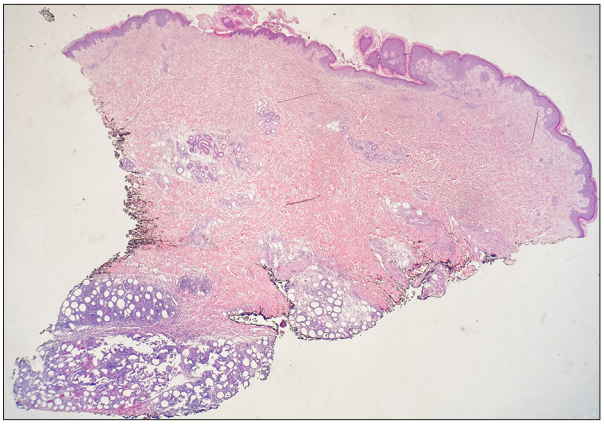

Figure 3. Excisional biopsy showing subcutaneous panniculitis-like T cell lymphoma involving the fat lobules with sparing of the overlying cutaneous tissue (×20, hematoxylin and eosin stain).

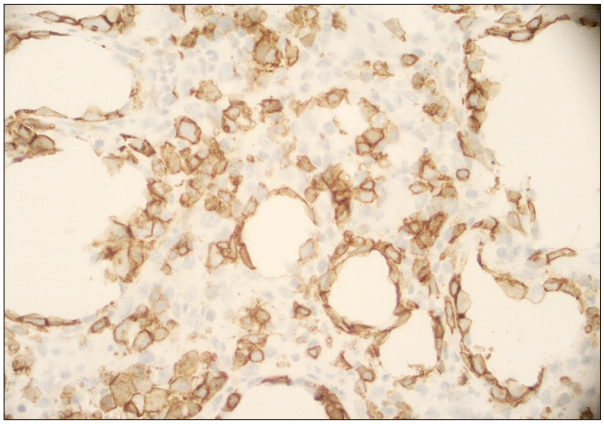

Figure 5. CD8 immunohistochemical stain highlights the atypical lymphocytes with hyperchromic nuclei in a membranous distribution, also demonstrating T cell lineage (×400).

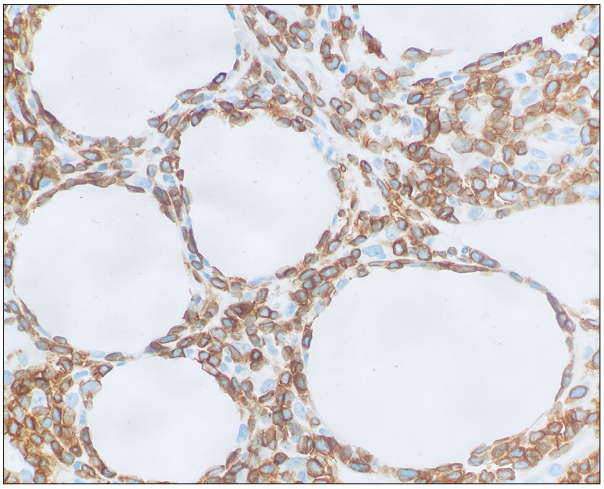

Figure 4. CD3 immunohistochemical stain of the atypical lymphocytes with hyperchromic nuclei in a membranous distribution, demonstrating T cell lineage (×400).

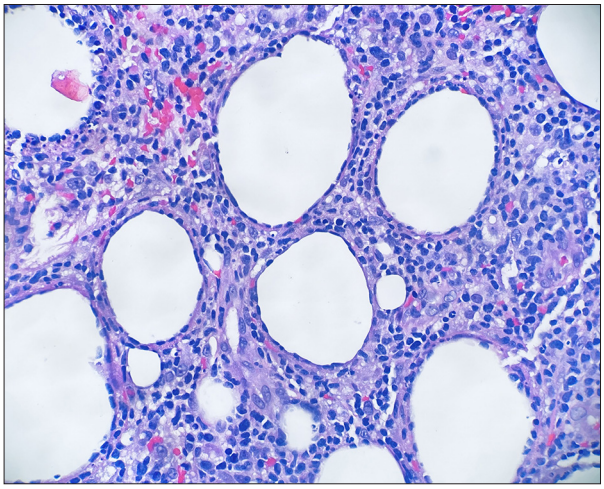

Figure 6. Rimming of the adipocytes by lymphocytes with nuclear atypia (×400, hematoxylin and eosin stain).

was 60.7 mg/L. Serologic results for hepatitis, human immunodeficiency virus, and *Coccidioides* were negative. A lower-extremity ultrasound was negative for blood clots. Computed tomography (CT) of the extremities showed soft-tissue edema consistent with cellulitis and no abscess. The pathology from the excisional biopsy was reported as deep adipose tissue abscess. After having persistant fevers and receiving only partial relief with intravenous antibiotics, the patient underwent incison and drainage with fasciotomy of the right thigh and left arm. Intraoperatively, 30-40 mL of yellow murky fluid was aspirated. Bacterial, mycobacterial, and fungal cultures remained negative. The patient's fevers resolved but he continued to have significant areas of induration, with new areas developing on the left forearm. The patient was discharged on trimethoprim/sulfamethoxazole. The tissue from the biopsy site was reviewed by a hematopathologist and dermatopathologist at our hospital, who suspected subcutaneous panniculitis-like T cell lymphoma. Histopathology demonstrated involvement of the fat lobules, with intermediate-size lymphoid cells with irregular hyperchromatic nuclei rimming individual fat cells. Immunohistochemistry was positive for CD3, CD8, granzyme B, and TIA1. A CD56 stain was negative. CD4 was positive in intermixed macrophages but not in the tumor cells. Karyorrhexis was prominent, with occasional areas of necrosis (**Figures 3–6**). A diagnosis of subcutaneous panniculitis-like T cell lymphoma was made. Subsequently, the patient developed HLH. He met the following criteria for diagnosis of HLH: fever, splenomegaly, hyperferritinemia, hypertriglyceridemia, and cytopenia (anemia and thrombocytopenia). In addition, on scanning the aspirate smear, the bone marrow biopsy demonstrated hemophagocytic histiocytes and was mildly hypercellular (60–70% cellular) with trilineage hematopoiesis

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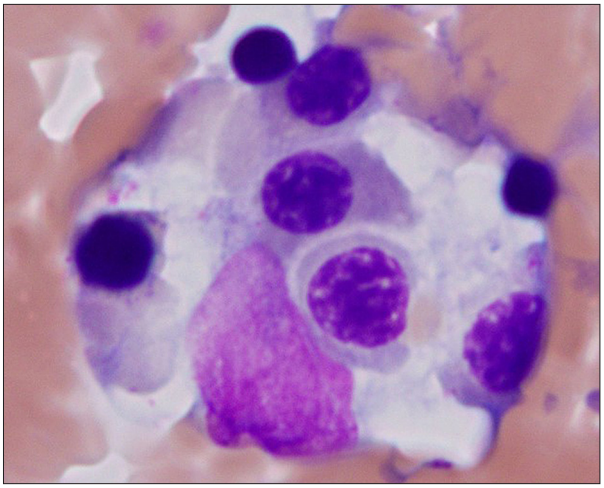

Figure 7. Histiocyte with phagocytosed erythroid precursors (Wright stain, ×100 magnification).

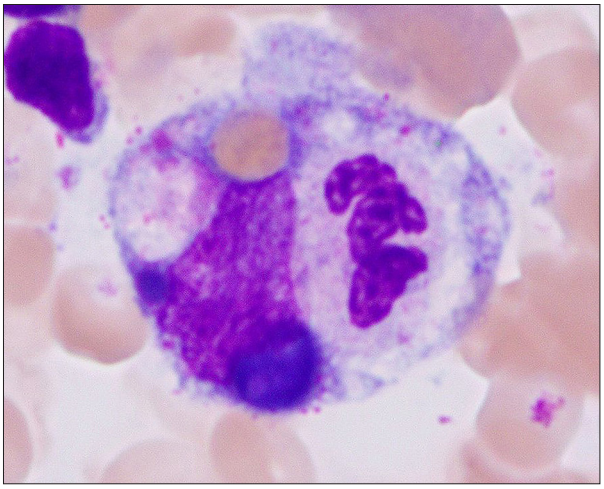

Figure 8. Histiocyte with phagocytosed neutrophil (Wright stain, ×100 magnification).

(**Figures 7–9**). As a result, the patient was started on a cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone, and etoposide phosphate (CHOP-E) chemotherapy regimen. The patient received 7 cycles of chemotherapy over a period of 4 months. Several follow-up positron emission tomography (PET)/CT scans and biopsies showed disease remission and no signs of systemic disease. Subsequently, he underwent another round of chemotherapy to prepare for autologous peripheral blood stem cell transplantation as consolidation therapy.

Discussion

SPTCL has previously had 2 phenotypes that have been reclassified by the WHO. The αβ phenotype is now known as SPTCL and the γδ phenotype has been reclassified to PCGD-TCL [1,10,12]. These diseases have been reclassified because of their differing prognoses and treatment options. Lymphomas with αβ phenotype are CD4–, CD8+, and CD56–. They have an indolent course with a 5-year disease-specific survival rate of 85.7%. Lymphomas with γδ phenotype are CD4–, CD8–, and CD56+ and have an aggressive course [6,12].

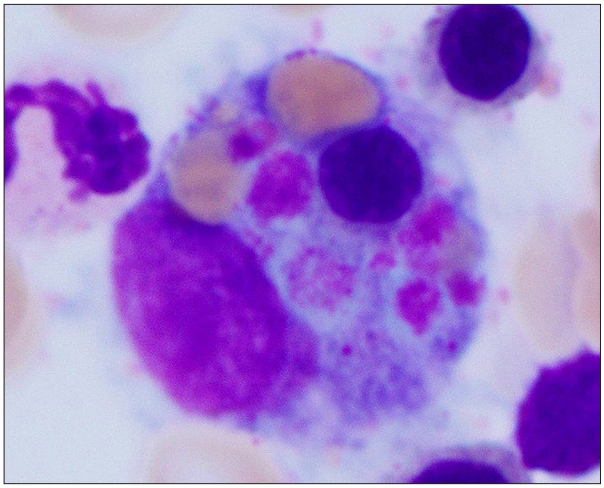

Figure 9. Histiocyte with phagocytosed erythroid precursor and platelets (Wright stain, ×100 magnification).

Histopathologically, these lymphomas are characterized by a dense infiltration of lymphocytes and histiocytes into subcutaneous fat tissue; fat necrosis arranges in a lobular pattern (**Figure 3**) [5,6,12,13]. Cytologically, the atypical lymphocytes present with irregular hyperchromatic nuclei (**Figures 4, 5**) [12]. The most characteristic feature of this disease is the rimming of individual fat spaces by neoplastic lymphocytes (**Figure 6**) [2,6,12].

Clinically and histopathologically, SPTCL can be difficult to distinguish from benign LEP. In addition, patients with cutaneous lymphomas may partially respond to steroid treatment, leading to a delayed actual diagnosis [1,14,15]. LEP is observed in 1–3% of patients with discoid lupus erythematous or systemic lupus erythematous [16]. Histopathologically, benign panniculitis also shows infiltrates containing lymphocytes and histiocytes [6,17]. In addition, rimming of fat lobules by lymphocytes, a typical feature of SPTCL, can be found in up to 45% of LEP cases. However, there are some histopathologic differences. Septal fibrosis, lymphoid follicles, and plasma cells are commonly seen in LEP and are absent in SPTCL. In addition, the presence of predominantly CD8+ T lymphocytes, erythrophagocytosis by histiocytes, and low-density haphazard epitheliotropism by small atypical lymphocytes are mainly seen in SPTCL. Clinically, SPCTL can be distinguished from LEP by the presence of constitutional symptoms [16,18].

The most common documented bone marrow abnormality is HLH, which can present in both phenotypes [12], although it

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is more commonly associated with the γδ phenotype [1]. HLH is seen in 15–20% of patients with SPTCL and has a high mortality rate [5]. Improvements in survival are expected with early diagnosis and treatment. For example, in familial hemophagocytic lymphohistiocytosis, a primary autosomal recessive disorder, the median survival is less than 2 months after diagnosis if untreated [11]. In a retrospective analysis of 162 patients, half of the 68 patient that did not survive died within 1 month of diagnosis, many of whom had hematologic malignancies [19]. Clinical features include cytopenia, fever, splenomegaly, and hepatitis, as seen in our patient. The diagnosis of HLH is made when 5 of the following 8 criteria are met: fever, splenomegaly, bicytopenia, hypertriglyceridemia or hypofibrinogenemia, hemophagocytosis seen on bone marrow biopsy, low/absent natural killer-cell activity, hyperferritinemia, and highly soluble interleukin-2 receptor levels [2,10,11,20,21].

For patients with the indolent αβ T cell receptor phenotype, oral steroids in combination with methotrexate or cyclosporine A are considered first-line therapy [12]. There is no standard chemotherapy regimen for the γδ phenotype or SPTCL not responding to first-line therapy. One of the most common initial regimens is the CHOP-E chemotherapy regimen. Refractory disease is treated with other regimens that commonly include cytarabine and cisplatin [2]. The disease response to chemotherapy is monitored by fluorodeoxyglucose (FDG) PET/CT. When extracutaneous FDG uptake is observed, biopsy confirmation is recommended [12]. For patients who have HLH, initial treatment includes etoposide and dexamethasone as per HLH-94 protocol. The estimated 3-year probability of overall survival in HLH-94 is 55%. Since then, cyclosporin has been added as per HLH-2004 protocol [11]. If patients are refractory to initial treatment, hematopoietic stem cell transplantation (HSCT) is indicated [11,22,23]. Patients undergo pretreatment with chemotherapy regimens such as ranimustine, cytarabine, etoposide, and cyclophosphamide) or ranimustine, carboplatin, etoposide, and cyclophosphamide before autologous peripheral blood stem cell transplantation [2,12,24]. The estimated overall 3-year probability of survival after HSCT for HLH secondary to all causes is 64% [11]. However, 40–70% can have chronic graft versus host disease [2].

Conclusions

Here, we present a case of a patient who was misdiagnosed as having cellulitis and subcutaneous abscesses. He was refractory to multiple courses of antibiotic treatment. He was eventually diagnosed with SPTCL and developed HLH. The differential diagnosis for SPTCL includes eczema, psoriasis, dermatitis, cellulitis, or LEP, making diagnosis difficult. In addition, HLH is more often associated with the PCGD-TCL subtype rather than SPTCL. In patients with HLH, poorer outcomes are observed when there is delayed diagnosis and treatment. Therefore, clinicians should remain vigilant about alternative diagnoses in patients presenting with skin lesions unresponsive to antibiotics and should perform a biopsy sooner to arrive at the correct diagnosis and prevent poor outcomes.

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