Recurrent Fevers and Painful Subcutaneous Nodules: A Case of Subcutaneous Panniculitis-like T-Cell Lymphoma

Rachel L. Axman1, Brian Wolf2, Susan Lin2, Benjamin Schwartz2, Urmi Khanna2, Fahad Zafar2, Melvyn Hecht2, Isabel M. McFarlane1,*

1Department of Internal Medicine, State University of New York, Downstate Health Sciences University, Brooklyn, NY, USA 11203
2Department of Medicine, Maimonides Medical Center, Department of Medicine, Brooklyn, NY 11219
*Corresponding author: Isabel McFarlane@downstate.edu

Received March 04, 2021; Revised April 07, 2021; Accepted April 16, 2021

Abstract Background: Subcutaneous Panniculitis-Like T-Cell Lymphoma is a cytotoxic T-cell lymphoma that infiltrates subcutaneous adipose tissue and rarely involves the lymph nodes. SPTCL accounts for less than 1% of non-Hodgkin’s lymphomas. Lesions are commonly localized to the trunk and lower extremities and may be relapsing and remitting in nature. Systemic symptoms such as fever and night sweats are common. SPTCL may closely mimic cellulitis, and other causes of skin and soft tissue infections. Definitive diagnosis is made with tissue biopsy showing atypical lymphocytes rimming adipocytes. There is no current standard of treatment. Prognosis is favorable with a 5-year survival rate as high as 91%. Case Report: A 40-year-old Chinese female presented with a two-week history of recurrent fevers and painful subcutaneous nodules and plaques, initially thought to be infectious in nature. Tissue sampling demonstrated CD4+ and CD8+ T-cells rimming adipocytes with a high Ki-67 proliferation index and an alpha beta T-cell receptor subtype. A diagnosis of SPTCL was established and the patient was treated with multiagent chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP therapy), which resulted in resolution of her constitutional symptoms and cutaneous. Conclusion: SPTCL is a challenging diagnosis due to the wide array of etiologies of panniculitides and its close clinical resemblance to soft tissue infection. Early tissue biopsy should be employed to expedite management.

Keywords: subcutaneous panniculitis-like t-cell lymphoma, subcutaneous nodules, CD4+/CD8+ T-cells rimming adipocytes

Cite This Article: Rachel L. Axman, Brian Wolf, Susan Lin, Benjamin Schwartz, Urmi Khanna, Fahad Zafar, Melvyn Hecht, and Isabel M. McFarlane, “Recurrent Fevers and Painful Subcutaneous Nodules: A Case of Subcutaneous Panniculitis-like T-Cell Lymphoma.” American Journal of Medical Case Reports, vol. 9, no. 7 (2021): 367-371. doi: 10.12691/ajmcr-9-7-7.

1. Introduction

Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL) is a cytotoxic T-cell lymphoma that preferentially infiltrates the subcutaneous adipose tissue and rarely involves the lymph nodes [1,2,3]. Current data on SPTCL is limited to case reports and small case series due to the rarity of the disease. Thus, there is no standard of treatment established for these patients [4,5]. Resembling panniculitis, SPTCL presents a diagnostic challenge with a differential ranging from infectious, inflammatory, traumatic, or, in our case, malignant etiologies [1,2,3,4,5]. This vast range of possibilities coupled with the low incidence of SPTCL pose a challenge to timely diagnosis and treatment of the disease. This unfortunately delays time to diagnosis and appropriate treatment for the patient as well as incurring excessive hospital resources.

We report a young woman who presented with fever, multiple subcutaneous lesions, and was initially treated for an infectious etiology with antibiotics until a skin biopsy revealed the diagnosis of SPTCL. This case report aims to describe a rare condition that may present as a diagnostic challenge leading to delayed time to diagnosis and increased hospital length of stay as well as to urge for the need for a standard of treatment to avoid dangerous side effects of over-treatment.

2. Case Report

A 40-year-old Chinese female with a past medical history of hyperthyroidism with prior thyroidectomy, presented with a two-week history of persistent fevers and painful subcutaneous nodules with superimposing erythema. The nodules were found on the left lower anterior abdominal wall, mons pubis, right popliteal fossa, and medial left and right thigh (See Figure 1A-D).
Figure 1. Location of subcutaneous nodules on presentation: (A) Left anterolateral abdominal wall, (B) Medial aspect of right thigh (C) Medial aspect of left thigh (D) Right popliteal fossa

Figure 2. Gallium scan showing multiple foci of activity corresponding to subcutaneous nodules, in particular the left anterior abdominal wall and left medial thigh
Four months prior to this presentation, the patient reported three painful abdominal “bumps”, which resolved after a course of trimethoprim/sulfamethoxazole. Initial blood cultures grew gram positive cocci, later determined to be Staph hominis and Staph epidermidis, however all subsequent blood cultures were negative. The patient was found hypotensive with a blood pressure of 100/60 mm Hg, febrile with a temperature of 101.8 F, tachycardic to 118 beats per minute, and had a leukocyte count of 3.5 K/μl (78.1% neutrophils, 15.5% lymphocyte, 5.7% monocyte, 0.2% basophil, 0.5% immune granulocyte); the patient met the criteria for sepsis and admitted for further medical care. The skin lesions at this point were considered erythema nodosum. Vancomycin was started for presumed bacteremia, but subsequent blood cultures did not demonstrate any bacterial growth. The patient continued to have fevers and painful subcutaneous nodules. A detailed sepsis work up, including transthoracic and transesophageal echocardiograms, was negative. A gallium scan showed multiple foci of activity in the soft tissues of the chest, abdomen, pelvis, and thighs (Figure 2) corresponding to the location of the lesions.

Figure 3. Core biopsy sample from the right thigh demonstrating CD4+ and CD8+ T-cells rimming adipocytes with a high Ki-67 proliferation index, consistent with SPTCL: (A) H&E Staining x 10 magnification, (B) Ki-67 Immunohistochemistry staining x 20 magnification, (C) CD-4 Immunohistochemistry staining x 20 magnification, (D) CD-8 Immunohistochemistry staining x 20 magnification

A punch biopsy was obtained from a nodule on the right thigh that demonstrated a T-cell predominance. Although these initial results were largely inconclusive, there were no features consistent with erythema nodosum, the initial outpatient diagnosis. A subsequent core biopsy showed CD4+ and CD8+ T-cells rimming adipocytes with a high Ki-67 proliferation index, consistent with SPTCL (Figure 3A-D). Flow cytometry demonstrated an alpha beta T-cell receptor subtype. One month after her initial presentation, the patient was initiated on a multiagent chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP therapy), which subsequently resulted in resolution of the subcutaneous lesions and persistent fevers. The patient received a total of 6 cycles of chemotherapy every 3 weeks (Figure 4). After the initial chemotherapy treatment, the patient endorsed improvement of her symptoms and resolution of the pain around previous nodule sites.

Figure 4. Resolution of subcutaneous nodules and plaques after CHOP therapy
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was first described by Gonzalez et al in 1991 as a lymphoma derived from cytotoxic T-cells that preferentially involved subcutaneous tissue. [1] A decade later, in 2001, it was recognized as a distinct neoplasm by the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues. Then in 2008, the WHO restricted SPTCL to the cytotoxic T-cell alpha-beta phenotype, separating the disease from the more aggressive gamma delta phenotype, the latter of which is now a new category of T-cell lymphoma [1,2,3,4,5,6,7,8,9]. SPTCL accounts for less than 1% of all non-Hodgkin’s lymphomas, but the true incidence is likely lower due to the previous grouping of the alpha-beta phenotype and gamma-delta phenotype together [1,2,3,4,5]. It bears a favorable prognosis with a 5-year survival rate as high as 91%, but can be difficult to diagnose given the extensive differential diagnosis for panniculitis including erythema nodosum, benign panniculitis, and lupus panniculitis, the latter of which can be especially challenging to distinguish [6,7,8,9,10].

Epidemiologic studies elicited an increased incidence of this condition in females (male: female ratio of 0.5) with the average age of onset being 36 (range of 9-79 years) [1,2,3]. A meta-analysis of 16,953 patients with cutaneous T-cell lymphomas, demonstrated a 15% increase in frequency in Asian populations of all cutaneous T-cell lymphomas and an even greater increase when looking specifically at SPTCL [4]. In a case series of 63 patients, a history of autoimmune disease was reported in 19% of cases. [3]

SPTCL often follows an indolent clinical course, with subtle painless lesions in the beginning of the disease process that appear similar to benign dermatologic conditions. SPTCL lesions are typically non-ulcerated, multifocal and commonly found on the trunk and lower extremities, but lesions on the upper extremities and face have also been reported [1,2,3,4,5,6,7,8,9]. By contrast, Lupus erythematosus profundus (LEP) lesions are typically ulcerated and present on the head and face [4,6,8,10]. Erythema nodosum are classically localized to the shins. [8] SPTCL lesions tend to spontaneously regress early on in the disease process, which was notably reported by our patient. As a result, the lesions can appear to be in multiple stages of healing. Systemic symptoms, such as fever and weight loss, are reported in approximately half of cases [4]. In contrast to the nodules that our patient had, typically lesions are non-painful [2,3,4,11]. Rarely symptoms such as periorbital edema and facial edema may be present [12]. Serious sequela of SPTCL include hemophagocytosis syndrome (HPS), anemia, pancytopenia, and pleural effusions. HPS, a systemic cytokine response, presents as fever, hepatosplenomegaly, pancytopenia, and coagulopathy and is considered a poor prognostic sign. It is seen an estimated 15-20% of cases of SPTCL and approximately 45% of cutaneous γδ T-cell lymphoma cases [2,3,4,5,7,13].

While clinical features help to raise suspicion of SPTCL, a definitive diagnosis cannot be made without a biopsy. The histopathological feature most consistent with SPTCL is rimming of adipocytes with neoplastic T-cells containing hyperchromatic nuclei and irregular nuclear membranes [3,14]. This infiltration rarely extends to the superficial dermis or epidermis. Likewise, angioinvasion is uncommon [3,4,14]. Fat necrosis and karyorrhexis may be seen. The neoplastic cells are CD3+, CD4-, CD8+, and CD56-[1,2,3,4]. Fine Needle Aspirate Cytology (FNAC) may be used to aid in the diagnosis as well. Aspirate from a swelling of SPTCL shows cellular atypical lymphoid cells, admixed with clusters of adipocytes, and rare plasma cells and neutrophils, compared to a high abundance of plasma cells and neutrophils in panniculitis lesions. [14]

Chemotherapy (single or multimodal) was the standard of care when both the alpha-beta and gamma-delta subtype were considered SPTCL, but after the distinction of the gamma-delta type in 2008, it remains unclear whether chemotherapy is necessary in alpha-beta SPTCL cases. [11,13,15,16,17,18,19] There are reports of alpha-beta patients responding to corticosteroids and immunosuppressive therapy, such as cyclosporine alone as well as Bexarotene [4,7,8,13,17,18]. However, these reports are either case reports or small series, prompting the need for further investigation to determine the most effective treatment. Our patient successfully tolerated CHOP therapy, with the only side effect being leukopenia, to 0.4 K/μl, with 3.6% neutrophils, which improved to 5 K/μl, with 69.1% neutrophils, after treatment with pegfilgrastim. She remains in remission and is under regular follow up with the hematology-oncology division.

4. Conclusion

SPTCL is an exceedingly rare condition. Although it bears a favorable prognosis, it can be very challenging to diagnose. Significant advances in our understanding of this pathology have been made since its first description in 1991. Global epidemiology studies elicit certain risk factors such as female sex, and Asian descent. However, what remains challenging about SCPL T-cell lymphoma is that it includes a wide differential diagnosis. Systemic symptoms may act as a distractor and prompt an investigation into an infectious etiology, such as what we saw with this particular patient. This unfortunately delays time to diagnosis and appropriate treatment for the patient as well as incurring excessive hospital resources. Therefore, it is important to consider the diagnosis of SPTCL when a patient has painful, relapsing panniculitis-like lesions particularly on the trunk and lower extremities, persistent fever or other systemic symptoms, and demographics such as young adult, female gender, history of autoimmune disease, and Asian descent.

Acknowledgements

The photographs included in this publication were obtained with the patient’s permission.

References

[1] Gonzalez CL, Medeiros LJ, Braziel RM, et al. T-cell lymphoma involving subcutaneous tissue: a clinicopathologic entity commonly associated with hemophagocytic syndrome. Am J Surg Pathol. 1991; 15: 17-27.
[2] Parveen Z, Thompson K. Subcutaneous Panniculitis-like T-Cell Lymphoma: Redefinition of Diagnostic Criteria in the Recent World Health Organization–European Organization for Research and Treatment of Cancer Classification for Cutaneous Lymphomas. Arch Pathol Lab Med. 1 February 2009; 133(2): 303-308.

[3] Willemsz R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 Cases. Blood. 2008 Jan 15; 111(2): 836-45.

[4] Dobos G, Pohrt A, Ram-Wolff C, et al. Epidemiology of Cutaneous T-Cell Lymphomas: A Systematic Review and Meta-Analysis of 16,953 Patients. Cancers (Basel). 2020 Oct 11; 12(10): 2921.

[5] Mischick SR, Lynch DT. Subcutaneous Panniculitis Like T-cell Lymphoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Nov 9.

[6] López-Lerma I, Peñate Y, Gallardo F, et al. Subcutaneous panniculitis-like T-cell lymphoma: Clinical features, therapeutic approach, and outcome in a case series of 16 patients. J Am Acad Dermatol. 2018 Nov; 79(5): 892-898.

[7] Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program. 2009; 523-31.

[8] Requena L, Yus ES. Panniculitis. Part II. Mostly lobular panniculitis. J Am Acad Dermatol. 2001 Sep; 45(3): 325-61; quiz 362-4.

[9] Jaffe ES, Harris NL, Stein H, Vardiman JW. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumours. Lyon, France: IARC Press, 2001; pp. 351–352.

[10] Gonzalez EG, Selvi E, Lorenzini S, et al. Subcutaneous panniculitis-like T-cell lymphoma misdiagnosed as lupus erythematosus panniculitis. Clin Rheumatol. 2007; 26: 244-246.

[11] Guenov E, Schanz S, Hoetzeneker W, et al. Systemic corticosteroids for subcutaneous panniculitis-like T-cell lymphoma. Br J Dermatol. 2014 Oct; 171(4): 891-4.

[12] Hashimoto R, Uchiyama M, Maeno T. Case report of subcutaneous panniculitis-like T-cell lymphoma complicated by eyelid swelling. BMC Ophthalmol. 2016; 16: 117. Published 2016 Jul 20.

[13] Rojnuckarin P, Nakorn TN, Assanasen T, et al. Cyclosporin in subcutaneous panniculitis-like T-cell lymphoma. Leuk Lymphoma. 2007 Mar; 48(3): 560-3.

[14] Gochhait, D., Kekade, S., Devi, D., Srinivas, B. H., Siddaraju, N., & Chandrashekar, L. (2019). Subcutaneous Panniculitis-Like T Cell Lymphoma: Approach to Differential Diagnosis on Cytology. Journal of Adolescent and Young Adult Oncology.

[15] Fuji K. New Therapies and Immunological Findings in Cutaneous T-Cell Lymphoma. Front Oncol. 2018 Jun; 8: 198.

[16] Mizutani S, Kuroda J, Shimura Y, et al. Cyclosporine A for chemotherapy-resistant subcutaneous panniculitis-like T-cell lymphoma with hemophagocytic syndrome. Acta Haematol. 2011; 126(1): 8-12.

[17] Mehta N, Wayne AS, Kim YH, et al. Bexarotene is active against subcutaneous panniculitis-like T-cell lymphoma in adult and pediatric populations. Clin Lymphoma Myeloma Leuk. 2012 Feb; 12(1): 20-5.

[18] Michonneau D, Petrella T, Ortonne N, et al. Subcutaneous Panniculitis-like T-cell Lymphoma: Immunosuppressive Drugs Induce Better Response than Polychemotherapy. Acta Derm Venereol. 2017; 97(3): 358-364.

[19] Zhang H, Gupta R, Wang JC, et al. Subcutaneous panniculitis-like T-cell lymphoma in a patient with long-term remission with standard chemotherapy. J Natl Med Assoc. 2007 Oct; 99(10): 1190-2.