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Subcutaneous Panniculitis-like T-cell Lymphoma: Review of Therapies

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Abstract

Subcutaneous Panniculitis-like T-cell Lymphoma (SPTCL) is a rare subtype of cutaneous T-cell lymphoma derived from alpha/beta cytotoxic T-cells. It is known to follow an indolent course with a favorable prognosis. We review current therapies used to treat this rare entity in order to increase awareness about possible options. No standardized therapy for SPTL currently exists. Local radiotherapy for indolent local disease has been found successful. For indolent disease with a more generalized distribution, immunosuppressive agents as well as low-dose chemotherapy may be used. For aggressive presentations, combination chemotherapy, anthracycline-based regimens, fludarabine-based regimens, and rarely high-dose chemotherapy followed by hematopoietic stem cell transplant (SCT) with moderate success. By being aware of possible therapeutic options, a physician can recommend the most appropriate treatment for the individual.

Keywords: Panniculitis-like T-cell lymphoma; Chemotherapy; Hematopoietic stem cell transplant

Background

Subcutaneous Panniculitis-like T-cell Lymphoma (SPTCL) is a rare cutaneous neoplasm of mature cytotoxic T cells. It presents with multiple skin colored to erythematous subcutaneous nodules, most often on extremities and trunk, but can also involve the face, back, and neck [1]. Cutaneous lesions can occur with systemic symptoms such as fever, malaise, anorexia, and weight loss; they can also cause lipodystrophy after resolution. While extra-cutaneous involvement is uncommon, there have been reports of bone marrow, lymph node, liver, spleen, lung, peripheral blood involvement, and even spontaneous regression [2-10]. The average age of presentation is mid to late thirty with a female predominance (male: female=0.5) [2].

SPTCL is associated with autoimmune disease in 20% of patients, specifically lupus erythematous (LE), juvenile rheumatoid arthritis, Sjogren disease, type I diabetes mellitus, idiopathic thrombocytopenia, multiple sclerosis, Kikuchi disease, and Raynaud disease [11-13]. It was recognized as a separate entity in the World Health Organization (WHO) classification based on observation of 83 cases and was subdivided into two entities in an updated classification based on clinical, pathological, immunophenotypical, and genotypical features [14]. It is recognized by its α/β T-cell receptor phenotype, indolent course, and more favorable prognosis. Primary cutaneous T-cell lymphoma (PCTCL), once grouped together with SPTCL, has a γ/δ T-cell receptor phenotype, is aggressive and has a poorer prognosis, and causes an increased risk of developing hemophagocytic syndrome (HPS) with the associated multi-organ complications [2]. HPS is characterized by fever, pancytopenia, hepatosplenomegaly, and coagulopathy and is associated with an aggressive outcome [10]. PCTCL tends to have metasis to various organs including lungs, liver, kidneys, and central nervous system. CD56 is an important marker in T-cell lymphomas of worse outcome in view of disseminated disease and hemophagocytosis [7]. PCTCL is usually CD56 positive and SPTCL is CD56 negative. The overall five year survival rate for SPTCL exceeds 80%; however, in the presence of HPS, it reduces to less than 50%. In cases of PCTCL, the five year survival rate is less than 20% [2]. Both comprise less than 1% of all T-cell lymphomas [15,16].

SPTCL is a challenge to diagnose histopathologically because the cytology can mimic nonspecific panniculitis or lobar panniculitis [15]. CD3+/CD4-/CD8+ cytotoxic T cells are present in the subcutaneous tissue mimicking panniculitis. The histopathologic differential diagnosis includes lupus panniculitis (lupus profundus) which presents clinically as indurated plaques on face, arms, trunk, breasts, buttocks, and thighs and clonality studies are needed to further differentiate. Atypical lymphocytic infiltrate with hyperchromatic nuclei are present and described as "rimming" individual adipocytes, although this is not specific. In the early stage, a heavy inflammatory infiltrate may predominate as the neoplastic infiltrates may lack significant atypia [17-19].

Imaging studies are used for further localization of nodules. CT shows multiple enhancing nodules in subcutaneous layer of involved body site [20], however this is also found in inflammatory panniculitis associated with systemic lupus erythematosus or rheumatoid arthritis, subcutaneous metastases from malignant melanoma or breast cancer, and nodules originating from bacterial and fungal infections or from parasitic infestations [21]. Studies have indicated the superiority of PET/CT over CT alone in detecting nodal involvement as it can help localize and augment the effectiveness of CT [22-25]. F-18 FDG-PET/CT is valuable for diagnostic work-up, staging, monitoring of response to therapy and recurrences, and detecting extracutaneous lesions [26].

Case 1

This is a 63 year old male with recurrent SPTCL (biopsy proven), status post bexarotene (4-6/2014; 2009-2010), radiotherapy to tumor nodule of left back (7/2014), MTX (8-11/2014), and romidepsin (11-12/2014), who admitted (1/2015) for recurrent fevers, and found to have thrombocytopenia (platelets of 5000) without any active bleeding. Past medical history was positive for asthma and disability due to exposures at Ground Zero. Patient denied any surgeries, family history of cancers, allergies, and toxic habits. Physical examination revealed multiple ulcerating lesions on bilateral extremities, without oozing, odor, bleeding, or surrounding erythema. Bone marrow biopsy revealed PCTCL, for which patient was given etoposide, filgrastim, allopurinol, and neupogen (Figures 1-3).

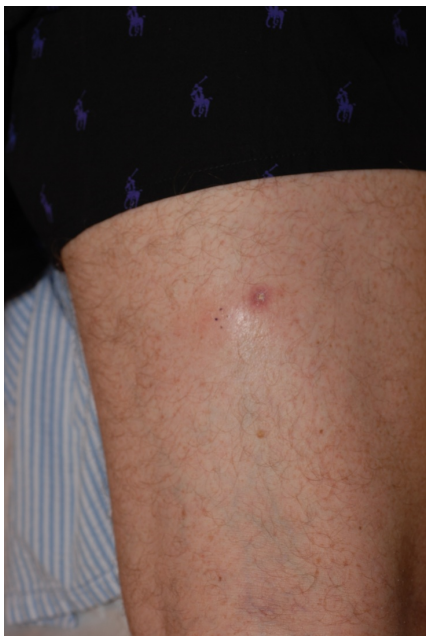

Figure 1: This is a 63 year old male who was diagnosed initially as SPTCL and treated with bexarotene in 2009.

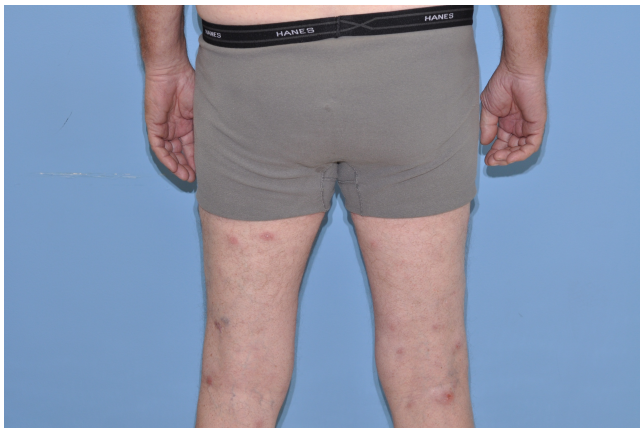

Figure 2: In 2014, Patient developed multiple recurrent SQ nodules.

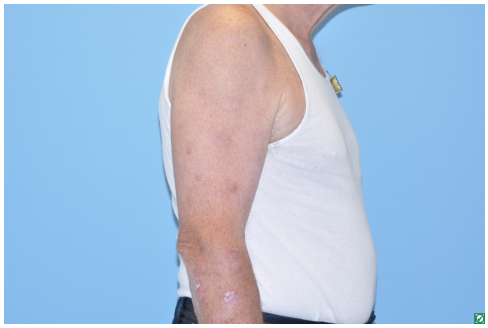

Figure3: Patient now had more ulcerating nodules.

Case 2

This is a 47 year old female with recurrent high fevers, parotid/submandibular/cervical lymphadenopathy and tender nodules on her legs (4/2014). Skin biopsy showed SPTCL. She had no response to MTX after 6 months. Past medical history is positive for discoid lupus erythematous for which she was treated with high dose steroids, azathioprine, and mycophenolic acid. Patient was started on bexarotene (2/2015) and responded with remission (Figures 4 and 5).

Figure 4: This is a 47 year old female with tender nodules on chest and legs.

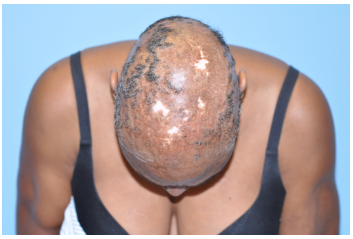

Figure 5: This is the same patient with discoid lupus erythematous on her scalp.

Discussion

Due to rarity of disease, no standardized therapy for SPTL currently exists. In general, for indolent local disease, local radiotherapy can be

used as an effective treatment modality [3,10,13,18,27,28]. For indolent disease with a more generalized distribution, immunosuppressive agents such as prednisone and cyclosporine, or systemic biologic agents, such as bexarotene and interferon, as well as low-dose chemotherapy with agents such as methotrexate may be used. Complete sustained remission with corticosteroids and MTX has been reported in one case report [29]. For aggressive presentations, combination chemotherapy such as CHOP (cyclophosphamide, Adriamycin, vincristine, prednisone), anthracycline-based regimens, fludarabine-based regimens, and rarely high-dose chemotherapy followed by hematopoietic stem cell transplant (SCT) with moderate success [3,10,14,19,27,28,30-34] . Fludarabine-based chemotherapies have shown overall remission rates of more than 70% in a few case reports [35,36]. Doxorubicin-based therapies have achieved complete or partial complete remission rates of 50% [37]. Because the presence of HPS at diagnosis is one of the most important prognostic factors that predict poor overall survival, it may be a useful parameter to determine if disease is indolent or aggressive [2,10]. The other factors associated with an unfavorable prognosis are low white blood count or elevated lactate dehydrogenase (LDH) [4].

The data on steroid use for the treatment of SPTCL show conflicting results. In a retrospective review of 156 patients, a 50% overall response rate with steroids was noted; however, duration of response was less than 6 months [10] and only 20% of these patients maintained a sustained remission (median 36.5 months). Combination chemotherapy resulted in 53% ORR after use of CHOP, but the responses were inconsistent in distribution with a range of 2-72 months. Thirteen patients with refractory disease were treated with high-dose chemotherapy followed by HSCT, with 92% achieving complete remission with a median duration for >14 months [4,10]. Another retrospective cross-sectional study based on a patient data repository from two tertiary care university hospitals in Switerzland and Germany found four of the five patients (80%) with SPTCL to undergo a complete remission after being treated with systemic corticosteroids [38]. A case has also been made of SPLTC being treated successfully with systemic steroids only [39].

There have also been conflicting results about the role of up-front anthracycline based combination chemotherapy. Patients with SPTCL were shown to have an overall response of 53% and median duration of complete remission of more than 11.5 months with CHOP or CHOP-like therapies [10]. A case report showed durable remission in a patient with SPTCL with HPS after CHOP [40]. However, another report showed only 2 of 11 SPTCL patients with HPS had durable survival after CHOP or CHOP-like therapies [2]. In another case, although remission was achieved with CHOP therapy, the duration was short [41]. A case of SPTCL with HPS resistant to CHOP regimen achieved complete remission after combination chemotherapy using BFM-90 protocol [35]. Thus, anthracycline based chemotherapy is not very successful in patients with SPTCL associated with HPS.

Autologous HSCT (hematopoietic stem cell transplant) is the standard consolidation treatment after salvage chemotherapy in a relapsed lymphoma, provided the lymphoma has been chemosensitive to the conventional salvage chemotherapy regimen. However, the role of autologous HSCT in the SPTCL has not been clarified because most information comes from case series. Some patients with SPTCL have recently undergone high dose chemotherapy followed by autologous HSCT, and most of them achieved complete remission with a median follow-up of 14 months but the possibility that failure after HSCT may be under-reported cannot be ruled out [2,4,31,33,42].

Cyclosporine is a calcineurin inhibitor and is a potent immunosuppressant. The mechanism of action of cyclosporine in SPTL is thought to be down regulation of cytokines as serum levels of interferon gamma and soluble interleukin-2 receptor were elevated during the active disease but normalized after cyclosporine [43]. Several reports suggest that SPTCL patients without HPS may benefit from cyclosporine and steroids [2,44]. Upfront use of cyclosporine was able to maintain durable remission in patient with disseminated SPTCL [37]. A 22-year-old girl with disseminated SPTCL attained complete clinical remission with single agent oral cyclosporine used as a first line therapy. A study with prednisolone (60 mg/day) and cyclosporine A (150 mg/day) showed a patient with SPTCL complicated by HPS was asymptomatic for at least 6 months [45]. A patient with recurrent SPTCL achieved a second long-term complete remission by repeated cyclosporine treatment [46]. From 2000 to 2001, the patient received anthracycline-based combination chemotherapy. However, the treatment did not induce long-term remission. In 2002, he received cyclosporine treatment for about 6 months. This resulted in a 5-year remission that ended in relapse in 2008. He received CsA treatment once again and attained a second long-term remission. This case suggests that re-treatment with CsA can be a good option for relapsed SPTCL cases and can result in long-term remission.

Romidepsin monotherapy has been reported to successfully treat two cases of patients with SPTCL and clinical features suggestive of HPS [47]. It is indicated for the treatment of the most common cutaneous T-cell lymphomas, mycosis fungoides and Sezary's syndrome, in patients with failed prior systemic therapy [48,49]. It is a potent histone deacetylase inhibitor isolated from *Chromobacterium violaceum* [50]. By inhibiting the acetylation of histone and nonhistone proteins, which broadly affects gene expression by enhancing cell-cycle arrest, apoptosis, growth inhibition, chromatin remodeling, tumor-suppressor gene transcription, and cellular differentiation [48,49,51-56].

Bexarotene is an oral retinoid (derivative of vitamin A) approved for treatment of Mycosis Fungoides. As a selective retinoid X receptor agonist, it Inhibits cell cycle progression, induces apoptosis and differentiation, prevents multidrug resistance, and inhibits angiogenesis and metastasis [57]. However, it is believed bexarotene's primary action is through inducing apoptosis of T-cells [58]. In a study done at our institution, 15 patients were treated with bexarotene. ORR was 77% with 54% CR and 23% PR. Median progression free survival 38.4 months and median duration of response was 26.3 months [30]. The most common toxicities noted with bexarotene are similar to those observed in patients with other types of cutaneous T-cell lymphomas including hypothyroidism and hypertriglyceridemia [59-62]. It represents a less toxic alternative to chemotherapy that can result in durable disease control. Patient 1 responded favorably to bexarotene for 5 years. However, upon relapse, the conversion of SPTCL to PCTCL is a new finding that has not been reported before. Clonal switching in this manner is unique and the exact mechanism requires further investigational studies. Patient 2 is currently undergoing bexarotene treatment.

Biologics have also been used to treat SPTCL. Denileukin diftitox was reported in two cases with duration of response for 6 months and more than 18 months [63]. Clinical regression of disease with corticosteroids and denileukin diftitox was seen in two cases with median duration of response for 6 months and more than 18 months. Furthermore, the addition of bexarotene to denileukin diftitox restored a clinical response in 1 of the patients after disease

progression, suggesting the activity of this combination in patients with SPTCL. McGinnes et al. reported a case with 9 month duration of response after Denileukin diftitox [64]. Interferon alpha is also reported to be active in refractory SPTCL [10].

The pathogenesis of SPTCL remains unclear. Many malignant lymphomas are induced by chronic inflammation secondary to a viral or bacterial infection. EBV is well known to cause malignant lymphomas of B-cell type. Although SPTCLs are usually negative for EBV [3,18,65], it has been found to occur in the Asian population [66]. SPTCL associated with an EBV infection has an aggressive biologic behavior [67,68]. Staining for EBV may be a valuable adjunct in differentiating SPTCL from extranodal natural killer (NK)/T-cell lymphoma, nasal type, which may sometimes also present with prominent subcutaneous involvement [3,65]. One particular case report of NK/T-cell lymphoma had clinical and morphological features that resembled SPTCL, however further testing of the neoplastic cells revealed EBV positivity with perinuclear polyclonal CD3 staining and membranous CD56 reactivity suggestive of NK/T-cell lymphoma [69]. The authors did not find any studies correlating other herpes viral infections with SPTCL. Bacterial infection may cause lobular panniculitis mimicking SPTCL [70], however a more prominent association with SPTCL has not been reported.

The Initial diagnosis of SPTCL may be elusive and delayed, due to its indolent nature, systemic manifestations, and similarity to inflammatory or infectious processes. For this reason, whole-body MRI has been proposed as an initial and follow-up imaging modality to assess SPTCL [71]. On MRI, nodular enhancing areas can be seen infiltrating the subcutaneous tissues with surrounding lymphatic congestion. An area of intermediate T2-weighted signal (relative to skeletal muscle) can be seen at the center of the lesions that is helpful in differentiating a peripheral T-cell lymphoma from an inflammatory or infectious process. Thus, the differential diagnosis of SPTCL on MRI may include rheumatoid nodules, connective tissue diseases such as lupus [72], infectious etiologies, or metastasis from melanoma or primary breast cancer.

The relationship between SPTCL and lupus erythematous panniculitis [72], which may be indistinguishable clinically, is controversial [73,74]. In a detailed report on 11 cases of LEP, Massone et al. proposed histopathological criteria that would assist in differentiating between these two entities, thereby suggesting they are separate entities [73]. Useful histopathologic criteria favoring a diagnosis of LEP included epidermal involvement, mucin depositions, the presence of reactive germinal centers, clusters of B cells or considerable numbers of admixed plasma cells, and polyclonal TCRgamma gene rearrangement. In contrast, Margo et al. emphasized the overlapping features between LEP and SPTCL, thereby suggesting both conditions form a spectrum of disease [74]. Willemze et al. make a case for screening all suspected SPTCL cases for LE as four SPTCL patients had a definitive diagnosis of LE and at least four SPTCL patients had initially been misinterpreted as lupus panniculitis [14]. The group advocated for the preferential use of systemic steroids over systemic chemotherapy. Thus, clinical features, histopathology, immunophenotyping, molecular analysis, and repeat biopsies are needed to differentiate malignant lymphomas involving the subcutis from LEP.

Conclusion

Clinicians should be aware of the clinical presentation of SPTCL as it an indolent disease that has a favorable prognosis with treatment. While no standardized treatment regimen exists, various options are available depending on the severity. By being aware of possible therapeutic options, a physician can recommend the most appropriate treatment for the individual.

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