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Clinical and Pathological Characteristics and Outcomes Among Patients With Subcutaneous Panniculitis-like T-Cell Lymphoma and Related Adipotropic Lymphoproliferative Disorders

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IMPORTANCE There is a knowledge gap about subcutaneous panniculitis-like T-cell lymphoma (SPTCL) owing to its rarity and diagnostic difficulty, resulting in an absence of well-documented large case series published to date.

OBJECTIVE To generate consensus knowledge by a joint multi-institutional review of SPTCL and related conditions.

DESIGN, SETTING, AND PARTICIPANTS This retrospective clinical and pathological review included cases initially diagnosed as SPTCL at 6 large US academic centers. All cases were reviewed by a group of pathologists, dermatologists, and oncologists with expertise in cutaneous lymphomas. Through a process of group consensus applying defined clinical and pathological diagnostic criteria, the cohort was classified as (1) SPTCL or (2) adipotropic lymphoproliferative disorder (ALPD) for similar cases with incomplete histopathological criteria for SPTCL designation.

EXPOSURES Cases of SPTCL diagnosed between 1998 and 2018.

MAIN OUTCOMES AND MEASURES The main outcome was disease presentation and evolution, including response to therapy, disease progression, and development of hemophagocytic lymphohistiocytosis.

RESULTS The cohort of 95 patients (median [range] age, 38 [2-81] years; female-to-male ratio, 2.7) included 75 cases of SPTCL and 20 cases of ALPD. The clinical presentation was similar for both groups with multiple (61 of 72 [85%]) or single (11 of 72 [15%]) tender nodules mostly involving extremities, occasionally resulting in lipoatrophy. Hemophagocytic lymphohistiocytosis (HLH) was only observed in SPTCL cases. With a mean follow-up of 56 months, 60 of 90 patients (67%) achieved complete remission with a median (range) of 3 (1-7) cumulative therapies. Relapse was common. None of the patients died of disease progression or HLH. Two patients with ALPD eventually progressed to SPTCL without associated systemic symptoms or HLH.

CONCLUSIONS AND RELEVANCE In this case series of patients initially diagnosed as having SPTCL, results showed no evidence of systemic tumoral progression beyond the adipose tissue. The SPTCL experience in this study confirmed an indolent course and favorable response to a variety of treatments ranging from immune modulation to chemotherapy followed by hematopoietic stem cell transplantation. Morbidity was primarily associated with HLH.

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Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was initially reported by Gonzalez et al[1] and accepted as a distinct entity by the World Health Organization[2] in 2001, depicting a lymphoma with a dismal prognosis mostly accentuated by the inclusion of subcutaneous γδ T-cell lymphomas in the same category. The distinction between αβ and γδ T-cell lymphomas presenting with a panniculitis-like pattern was not possible until reliable anti-T-cell receptor (TCR) heterodimer markers for routine histology became available in the early 2000s. The first and only, to our knowledge, large series of SPTCL was published by Willemze et al[3] in 2008, with 63 cases excluding γδ T-cell lymphomas. The diagnosis of SPTCL has remained challenging owing to frequent cases demonstrating subtle atypia, T-cell clonality, and overlapping features with SPTCL and lupus erythematosus panniculitis (LEP).[4,5] While genome sequencing has not identified common drivers of other T-cell lymphomas, recent reports of frequent *HAVCR2* germline biallelic alterations in SPTCL have raised the hypothesis of an immune dysregulation with the potential risk of hemophagocytic lymphohistiocytosis (HLH).[6]

Owing to the rarity of SPTCL, changing definitions for subcutaneous tissue lymphomas, and the unsettled diagnostic classification for the aforementioned ambiguous presentations, substantial uncertainty remains regarding reliable diagnostic criteria and therapeutic guidelines for SPTCL. This collaborative multicenter study aims to evaluate a large cohort of patients with SPTCL and related subcutaneous lymphocytic conditions, with the goal of describing their clinical and pathological presentation, therapeutic management, disease course, and outcome.

Key Points

Question What can we learn about subcutaneous panniculitis-like T-cell lymphoma (SPTCL) from the joint experience of 6 large US academic cutaneous lymphoma centers?

Findings In this case series of 95 patients (75 with SPTCL and 20 with adipotropic lymphoproliferative disorder), there was a broad spectrum of SPTCL presentations from an indolent subcutaneous lymphoid infiltrate to cases with potential life-threatening hemophagocytic syndrome; however, no metastatic involvement of mesenchymal organs or lymph nodes was identified. Patients with SPTCL showed a good response to a variety of therapies ranging from immunomodulatory therapies to chemotherapies followed by hematopoietic stem cell transplantation.

Meaning Subcutaneous panniculitis-like T-cell lymphoma can be challenging to diagnose and has a diverse spectrum of clinical presentation, response, and outcome; the rarity of this condition calls for international collaboration to establish diagnostic and therapeutic guidelines.

Methods

This retrospective, multicenter cohort study is the result of 2 workshops attended by the same group of pathologists, oncologists, and dermatologists with expertise in cutaneous lymphomas from 6 large academic centers with the goal to review each institutional experience with SPTCL and related subcutaneous lymphocytic conditions. The study was approved under the Northwestern University Institutional Review Board (STU00200981) under an institutional review board–approved Northwestern University Cutaneous Lymphoma umbrella project encompassing all centers. All data reviewed were deidentified and participant consents were obtained (or waived) following each institutional policy.

Electronic medical records were reviewed to abstract data including staging results, laboratory and imaging findings, response to therapy, and outcomes. These data were presented to the group for collective review and discussion. Three categories were used to define extent of skin involvement: T1 = solitary skin lesion; T2 = multiple lesions limited to 1 or 2 adjacent anatomical regions; T3 = generalized skin involvement.[7] We captured the designation of HLH cases as diagnosed at each institution and corroborated the diagnosis with assessment of a score for the diagnosis of reactive hemophagocytic syndrome called the HScore and enumerating defining criteria for each case.[8,9] Histopathological and immunohistochemistry material was also reviewed by the group. Based on the combination of clinical, histopathological, and immunophenotypic features, a consensus diagnosis was rendered.

Eligibility criteria included patients presenting with subcutaneous nodules showing a predominantly lobular infiltrate predominantly composed of lymphocytes with atypia expressing CD8 and βF1 (αβ TCR heterodimer marker) and assessed to be consistent with SPTCL. The lymphoid infiltrate had to be negative for Epstein-Barr virus RNA expression using Epstein-Barr encoding region in situ hybridization and γ or δ TCR markers (clone γ3.20, Thermo Fisher Scientific; and H-41, Santa Cruz Biotechnology). An extensive immunohistochemistry panel of monoclonal antibodies against CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD45RA, CD56, TIM-3 (ab241332; Abcam), TIA-1 (T-cell–restricted intracellular antigen 1), granzyme B, and TCR clonality analysis by polymerase chain reaction or high-throughput sequencing was performed in most cases.

Skin biopsies including subcutaneous tissue from 106 identified patients were reviewed, and 11 cases were excluded because of insufficient clinical data or inadequate pathology material. Several histological parameters—including the distribution, morphology, and density of the lymphoid infiltrate; presence or absence of epidermal necrosis; interface reaction; hemorrhage; vasculitis; granuloma formation; mucin deposits; karyorrhexis; or hemophagocytosis—were assessed by the group on a multiheaded microscope. Microscopic review of cases, including measurement of histologic and immunohistochemical data points classic for SPTCL, was performed simultaneously by the group while presenting basic clinical data of each case, as is routinely done in dermatopathology. For a case to be included in the cohort and designated as SPTCL or ALPD, there had to be agreement among the panel of 6 dermatopathologists that the case could reproducibly be included under that designation. While some cases engendered scholarly debate, consensus by a supermajority was ultimately reached in the included cases. The 95 selected cases were classified as SPTCL or ALPD, the latter term designating

Table 1. Patient Population Characteristics

Characteristic	No. (%)		
	SPTCL and ALPD (n = 95)	SPTCL (n = 75)	ALPD (n = 20)
Age, median (range), y	38 (2-81)	38.5 (2-80)	32 (3-81)
Female-to-male ratio	2.7	2.5	3.8
Duration until diagnosis, mo	26.4	18.7	56.6
Autoimmune diseases	23/85 (27)	18/66 (27)	5/19 (26)
Lupus erythematosus	7/85 (8)	5/66 (8)	2/19 (10)
Family history: autoimmunity	9/71 (13)	8/53 (15)	1/18 (6)
Disease extent (T1-T3)			
T1	11 (12)	11 (15)	0
T2	37 (39)	28 (37)	9 (45)
T3	47 (50)	36 (48)	11 (55)
Lipoatrophy	23/79 (29)	19/63 (30)	4/16 (25)
Anatomical involvement			
Head and neck	26/93 (28)	20/74 (27)	6/19 (32)
Trunk	51/93 (55)	43/74 (58)	8/19 (42)
Upper extremities	49/93 (53)	39/74 (53)	10/19 (53)
Lower extremities	63/93 (68)	47/74 (62)	16/19 (84)

Abbreviations: ALPD, adipotropic lymphoproliferative disorder; SPTCL, subcutaneous panniculitis-like T-cell lymphoma.

cases with incomplete histopathological criteria and failure to achieve group consensus for a diagnosis of SPTCL. We realize that the diagnostic designations of SPTCL and ALPD are imperfect because the conditions overlap, but in general, ALPD cases were deemed histopathologically suspicious or borderline for SPTCL but did not meet criteria for definitive diagnosis as SPTCL, characterized by a lower density of predominantly small lymphocytes with minimal atypia and a low proliferative rate. In addition, ALPD was characterized by a mixture of CD4-positive and CD8-positive T cells with scattered B cells within the infiltrate but lacking the overwhelming CD8-positive population of bona fide SPTCL. Clinically, the course was mostly indolent without constitutional symptoms or HLH.

Descriptive statistics including medians (with ranges) and counts (with percentages) were determined and compared using Mann-Whitney *U* and Fisher exact tests, respectively. Because this was a retrospective analysis, all analyses were done on the available data, and consequently, the denominator of each parameter was not uniform. All tests were performed using SPSS, version 20.0.0 software (IBM Corporation) with a type I error rate of 5%. *P* values were 2-tailed with $P < .05$ considered indicative of a trend.

Results

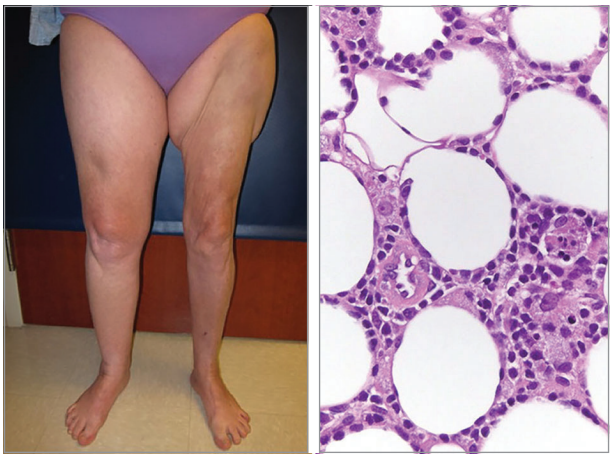
The cohort included 95 cases (75 SPTCL and 20 ALPD) with a median (range) age of 38 (2-81) years and a female-to-male ratio of 2.7. The demographic data of both groups are summarized in **Table 1**. A similar rate of autoimmunity (18 of 66 [27%] and 5 of 19 [26%], respectively) was noted in both groups, with lupus erythematosus reported in 7 of 23 autoimmunity cases (Table 1). A family history of autoimmunity was also documented in 8 of 53 (15%) SPTCL cases. One patient developed SPTCL during pregnancy, but otherwise there were no patients with familial or acquired immunodeficiencies.

Most of 95 patients with SPTCL and ALPD presented with multiple tender, deep nodules with variable extent of involvement (T1 = 11 [12%]; T2 = 37 [39%]; T3 = 47 [50%]), with the legs being the most common site of involvement in 68% (63 of 93 patients). Ulceration was not observed. Lipoatrophy was documented in 23 of 79 (29%) cases (SPTCL = 19 of 63 [30%]; ALPD = 4 of 16 [25%]), mostly involving sites of prior disease, but extensive lipoatrophy distant from disease sites was also noted in a subset of patients (**Figure**, A). Hepatomegaly and/or splenomegaly was reported in 9 of 59 (15%) and shotty palpable adenopathy in 6 of 44 (14%). Overall constitutional symptoms were reported in 54 of 71 patients with SPTCL, including fever (41 of 54 [76%]), night sweats, and weight loss (28 of 54 [52%]). Hemophagocytic lymphohistiocytosis was documented in 10 of 54 (18%) cases with complete information, with a mean HScore of 164.1 (46.91% of HLH probability; 2.48%-98.49% HLH probability range; 108-190 HScore range) and mean of 3.6 qualifying criteria. Cases of HLH were more likely to have extensive disease (T1 = 2; T2 = 0; T3 = 8) than non-HLH cases; however, 2 HLH cases initially presented with a single subcutaneous nodule (T1). Unlike most SPTCL cases, ALPD cases failed to fulfill any HLH criteria (**Table 2**).

Positron emission tomography/computed tomography or computed tomography imaging results were abnormal in 59 of 63 cases (94%), mostly involving the subcutaneous fat (median [range] standardized uptake value, 8.8 [1.4-8.8]), but positron emission tomography avid adenopathy was noted in 23 of 63 cases (median [range] standardized uptake value, 5.45 [2.4-9.5]) and 1 patient with pericardial fat pad and another patient with perirenal fat and pleural effusion. However, the only 2 nodal biopsies obtained revealed disease involvement only in the perinodal fat pad and sinus histiocytosis without involvement of the nodal parenchyma. Imaging analysis was negative for parenchymal involvement in all cases. Abnormal bone marrow biopsy results were reported in 18 of 57 (32%) cases with hemophagocytosis noted in 13 of 57 cases, includ-

Figure. Clinical and Pathological Illustrations

A Patient with SPTCL B Original magnification ×40



A, Clinical image showing extensive lipoatrophy of the left leg in a patient with subcutaneous panniculitis-like T-cell lymphoma (SPTCL). B, Skin biopsy specimen (hematoxylin-eosin) from a case of SPTCL showing subcutaneous tissue with dense lymphocytic infiltrate of medium-sized atypical lymphocytes, rimming the adipocytes.

ing 6 of 10 HLH cases, and subtle rimming of the marrow adipose tissue by CD8-positive T cells noted in 4 cases. However, peritrabecular tumoral aggregates were not observed in any cases. Other unrelated hematological abnormalities were discovered in 3 cases.

Skin and subcutaneous tissue biopsies of SPTCL cases showed a lobular infiltrate of predominantly medium-sized CD8-positive lymphocytes of variable density, rimming adipocytes or lipid vacuoles, necrosis, and hemorrhage (**Table 3**, Figure, B). A subset of medium to large cells was observed in 9 cases, but none of the cases demonstrated tumoral large cell transformation. In contrast, ALPD cases were characterized by small to medium lymphocytes with lower density, minimal atypia, and fewer cytotoxic features (hemorrhage, karyorrhexis, or necrosis). Similar to SPTCL, the lymphoid infiltrate in ALPD was characterized by a mixture of CD4-positive and CD8-positive T cells, but the overwhelming CD8-positive profile of SPTCL was not observed and the proliferative index was lower (Table 3). For the most part, the lymphoid infiltrate in SPTCL and ALPD retained pan–T-cell markers (CD2, CD5, CD7) and expressed cytotoxic markers (TIA-1, granzyme B) and TCR-βF1. However, scattered γδ T cells were commonly noted within the lobule without a rimming configuration. Additionally, CD56 and CD30 were mostly negative, and aggregates of plasmacytoid dendritic cells (CD123-positive) were mostly absent. Biopsies of both conditions showed a substantial histiocytic component, which was more pronounced in cases with necrosis. Histological evidence of hemophagocytosis was observed in 13 cases with poor correlation with clinical HLH (1 of 13 cases). In addition, TIM-3 perinuclear dot-like pattern was noted in 1 of 5 SPTCL cases with HLH vs 7 of 19 SPTCL cases without HLH (not significant), but none of the ALPD cases showed the perinuclear dot-like pattern.

After a mean follow-up of 56 months, 67% achieved complete remission (CR) with a median (range) of 3 (1-7) cumulative therapies (**Table 4**). Relapse was common but did not appear to be associated with prognosis and was often characterized by less severe episodes. None of the patients died of disease progression or HLH. The initial therapeutic approach included polychemotherapy (mostly CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] or etoposide based) with a response in 16 of 22 (73%), followed by immunomodulation (cyclosporine, steroids, and/or methotrexate with a response in 15 of 21 [71%]), bexarotene with a response in 2 of 5 (40%), radiation therapy (response in 2 of 2), observation (2), and surgery (1).

Overall, immune-modulatory therapies including systemic steroids, cyclosporine, methotrexate, and azathioprine as monotherapies or combination were administered in 72 occasions. The overall response rate was 52% (34 of 65; 19 CR, 15 partial response [PR]) with 7 unknown outcomes and 52 of 70 (74%) cases requiring additional therapies. Various chemotherapies resulted in a response rate of 72% (50 of 69; 34 CR, 16 PR), and 51 patients (73%) required additional therapies (Table 4).

Most patients treated with oral cyclosporine had a response (94%) (Table 4). One patient refractory to cyclosporine had severe HLH and achieved CR after multiple chemotherapies and allogeneic hematopoietic stem cell transplantation (HSCT). Methotrexate showed a positive response as a first-line agent in 7 of 7 patients (4 SPTCL, 3 ALPD) all without signs of HLH. Six of 7 patients had limited cutaneous recurrence after response, and 1 patient with recurrence was successfully treated with denileukin diftitox. A response to bexarotene was observed in 4 of 16 patients (2 CR, 2 PR), and all 16 required additional therapies. Stem cell transplantation was required in 6 of 10 patients with more severe disease and HLH (5 allogeneic HSCT and 1 autologous HSCT) with complete responses, while 2 patients with HLH achieved a complete response with only cyclosporine and systemic steroids.

The most common treatment for patients with ALPD was systemic steroids, methotrexate, or a combination of both with a response rate of 87% (13 of 15). Bexarotene was added in 2 cases as a second line of therapy with resolution in 1 case. One patient with ALPD received multiagent chemotherapy followed by an autologous HSCT after subcutaneous progression.

Eighteen patients presented at younger than 20 years (SPTCL = 13; ALPD = 5), and only 1 with SPTCL developed HLH. All patients achieved remission, with 8 patients requiring chemotherapy, 1 patient undergoing allogeneic HSCT, and 2 patients undergoing autologous HSCT.

Discussion

Several important conclusions can be drawn from the present study. The rarity of this condition is demonstrated by the relatively small size of the cohort on a detailed analysis of SPTCL cases from 6 large US cutaneous lymphoma academic centers. The study also highlights the difficulties in establish-

Table 2. Comparison of HLH-Positive SPTCL vs HLH-Negative SPTCL vs ALPD

Symptom/HLH criteria	No./total No. (%)		
	SPTCL		
	HLH positive (n = 10)	HLH negative (n = 62)	ALPD (n = 20)
Fever	10/10 (100)	30/60 (50)	7/17 (41)
Ferritin elevation	8/9 (89)	14/21 (67)	2/4 (50)
Median, ng/mL	3724.0	526.0	204.3
Neutropenia	1/10 (10)	10/44 (23)	2/15 (13)
Lymphocytopenia	9/9 (100)	17/37 (46)	3/15 (20)
LDH elevation	10/10 (100)	22/46 (48)	2/11 (18)
Elevated AST	9/9 (100)	12/35 (34)	3/9 (33)
Extensive cutaneous involvement (≥T2)	8/10 (80)	53/62 (86)	20/20 (100)
HPS in skin or BM biopsy	10/10 (100)	23/41 (56)	11/19 (58)
TIM-3	1/5 (20)	7/19 (37)	0/7
HLH criteria and scores			
HLH, median criteria (range)	4 (2-5)	1 (0-3)	0 (0-1)
HScore, median (range)	168.5 (108-235)	19 (0-139)	0 (0-143)
HLH, median probability (range)	51.4 (2.4-98.5)	0.01 (0-14.5)	0.003 (0-37.0)

Abbreviations: ALPD, adipotropic lymphoproliferative disorder; AST, aspartate aminotransferase; BM, bone marrow; HLH, hemophagocytic lymphohistiocytosis; HPS, microscopic evidence of hemophagocytosis; LDH, lactate dehydrogenase; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; TIM-3, T-cell immunoglobulin and mucin domain 3.

SI conversion factor: To convert ferritin to µg/L, multiply by 1.0.

Table 3. Comparison of Pathological Features of SPTCL vs ALPD

Pathological feature	No./total No. (%)		*P* value
	SPTCL (n = 75)	ALPD (n = 20)	
CD4:CD8 ratio of $CD3^+$ cells	1:5.2	1:2.9	.01[a]
Ki-67, mean, %	45	17	<.001[a]
Clonal TCR	37/47 (79)	11/17 (65)	NS
Interface dermatitis	19/50 (38)	9/17 (53)	NS
Mucin deposits	35/50 (70)	9/17 (53)	NS
Density			
Low	18/68 (26)	11/19 (58)	NS
Intermediate	35/68 (52)	5/19 (26)	NS
High	15/68 (22)	3/19 (16)	NS
Atypia			
None	20/50 (40)	10/14 (71)	NS
Intermediate	22/50 (44)	2/14 (14)	NS
High	8/50 (16)	0/14	NS
HPS in skin biopsy			
None/low	49/61 (80)	16/17 (94)	NS
Moderate/high	12/61 (20)	1/17 (6)	NS
Necrosis	52/69 (75)	15/18 (83)	NS
Mild	26/69 (38)	10/18 (56)	NS
Intermediate	16/69 (23)	4/18 (22)	NS
Extensive	10/69 (14)	1/18 (6)	NS

Abbreviations: ALPD, adipotropic lymphoproliferative disorder; HPS, hemophagocytic syndrome; NS, nonsignificant; SPTCL, subcutaneous panniculitis-like T-cell lymphomas; TCR, T-cell receptor.

[a] *P* value was only significant for CD4:CD8 ratio and Ki-67. No statistical significance was observed for the remaining parameters.

ing a definitive diagnosis with a distinct group of cases presenting with ambiguous pathology. Besides the 75 SPTCL cases with consensus agreement among the group, we identified 20 cases that were considered suspicious for SPTCL characterized by a similar rate of T-cell clonality, lower grade of cytologic atypia, higher CD4:CD8 ratio, and milder signs of cytotoxicity. These cases share with SPTCL a high incidence of autoimmunity and lipoatrophy but are characterized by an indolent course without systemic symptoms or HLH progression. As previously reported, these ambiguous ALPD cases underscore a spectrum of presentations that has not been formally recognized and categorized.[4,10] These presentations often reported as atypical lymphocytic lobular panniculitis are notoriously difficult to diagnose and occasionally progress to bona fide SPTCL,[11] as noted in 2 of the current cohort's cases. Adipotropic lymphoproliferative disorder may also be difficult to differentiate from LEP, but the detection of T-cell clonality and the lack of B-cell and plasmacytoid dendritic cell aggregates may provide helpful clues.[12] As previously reported, rare cases showed SPTCL in some microscopic sections, while other sites exhibited milder features most consistent with ALPD or LEP.[13] A recent gene expression analysis of SPTCL, LEP, and similar

Table 4. Summary of Treatments and Outcomes in the SPTCL Cohort

Treatment	No.	Response rate, %	CR/PR	No. (%)		
				No response	Unknown	Additional treatments
Immunomodulatory therapies	72	52	19/15	31 (44)	7 (9.7)	52/70 (74)
Cyclosporine	17	94	10/5	1 (6)	1 (6)	NA
Methotrexate	14	58	5/2	5 (36)	2 (15)	NA
Bexarotene	17	25	2/2	12 (71)	1 (5)	NA
Systemic steroids	20	33	2/4	12 (68)	2 (10)	NA
Other	4	67	0/2	1 (50)	1 (25)	NA
Chemotherapy[a]	73	72	34/16	18 (26)	4 (5)	51 (73)
Chemotherapy + HSCT	7	86	6/0	1 (14)	0	NA

Abbreviations: CR, complete remission; HSCT, hematopoietic stem cell transplantation; NA, not applicable; PR, partial response; SPTCL, subcutaneous panniculitis-like T-cell lymphoma.

[a] Chemotherapies included CHO(E)P (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), ICE (ifosfamide, carboplatin, etoposide), SMILE (dexamethasone, methotrexate, ifosfamide, etoposide), CDE (cyclophosphamide, doxorubicin, etoposide), CMED (cyclophosphamide, etoposide, methotrexate, dexamethasone), gemcitabine, oxaliplatin, denileukin diftitox, romidepsin, pralatrexate, and alemtuzumab.

overlapping cases showed that while most overlapping cases tend to cluster with LEP, some had an SPTCL molecular pattern.[5] Following World Health Organization terminology, we propose the term *adipotropic T-cell lymphoproliferative disorder* because they lack morphological evidence of lymphoma and the course is indolent. In contrast, SPTCL cases are characterized by an overwhelmingly proportion of CD8-positive medium-sized atypical lymphocytes that typically retain pan-T-cell markers and express αβ TCR markers. We also noted a subpopulation of γδ T cells in SPTCL, as high in some cases as 20% of the infiltrate, which may raise a diagnostic dilemma. Awareness of this pitfall is important, in view of the poor prognosis of panniculitic γδ T-cell lymphomas.[14]

The morphologic characteristics and clinical course of SPTCL differs from other T-cell lymphomas. Morphologically, confluent tumoral growth, large cell transformation, and expansion of the lymphoid population beyond the subcutaneous tissue and periadnexal fat pad are not identified. Most notable, with the exception of occasional rimming of bone marrow, mesentery, or perinodal adipocytes, our experience as well as a literature review failed to reveal convincing evidence of tumoral growth in nodal or parenchymal organs.[15-17] This lack of tumoral progression and the durable responses with immune suppression are consistent with the proposed concept that SPTCL is the result of immune dysregulation with a failure of the innate immune system to downregulate a clonal T-cell expansion with limited growth potential.[6]

Genomic sequencing of SPTCL has revealed various alterations of epigenetic modifiers, while failing to identify any driver variations or even common variations with other T-cell lymphomas.[18] A recent publication showed frequent sequence variations in the *HAVCR2* gene in patients with SPTCL.[6] The *HAVCR2* gene encodes for TIM-3 (T-cell immunoglobulin and mucin-domain protein 3), a membrane modulator of immune response expressed in subsets of T cells ($CD8^+$ and NK cells) involved in the innate system.[6,19] A subset of patients with SPTCL have biallelic *HAVCR2* germline variations resulting in misfolding of TIM-3, which abrogates the expression of this negative immune checkpoint inhibitor resulting in lower CD4-positive regulatory T cells, hemophagocytosis, and uncontrolled activation of the innate immune system. Sequence variations in the *HAVCR2* gene appear to be more prevalent in patients of Asian ancestry compared with White patients and affect younger patients who are thus more susceptible to HLH complications.[19,20] A perinuclear dot pattern rather than the expected membranous pattern has been demonstrated with TIM-3 immunohistochemistry in patients with the *HAVCR2* sequence variation.[6] Besides the retrospective nature and incomplete clinical data of the present cohort, the main limitation of the study is the lack of *HAVCR2* germline variations data, owing to its recent discovery. However, we identified this perinuclear TIM-3 pattern in a subset of cases without racial or HLH correlation in the current study's small cohort. Checking for *HAVCR2* germline variations and possibly other genomic sequence variations associated with autoimmunity and HLH (eg, perforin, FAS, caspase genes) could help identify patients with SPTCL and ALPD at risk for poor outcome who may benefit from a personalized therapeutic approach.

Extensive lipoatrophy of the subcutaneous tissue involving affected as well as unaffected sites was a common finding noted in 29% of SPTCL cases. Lipoatrophy may result from local or distant CD8-positive T-cell activation. Similar facial and limb lipoatrophy has been associated with CD8-positive T-cell activation in patients with advanced HIV with low CD4 T-cell blood counts, and generalized acquired lipodystrophy has also been reported in a young woman with SPTCL.[21,22] Lipoatrophy was also noted in ALPD cases, but mostly confined to the sites of disease involvement rather than distant sites, as observed in some SPTCL cases.

Our experience suggests that immunomodulatory therapies are often effective and should be considered prior to more aggressive or toxic approaches. We propose that oral prednisone possibly combined with methotrexate could be considered as the first-line therapy for patients with ALPD and mild SPTCL cases without systemic symptoms or HLH. We also believe that cyclosporine may be considered as the initial treatment for SPTCL cases with constitutional symptoms including early signs of HLH, prior to single-agent or multiagent chemotherapies. While this proposal is supported by European groups that recently reported a similar response to cy-

closporine in SPTCL,[23,24] we recognize that the available data are insufficient to establish concrete guidelines. In contrast to previous reports, the favorable outcome of the current cohort without fatalities is similar to the low mortality reported by a large French cohort[20] and probably attributable to the exclusion of the more aggressive gamma-delta lymphomas from the series and the increased use of immune-modulatory therapy as initial therapies. Despite the favorable outcomes with methotrexate and cyclosporine, etoposide-based polychemotherapy and HSCT may still be required and can be effective for patients with severe HLH, as well as salvage therapy for patients with disease progression after not responding to initial milder therapies. Many of the cases in which combination chemotherapy was used up-front were older cases, before newer single agents, such as romidepsin or pralatrexate, were available. These new agents may become an alternative therapeutic option for patients with mild to moderate signs of HLH.[25,26] We have observed durable benefit from these new agents as a bridge to allogeneic HSCT. Prospective germline *HAVCR2* sequencing may help identify high-risk patients with HLH in need of more decisive therapies.

Limitations

This study has limitations. These include the retrospective nature of the study and the lack of germline variations data from the cohort.

Conclusions

In this case series, findings highlight the difficulties in gathering adequate experience to propose management guidelines for SPTCL. We are proposing a prospective international collaborative registry to delineate the best diagnostic and therapeutic practice for such rare and potentially lethal conditions.

ARTICLE INFORMATION

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