

Original Article

Subcutaneous panniculitis-like T-cell lymphoma with hemophagocytic syndrome: a clinical and pathologic study of 6 cases

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Abstract: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare cutaneous lymphoma characterized by neoplastic T cell infiltration of the subcutaneous tissue. Approximately 15% of patients with SPTCL show hemophagocytic syndrome (HPS). This study aimed to analyze patients diagnosed with SPTCL and HPS. We retrospectively reviewed 6 cases of SPTCL with HPS, and described the clinicopathologic features, immunophenotypic findings, treatment, and prognosis. All patients initially presented with HPS. Mean patient age was 24 years (range: 17-31 years), with a male predominance. Histologically, biopsies from all patients showed infiltrates of small-to-medium lymphoid cells mimicking panniculitis. All cases were positive for CD2, CD3, CD7, CD8, TIA1, Granzyme-B, and TCRBF1, and negative for CD4, CD20, CD56, CD30, and Epstein-Barr virus in situ hybridization. TCR gene rearrangement was clonal in 2 of 2 analyzed cases. One patient refused treatment and died after 2 weeks, and the remaining 5 patients received chemotherapy based on the cyclophosphamide, doxorubicin, vincristine, and prednisolone regimen. In addition, 3 patients received autologous or allogeneic hematopoietic stem cell transplantation (HSCT). Clinical follow-up data was available for 5 of 5 treated patients. Two patients died with disease and 3 patients were alive with no evidence of disease during the follow-up period. SPTCL with HPS is very rare, and patients can present with HPS as the first symptom. Some patients show rapid disease progression, and the application of high dosage chemotherapy combined with autologous or allogeneic HSCT should be considered.

Keywords: Subcutaneous panniculitis-like T-cell lymphoma, hemophagocytic syndrome, immunohistochemistry

Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare cutaneous lymphoma characterized by neoplastic T cell infiltration of the subcutaneous tissue, mimicking panniculitis. Approximately 14-17% of these patients have hemophagocytic syndrome (HPS) [1, 2]. Few published case reports to date have assessed patients with SPTCL associated with HPS [3-5]. We retrospectively analyzed the clinical and pathological features of 6 patients with SPTCL and HPS, including the treatment and prognosis.

Materials and methods

Case selection

We searched the surgical pathology files of the Beijing Friendship Hospital, which is affiliated

with the Capital Medical University Department of Pathology, for SPTCL and HPS involvement, from December 2009 to December 2015. Six cases were accepted after a detailed clinicopathologic and immunophenotypic analysis. All patients initially presented with HPS, and were diagnosed with SPTCL during HPS treatment or follow-up.

Histology and immunohistochemistry

Representative histopathological sections and immunohistochemical slides were reviewed by two hematopathologists and diagnosed as SPTCL according to the new World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification [6]. Immunophenotypic analysis was performed on paraffin-embedded tissue sections via enzymatic retrieval for TCRBF1; for

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Table 1. Clinical features, treatment, and follow-up of 6 patients with SPTCL and HPS

| Case | Age (years) | Sex | Extent and site of cutaneous involvement | Bone marrow involved | Treatment | Outcome (months) |
|------|-------------|-----|---|----------------------|-------------------|------------------|
| 1 | 31 | F | Multiple, upper and lower extremities | No | CHOP | Alive (73) |
| 2 | 25 | M | Multiple, upper and lower extremities | No | CHOP | Alive (48) |
| 3 | 17 | M | Multiple, upper extremities and trunk | No | CHOP and AlloHSCT | Died (9) |
| 4 | 24 | M | Multiple, left lower extremity | No | CHOP and AlloHSCT | Died (6) |
| 5 | 17 | M | Multiple, upper and lower extremities and trunk | Yes | CHOP and AutoHSCT | Alive (31) |
| 6 | 27 | M | Multiple, upper and lower extremities and trunk | No | - | Died (0.5) |

F: female, M: male, CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone, AlloHSCT: allogeneic hematopoietic stem cell transplantation, AutoHSCT: autologous or allogeneic hematopoietic stem cell transplantation.

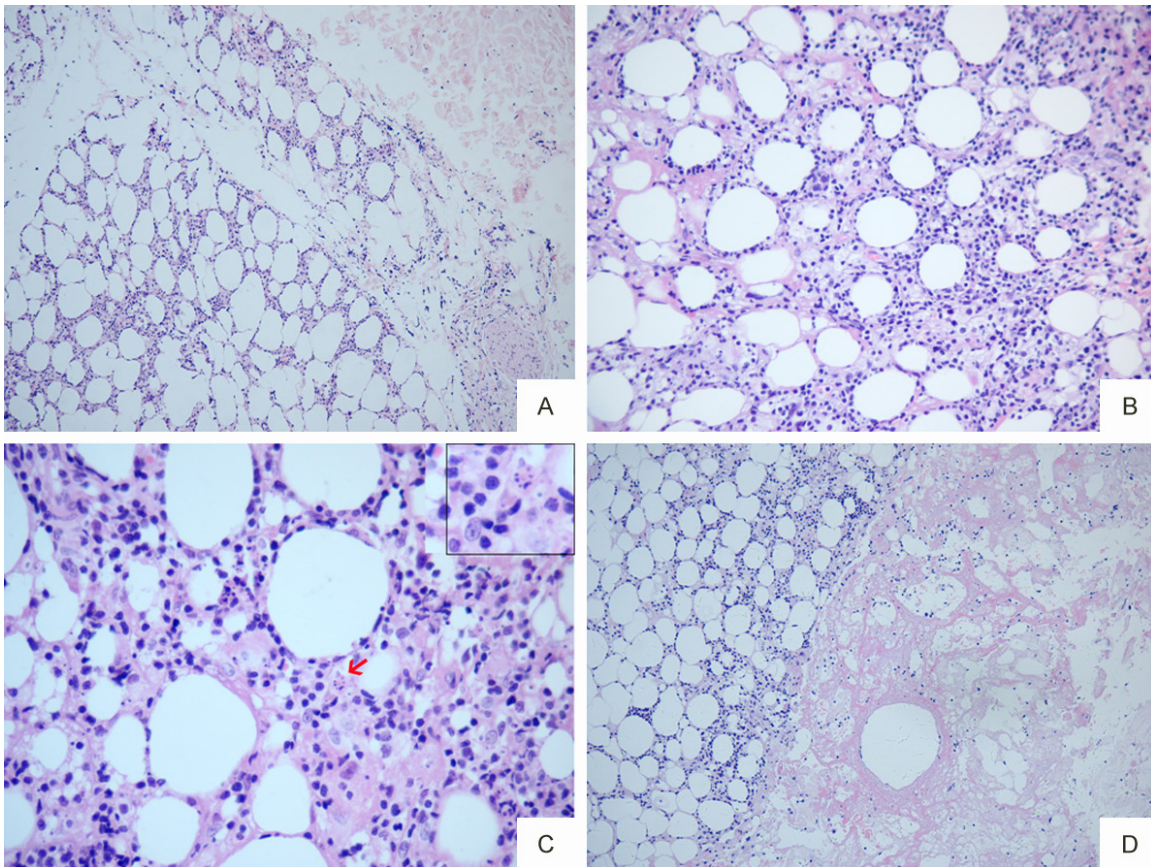


Figure 1. Histopathologic findings in patients with subcutaneous panniculitis-like T-cell lymphoma. A. Atypical lymphocyte infiltration in a panniculitis-like pattern (H&E stain, $\times 100$). B. Atypical lymphocytes rimming adipocytes (H&E stain, $\times 200$). C. Karyorrhexis and “bean bag cells” (arrow) (H&E stain, $\times 400$). D. Extensive necrosis (H&E stain, $\times 100$).

all other antibodies, we used an EnVision 2-step method after antigen retrieval by pressure-cooking the slides in EGTA/Tris buffer (pH 9.0) for 2.5 min. A panel of appropriate antibodies was then selected from the following for immunohistochemical stains: CD2, CD3, CD5, CD7, CD4, CD8, CD20, CD56, CD30, T-cell-restricted intracellular antigen (TIA)-1, Granzyme-B, TCR-BF1, TCR $\gamma\delta$, and Ki-67.

In situ hybridization (ISH) for Epstein-Barr virus (EBV)

The EBV probe In Situ Hybridization Kit (Triplex International Biosciences Co. Ltd., Fujian, China) was used to detect EBV-encoded RNA (EBER) according to the previously described protocol [7]. Positive signals were brown and localized within the nuclei. A known EBER-

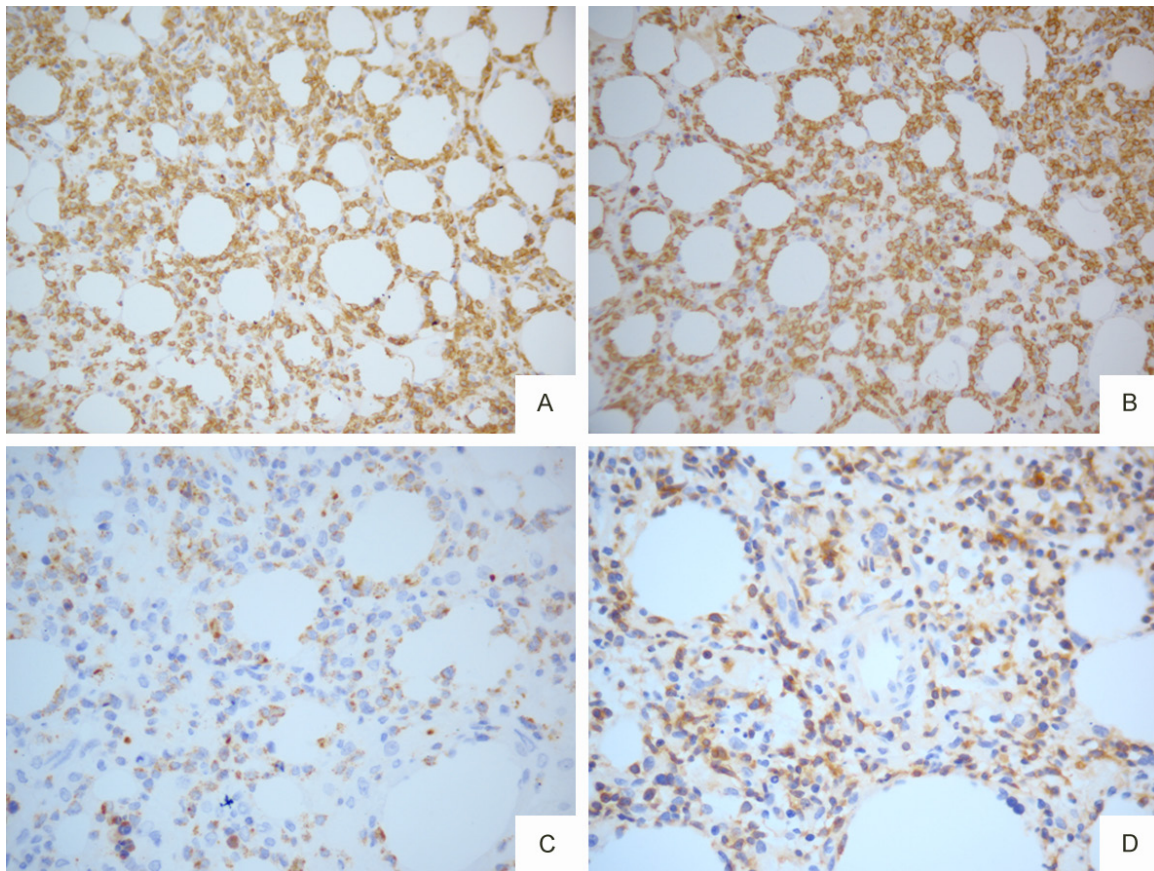


Figure 2. Immunohistochemical analysis in patients with subcutaneous panniculitis-like T-cell lymphoma, showing that neoplastic cells in the subcutis were positive of (A) CD3 ($\times 200$), (B) CD8 ($\times 200$). (C) Granzyme B ($\times 400$). (D) TCRBF1 ($\times 400$).

positive case was used as a positive control, and an EBER-negative case of lymphoid hyperplasia of the lymph node was used as a negative control.

TCR gene rearrangement

TCR gene rearrangement was performed using polymerase chain reaction (PCR), based on the 'Biomed-2' primers (InVivoScribe Technologies, San Diego, CA, USA). DNA was extracted from the formalin-fixed, paraffin-embedded tissue specimens from 2 patients using TIANamp FFPE DNA Kit (DP331) (TIANGEN, Beijing, China) in accordance with the manufacturer's instructions.

Results

Clinical findings

The clinical features, treatment, and follow-up of the 6 patients are reported in **Table 1**.

Patient age ranged from 17 to 31 years (mean age: 24 years); 5 were male and 1 was female. All patients initially presented with HPS. Signs and symptoms included fever, splenomegaly, elevated serum ferritin level, abnormal liver function tests, and hemophagocytic phenomena on bone marrow biopsy. HPS was definitely diagnosed according to the International Hemophagocytic Lymphohistiocytosis-2004 diagnostic criteria [8]. In all patients, a malignant neoplasm was not diagnosed on initial evaluation. Positron emission tomography-computed tomography (PET-CT) was performed in 4 patients and contrast CT was performed in the remaining 2 patients. During therapy and follow-up, the patients developed multiple subcutaneous nodules involving various sites, including the trunk and extremities. The nodules ranged in size (maximum dimension) from 0.5 cm to 15 cm. SPTCL were diagnosed by subcutaneous biopsy. The diagnosis of lymphoma was made 5-18 months after the initial diagnosis of HPS.

Table 2. Immunophenotypic features of patients with SPTCL and HPS

| Stain | Positive/total cases (%) |
|--------------------|--------------------------|
| CD2 | 6/6 (100) |
| CD3 | 6/6 (100) |
| CD5 | 5/6 (83) |
| CD7 | 6/6 (100) |
| CD4 | 0/6 (0) |
| CD8 | 6/6 (100) |
| CD20 | 0/6 (0) |
| CD56 | 0/6 (0) |
| CD30 | 0/6 (0) |
| TIA1 | 6/6 (100) |
| Granzyme-B | 6/6 (100) |
| TCRBF1 | 6/6 (100) |
| TCR $\gamma\delta$ | 0/6 (0) |

Histological findings

The biopsy specimens of all 6 patients demonstrated an atypical lymphocytic infiltrate located in the subcutaneous tissue, resembling lobular panniculitis at low power (**Figure 1A**). The overlying epidermis and dermis were uninvolved. The atypical lymphoid cells were small to medium sized, with hyper-chromatic irregularly contoured nuclei. A diagnostic feature in SPTCL is rimming of adipocytes by neoplastic cells, described as adipotropism (**Figure 1B**), which we observed in all our cases. Areas of karyorrhexis and “bean bag cells” (histiocytes with ingested nuclear fragments) were seen in all cases (**Figure 1C**). Three patients showed evidence of necrosis (**Figure 1D**). No cases showed angioinvasion or angiodestruction. One of the 6 cases (case 5) demonstrated bone marrow involvement.

Immunophenotype, EBV status, and TCR gene rearrangement

All cases were CD3 positive (**Figure 2A**), CD8 positive (**Figure 2B**), TIA-1 positive, Granzyme B positive (**Figure 2C**), CD4 negative, and CD56 negative. Immunophenotyping showed loss of CD5 in 5 of 6 cases (86%). CD30 was negative in all cases. Staining for TCRBF1 was positive in all cases (**Figure 2D**), confirming the alpha/beta T-cell phenotype. The immunophenotypic results are summarized in **Table 2**. EBV infection was not detected in any case by in situ hybridization for EBER. Two cases showed TCR clonal gene rearrangement.

Treatment and follow-up

One patient refused treatment and died 2 weeks after diagnosis (case 6), and the remaining 5 patients received chemotherapy based on the cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) regimen. In addition, 1 patient (case 5) received autologous hematopoietic stem cell transplantation (HSCT) and 2 patients (case 3 and 4) received allogeneic HSCT following chemotherapy. Clinical follow-up was available in all 5 treated patients, over a duration ranging from 6 to 73 months. Two patients died of disease (case 3 and 4). The remaining 3 patients (case 1, 2 and 5) were alive with no evidence of disease during the follow-up period.

Discussion

WHO-EORTC classification of primary cutaneous lymphoma restricts the diagnosis of SPTCL to lymphoma expressing the TCR $\alpha\beta$ phenotype, placing those expressing the TCR $\gamma\delta$ phenotype into a new provisional category of cutaneous $\gamma\delta$ T-cell lymphoma [6]. In contrast to cutaneous $\gamma\delta$ T-cell lymphoma, the incidence of SPTCL associated with HPS is relatively low. In a large European cohort of 63 patients with SPTCL, HPS was uncommon (17%) [1]. We analyzed the clinical and pathological features of 6 patients with SPTCL associated with HPS, including the treatment and prognosis.

On reviewing the literature [1-5], we could find only 17 reported cases of SPTCL with HPS. Thus, a total of 23 cases of SPTCL associated with HPS are now reported, including the patients presented here. SPTCL with HPS occurs in children and adults (age range: 0.7-31 years). Skin lesions present as subcutaneous nodules involving various sites including the trunk and extremities. In our series, males were predominant. All of our patients presented with HPS as the initial symptom. Signs and symptoms included fever, splenomegaly, elevated serum ferritin level, abnormal liver function tests, and hemophagocytic phenomena on bone marrow biopsy. None of our patients were initially diagnosed with malignancy, despite the use of PET-CT and contrast CT studies. During follow-up, our patients presented with subcutaneous nodules, which led to the diagnosis of lymphoma.

Rimming of adipocytes by neoplastic cells is recognized as a useful but non-specific diagnostic feature of SPTCL, as it can be observed in a variety of lesions, including both primary and secondary cutaneous lymphomas and leukemias of various lineages and differentiation [9, 10]. Although SPTCL is often confined to the subcutis, subtle and focal involvement of the bone marrow by lymphoma occurs and can be identified histologically and confirmed using standard immunohistochemistry [11]. In our series, one patient demonstrated bone marrow involvement.

SPTCL shows characteristic immunophenotypic features. The cells have a mature $\alpha\beta$ T-cell phenotype, are usually CD8-positive, and express cytotoxic molecules, including Granzyme B and TIA1. The cells express TCRBF1 and are negative for CD56 and CD30. Pan-T cell antigens are lost to varying degrees; our patients showed loss of CD5 (5/6). Pan-T cell antigen loss is useful as an auxiliary approach to the diagnosis of T cell lymphoma. EBV is generally absent in SPTCL, but can rarely be detected, especially in Asian populations [12]. In our series, all cases were EBV-negative based on in situ hybridization. TCR gene rearrangement was performed as an adjuvant diagnostic method, due to the small biopsy size and few neoplastic cells present on microscopy. We detected TCR clonality in 2 of 2 cases, confirming the diagnosis.

SPTCL should be differentiated from lupus erythematosus panniculitis (LEP). Useful histopathologic criteria favoring LEP include epidermal involvement, lymphoid follicles with reactive germinal centers, mixed cell infiltrates with prominent plasma cells, clusters of B lymphocytes, and polyclonal TCR-gamma gene rearrangement [13]. Primary cutaneous NK/T-cell lymphoma is invariably CD56-positive and shows a predominant dermal infiltration, with angioinvasion, angiodestruction, and EBV-positivity. Additionally, primary cutaneous $\gamma\delta$ T-cell lymphoma should be included in the differential diagnosis of SPTCL, as both lymphoma subtypes show subcutis involvement. Morphologically, epidermal and/or dermal involvement is present in primary cutaneous $\gamma\delta$ T-cell lymphoma. Immunophenotypic differences included CD56-positivity and often lack expression of both CD4 and CD8 in cutaneous $\gamma\delta$ T-cell lymphoma [14].

SPTCL without associated HPS has an excellent prognosis and a protracted disease course, with 5-year survival rates > 80% [1, 15], and multiagent chemotherapy as first choice of treatment should be questioned. The presence of HPS is considered a strong adverse prognostic indicator. The 5-year survival rate for patients with SPTCL and HPS is significantly lower than for those without HPS (46% vs. 91%) [1]. In our case series, the mortality rate was 50%.

Conclusion

SPTCL with HPS is very rare, and shows a tendency to occur in children and young adults. Patients can present with HPS as the first symptom. Some patients show rapid disease progression, and the use of high-dosage chemotherapy combined with autologous or allogeneic HSCT should be considered.

Disclosure of conflict of interest

None.

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