A Case of Subcutaneous Panniculitic T-Cell Lymphoma in a Child

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We report a case of subcutaneous panniculitic T-cell lymphoma (SPTCL) which occurred in a 10-year-old Korean girl. Her disease presented as multiple erythematous subcutaneous nodules on the right cheek, left chest, abdomen, left flank, both calves, and left shin with systemic symptoms.

She had a protracted course of multiple erythematous subcutaneous nodules for 2 months often with spiking fever. Histopathologic findings for the subcutaneous nodules revealed lobular panniculitis-like findings composed of atypical small, bland lymphocytes and histiocytes. Characteristically, atypical lymphocytes rimmed individual fat cells in a lace-like pattern and some histiocytes occasionally phagocytosed WBCs. Bone marrow findings revealed increased phagocytic histiocytes with engulfed hematopoietic cell. The immunophenotypic studies showed CD45RO (UCHL1)+, CD20-, CD4-, CD8+ and CD56+ (focal), lysozyme+, CD45 (LCA)+ and EBV-. She received three cycles of high-dose cyclophosphamide, adriamycin, vincristine, prednisolone (CHOP) and methotrexate, intrathecal methotrexate and one cycle of fludarabine, mitoxantrone and dexamethasone (FND) chemotherapy. She died of acute renal failure during multiple chemotherapy. (Ann Dermatol 16(1) 31~38, 2004)

Key Words: Subcutaneous panniculitic T-cell lymphoma, Cutaneous T-cell lymphoma, Cytophagic histiocytic panniculitis, Hemophagocytosis

INTRODUCTION

Subcutaneous panniculitic T-cell lymphoma (SPTCL) is an unusual type of peripheral T-cell lymphoma with a unique immunophenotypic profile[1,2], presenting less than 1% of all non-Hodgkin lymphomas. It occurs in males and females equally, generally presenting in adulthood, and rarely in childhood[3-5]. According to review of literatures about SPTCL, some of the cases previously reported as malignant histiocytosis, fatal panniculitis, and cytophagic histiocytic panniculitis(CHP) most likely represented another example of this entity[6].

SPTCL has been included as a provisional clinicopathologic entity in the REAL and EORTC classifications[7,8], and was included recently as a definite category in the WHO classification for primary cutaneous lymphoma[9,10]. Some authors regard this one as a tumor of cytotoxic T lymphocytes although comprehensive investigations with a large series of SPTCL cases are limited till now[7,11]. SPTCL needs to be differentiated from benign causes of panniculitis and other cutaneous T cell lymphoma, especially nasal-type T/NK cell lymphoma, anaplastic large cell lymphoma (ALCL), and peripheral T cell lymphoma, all of which can present extranodally with an involvement of the subcutaneous tissue.

Usually, SPTCL presents with multiple erythemat-

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ous subcutaneous nodules or tumors involving the extremities and trunk, often accompanied by constitutional symptoms that include fever, malaise, chills and weight loss. Systemic hemophagocytic syndrome (HPS) frequently occurs, accounting for many of the constitutional symptoms, however, systemic dissemination of lymphoma usually does not occur. Most patients with SPTCL follow an aggressive clinical course with short-duration survival, usually due to systemic HPS, but some follow indolent course with recurrent, self-healing lesions.

Due to the potentially increased risk of HPS in an early onset disease, we have to pay special attention to any cases of childhood SPTCL in diagnosis and treatment.

CASE REPORT

A 10-year-old girl visited department of dermatology, Dong-A University Hospital on July 19, 2002 with complaints of fever and multiple erythematous subcutaneous masses. She suffered from a daily spiking fever intractable to antibiotic treatment since February 2002. And the erythematous tender plaque appeared on the right buttock despite antibiotic treatment since May 2002. Although she was treated with continuous antibiotic treatment under the impression of cellulitis, the lesions increased gradually with spiking fever. Multiple subcutaneous masses appeared on her right cheek, left chest, abdomen, left flank, both calves, and left shin 3 weeks ago (Fig. 1).

Physical examination revealed a temperature of

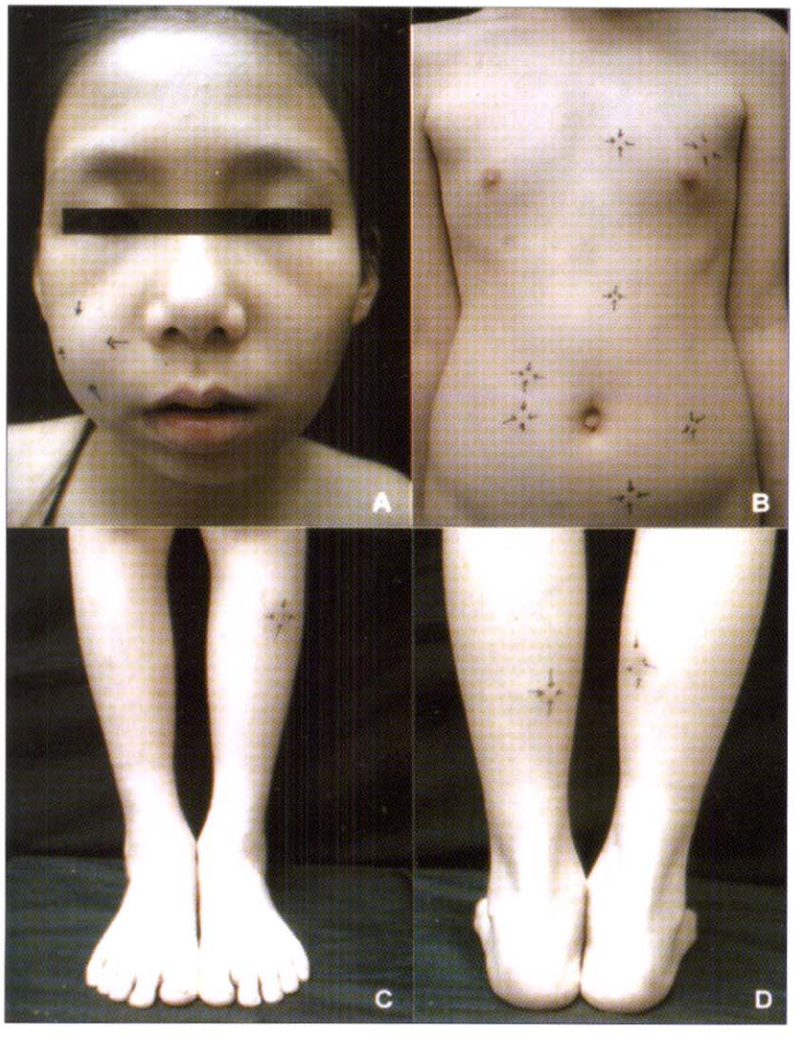

Fig. 1. Multiple tender subcutaneous nodules on face (A), trunk (B), and erythematous scaly subcutaneous nodules on lower extremities (C, D).

39.2℃, a pulse rate of 106 beats/min, and an respiratory rate of 24/min. There was no evidence of peripheral lymphadenopathy, and there were no other significant physical findings. Laboratory tests revealed findings of anemia; hemoglobin 10.0g/dl, hematocrit 29.4%, RBC 4.02×10^6/μl, and leukocytopenia; WBC 1620/μl but platelet count ranged within normal limit; 279×10^3/μl. Evaluating work-up including blood cultures, ANA, RA factors, HIV, and hepatitis B and C antibodies revealed negative findings. The abdominal ultrasound showed mild hepatosplenomegaly. Bone marrow biopsy showed increased phagocytic histiocytes with engulfed hematopoietic cells in a slightly hypocelluar marrow (Fig. 2). An excisional biopsy from the nodule of left flank showed a lobular panniculitis-like finding composed of atypical small, bland lymphocytes and histiocytes. Characteristically, atypical lymphocytes rimmed individual fat cells in a lace-like pattern and some histiocytes occasionally phagocytosed WBCs (Fig. 3). Atypical lymphocytes and histiocytes spared the dermal appendages and showed neither angioinvasive or angiodestructive features. Immunohistochemistry revealed the atypical lymphocytes expressed CD45RO (UCHL1)+, CD20-, CD4-, CD8+, CD56+ (focal), lysozyme+, LCA+ and EBV- (Fig. 4). Atypical T lymphocytes rimming fat cells showed CD8+ phenotypes. From

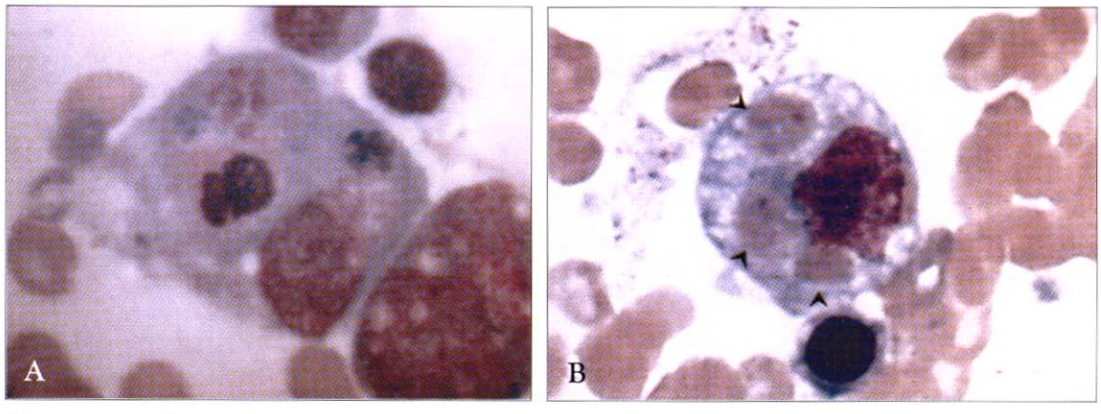

Fig. 2. Bone marrow biopsy shows histiocyte phagocyses all kinds of bone marrow cells (Wright Giemsa stain, × 1000) (A). Phagocytic histiocyte engulfed mainly erythrocytes. (arrowhead, Wright Giemsa stain, × 1000) (B).

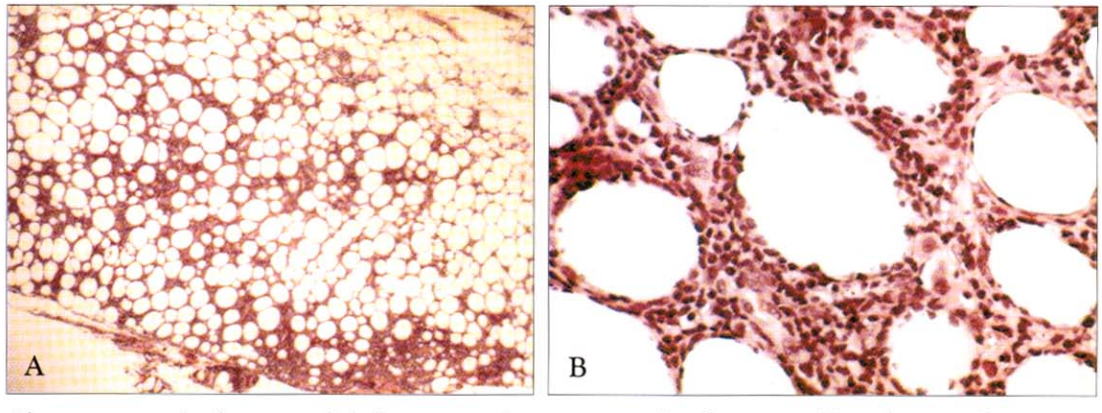

Fig. 3. Photomicrograph showing a lobular panniculitic pattern of infiltration of lymphoma cells. (H&E stain, × 40) (A). Localization of neoplastic infiltrate in the subcutis with rimming of individual fat cells in a lacelike manner resembling lymphoid cells with hyperchromatic round to somewhat irregular nuclei. (H&E stain, × 100) (B).

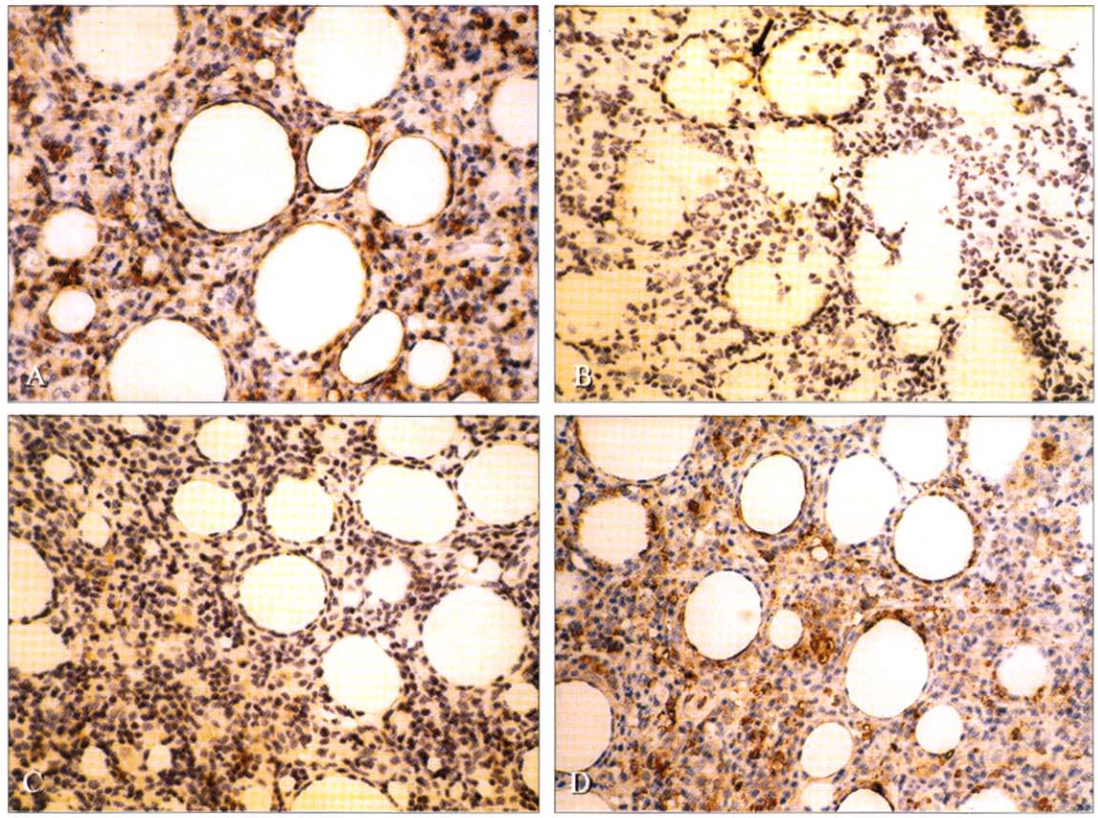

Fig. 4. Immunophenotyping of the SPTCL showed positive to UCHL1 (× 100) (A). The atypical lymphocytes rimming fat cells stained positive to CD8 antigen(arrow) (× 100) (B) and focally positive to CD56. (× 100) (C). Phagocytic cells stains positive cells to lysozyme antigen (× 100) (D).

Table 1.

Diagnostic criteria of hemophagocytic syndrome*
Fever (> 7days, ≥38.5℃)
Splenomegaly (≥3 cm below the costal margin)
Cytopenia (≥2 of 3 lineages in the peripheral blood and not caused by a hypocellular marrow)
Histopathological evidence of hemophagocytosis (bone marrow, spleen, liver or lymph node)
Hypertriglycemia (fasting triglyceride ≥2.0 mmol/l or >3 SD), and/or hypofibrinogenemia (≤1.5 g/l or <3 SD)

*Semin Oncol 1991;18:29-33

clinical and histologic findings, she was diagnosed as SPTCL with systemic HPS according to WHO classification for primary cutaneous lymphoma[12] (Table 1).

She transferred to the department of pediatrics, and received three courses combination chemotherapy of cyclophosphamide, adriamycin, vincristine, prednisolone and methotrexate, and intrathecal methorexate and cytarabine. During chemotherapy, she encountered febrile complications, oral moniliasis, viral pneumonia and pancytopenia. In spite of three courses chemotherapy, multiple nodules with bone marrow hemophagotytosis relapsed after brief partial remission on December 2002. And she was treated with a combination chemotherapy of fludarabine, mitoxantrone and dexamethasone (FND) with antibiotics. The skin lesions had not subsided completely in spite of chemotherapy. She died of

acute renal failure during multiple chemotherapy.

DISCUSSION

SPTCL is included now as a definite category in the WHO classification. Clinically, SPTCL may be associated with an aggressive course accompanied by systemic involvement and hemophagocytosis or an indolent course marked by recurrent skin lesions. Some features such as B symptoms (fever, and significant weight loss), cytopenia, involvement of multiple sites and hemophagocytosis tend to be associated with aggressive disease and a poor clinical outcome[13].

Perniciaro et al.[14] suggested that two distinct clinical presentations of SPTCL exist, which is characterized by the protracted CHP-like phase and the rapidly progressive clinical course. HPS is a common cause of death in the SPTCL patient. The presence of HPS is very important in that it usually leads to a rapidly fatal complication in SPTCL[15]. However, SPTCL is sometimes indolent for months to years, but in most instances it can run a fulminant fatal course with HPS that rarely terminates in a leukemic phase[16].

In the past, the concept of CHP included a specific tissue reaction pattern seen in association not only with lymphoproliferative disorders, including SPTCL and NK-like T cell lymphomas, but with other disorders associated with immune dysregulation, infections, lipid-rich intravenous infusion and connective tissue disease[17]. Some cases might have been diagnosed as panniculitis, such as erythema nodosum and Weber-Christian disease, a lymphoproliferative process such as lymphomatoid granulomatosis, CHP and malignant histiocytosis. CHP was originally described as a primary histiocytic proliferative disorder characterized by fever, pancytopenia, subcutaneous nodules, liver failure, and terminal hemorrhagic diathesis[18]. However many cases of CHP are now being given the classification of a natural disease progression of SPTCL and the histologic appearances of CHP may be indistinguishable from SPTCL in some cases[19].

Histologic features of SPTCL include as follows; variable sized atypical small to medium-sized lymphoid cells and histiocytes usually infiltrates to the subcutaneous tissue with sparing of the dermis. A helpful diagnostic feature is the rimming of the neoplastic cells surrounding individual fat cells with reactive histiocytes; karyrrhexis, fat necrosis, and local or systemic cytophagocytosis are frequently seen. Immunophenotypically, SPTCL has a striking predominance of CD8-positive, with expression of cytotoxic molecules including granzyme B, T-cell intracellular antigen-1 (TIA-1) and perforin[2]. Most cases derived from γδ T cell showed often double-negative for CD4 and CD8 and positive for CD56.

SPTCL needs to be differentiated from benign causes of panniculitis and other cutaneous T cell lymphoma such as nasal-type NK/T cell lymphoma, ALCL, and peripheral T cell lymphoma, not other specified, all of which can present extranodally with involvement of the subcutaneous tissue. Briefly, benign panniculitis can be excluded by a lack of nuclear atypia in the infiltrating lymphoid cells, usually a mixture of B and T cells. SPTCL is more difficult to be differentiated from NK/T cell lymphoma because both diseases show the similar features in clinical, histopathological and immunophenotypic aspects[20] But in the latter, the neoplastic infiltrate is more confluent and tends to frequently extend into the dermis and epidermis resulting in angioinvasion and angiodestruction with coagulation necrosis. Moreover, NK/T cell lymphoma expresses germline TCR gene genotype and positive EBV genome besides CD56 positivity. ALCL similarly involves dermis and extends into the subcutaneous tissue, often with epidermal ulceration and focal angioinvasion and angiodestruction. And most of the malignant cells are CD30+, with a characteristic membrane and golgi pattern of staining. The demonstration of t(2;5)(p23;q35) chromosomal translocation, fusion protein p80NPM/ALK, or ALK-1, may be helpful in confirming the diagnosis.

This patient was treated with the rather aggressive regimens of three cycles CHOP and one cycle FND, but the tumor nodules were not completely remitted and her condition got worse intermittently with fever and pancytopenia. SPTCL has been treated with corticosteroids and combination chemotherapy such as CHOP or CHOP-E based regimen for treatment, but the response is variable with a high relapse rate[13,15]. Because of the high relapse rate in aggressive cases of SPTCL, other regimens such as FND regimen or combination therapy as high dose regimens with autologous peripheral stem cell transplantation have been used for treatment of SPTCL and some authors reported successful results[21-23].

To date, 13 cases were reported as SPTCL in

Table 2. Reported Cases of SPTCL in Korea

No.	Age/Sex	Immunohistochemical staining	Treatment	Outcome
1	30/F	CD3+ CD4-, CD8-, CD19-	Supportive	Die
2	45/F	UCHL1+, lysozyme+, LCA+ CD20-	Prednisolone	Wax and wane
3	30/F	UCHL1+, CD45+ CD20-	BACOP*, CHOP**	Alive
4	63/F	UCHL1+, CD45+ CD20-	CHOP	Die
5	34/F	UCHL1+, CD45+ CD20-, lysozyme-	Vincristine, Prednisolone	Wax and wane
6	41/F	UCHL1+, CD3+, LCA+ CD20-, CD30-	Prednisolone	Alive
7	48/F	UCHL1+, CD8+, LCA+, lysozyme+ CD20-, CD56-, EBV-	CHOP, ASCT†	Die
8	29/F	UCHL1+, CD8+, LCA+ CD20-, CD56-	Patient refusal	Die
9	32/M	CD3+, CD8+, TIA-1+ CD4-, CD30-, CD56-, EBV-	Cyclophosphamide, Prednisolone	no follow up
10	40/M	CD3+, CD8+, TIA-1+ CD4-, CD30-, CD56-, EBV-	Supportive	no follow up
11	41/M	CD3+, UCHL1+, CD4+, CD8+, CD68+ CD56-, EBV-	Cyclosporin	Alive
12	25/F	CD56+, TIA-1+, EBV+ CD3-, CD4-, CD8-, C20-	Cytoxan, Prednisolone, Cyclosporin	Die
13	67/F	CD3, CD8+, UCHL1+, CD56+, EBV+, LCA+ CD4-, CD20-	Cyclophosphamide, vincristine, prednisolone	Die
14	10/F	CD8+, UCHL1+, CD56+, lysozyme+, LCA+, CD4-, CD20-, EBV-	CHOP, FND†	Die

BACOP*: bleomycin, adriamycin, cyclophosphamide, vincristine, prednisolone
CHOP**: cyclophosphamide, adriamycin, vincristine, prednisolone
ASCT†: autologous stem cell transplantation
FND†: fludarabine, mitoxantrone, dexamethasone

Korea, but many authors have regarded SPTCL as a benign entity or not placed any aggressive chemotherapy (Table 2). We consider SPTCL as an aggressive entity, and needs looking into for any reliable prognostic markers to determine patients' clinical courses in the future. The expression of CD56 and rearrangement of TCR γδ as the valuable markers are generally associated with the HPS and a rapidly progressive fatal disease[1], which need aggressive chemotherapy as the treatment of choice.

Any case where SPTCL occurred in a child had not been reported in department of dermatology until now. Panniculitis is an uncommon condition in children and the clinical spectrum of children panniculitis varies from short, self-limited to persistent disease with a fatal outcome[24]. Therefore, we strongly suggest that a child who has recurrent panniculitis with systemic symptoms had better to

be considered as SPTCL.

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