ORIGINAL ARTICLE

Subcutaneous Panniculitic T-Cell Lymphoma-Review of Five Cases

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Summary

Subcutaneous panniculitic T-cell lymphoma (SPTL) is a rare variant of cutaneous T-cell lymphoma where lymphoma cells infiltrate preferentially into subcutaneous tissue. Five cases of SPTL were seen during the period from 2001-2004 at the Department of Dermatology, Hospital Kuala Lumpur. All five presented with multiple subcutaneous nodules on the face, trunk and limbs of one week to six months duration with associated fever and loss of weight. Physical examination showed multiple tender, erythematous indurated plaques and subcutaneous nodules on their face, trunk and limbs. One patient also presented with unhealing ulcerated nodules. Two patients had hepatosplenomegaly and one hepatomegaly. Two patients had pancytopaenia while the other three had leucopaenia. One patient had deranged liver function. Out of the five patients, three had bone marrow examination with haemophaegocytosis in two and one hypocellular marrow. Skin biopsy of all patients showed infiltration with atypical lymphoid cells in the upper dermis and subcutaneous fat. These neoplastic cells showed positivity for CD3 and CD30 in three patients with CD8 ,T1A-1 and LCA(Leucocyte common antigen) being positive in one patient. One patient treated with prednisolone and subcutaneous Roferon 3Mu three times a week since 2001 was in remission. Two patients who were planned for chemotherapy had deteriorated rapidly and succumbed to septicaemia from pancytopaenia. Subcutaneous panniculitic T-cell lymphoma has been reported to show two distinct clinical presentations. The first is characterized by an indolent course with good prognosis and the second with rapid clinical deterioration, haemophaegocytosis and death. Both presentations were seen in our five patients seem to demonstrate these two subtypes of SPTL.

Introduction

Subcutaneous panniculitic T-cell lymphoma (SPTL) is a rare variant of peripheral T-cell lymphoma characterized by preferential infiltration of lymphoma cells within the subcutaneous tissue[11]. Clinically, patients manifest with subcutaneous nodules, primarily affecting extremities and trunk and may be generalized. Ulceration is uncommon. Systemic symptoms including fever, fatigue and weight loss may be present. The disease may be complicated by hemophagocytic syndrome(HPS)[9], characterized by fever, pancytopenia, hepatosplenomegaly and hemophagocytosis in liver, bone marrow, lymph nodes and skin.

Materials and Methods

This is a retrospective review of SPTL diagnosed from 2001 to 2004 from the Department of Dermatology, Hospital Kuala Lumpur. All the case notes of patients diagnosed to have SPTL were reviewed. We had five cases of SPTL from 2001 to 2004. All the five cases histories, clinical examination, differential diagnosis, investigations, management and outcome are described in detail as below.

Case 1

A 13 year old girl presented with recurrent fever for three months with facial swelling and nodules on the face (Figure 1) and limbs. She also had violaceous and

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tender indurated plaques on the infraorbital region and dusky discoloration down her limbs with subcutaneous nodules which were better felt than seen (Figure 2). She had no organomegaly or lymphadenopathy.

Differential diagnoses of lupus panniculitis and erythema nodosum were entertained besides SPTL. Complete blood count showed leucopenia of 3.0 x 10^9/L, hemoglobin level of 11.0g/dl and platelet count of 300 x 10^9/L. Her liver and renal functions were normal. Serum LDH and ESR were raised at 1447 IU/L and 60 mm/h respectively. Other investigations including ANA, C3, C4 and CXR were normal. A skin biopsy showed prominent involvement of the septa and fat lobules with a predominantly mononuclear cell infiltrate (Figure 3a). This infiltrate is composed of small round lymphocytes, medium-sized and large lymphoid cells with atypia and irregular nuclear outline. Cellular debris are seen in some areas including histiocytes with nuclear dust. There was no vascular involvement. CD8+ which is a T-cell marker and T-cell intracellular antigen which is a cytotoxic molecule are positive (Figure 3b). CD 56 which is a Natual killer cell marker is negative.

Bone marrow and trephine showed normocellular marrow with occasional macrophages with haemophaegocytosis (Figure 4).

The patient was diagnosed to have SPTL and started on prednisolone 30mg daily and subcutanoues Roferon 3 Mu 3x a week. Her prednisolone was tapered off after six months and subcutaneous Roferon was given for two years. She responded well to the above treatment with complete resolution of her subcutaneous nodules. The LDH decreased to 263 IU/L after six months and she is currently in clinical remission.

Case 2

A 22 year old man presents with persistent fever for four months associated with multiple subcutaneous nodules which broke down easily on his limbs and trunk to form erosions. He was febrile, jaundiced and had hepatosplenomegaly. Differential diagnoses of lupus panniculitis and cutaneous vasculitis (Figure 5) were entertained besides SPTL.

Complete blood count showed pancytopenia with white cell count of 3.2 x 10^9/L hemoglobin level of 9.7g/dl and platelet count of 75 x 10^9/L. His ALT was raised, 344 U/L. HbsAg and AntiHCV were negative. Other investigations including ANA, renal function and CXR were normal. Bone marrow showed haemophaegocytosis. Skin biopsy showed dense infiltration of subcutaneous tissue by atypical lymphoid cells with hyperchromatic nuclei. These cells are positive for CD3 and CD30. He was started on prednisolone 60mg daily and referred to the hematologist for further management. He was planned for chemotherapy as his lesions did not respond to prednisolone. However, he deteriorated rapidly and succumbed to sepsis before commencement of chemotherapy.

Case 3

A 22 year old female presented with recurrent fever for one month and investigated for pyrexia of unknown origin. She then presented with a week history of erythematous nodules on the face, limbs and trunk and an ulcerated nodule on her chin (Figure 6). She was ill, febrile with gross hepatosplenomegaly and submandibular lymphadenopathy.

Complete blood count showed pancytopenia with white cell count of 0.7 x 10^9/L, hemoglobin level of 9.4g/dl, and a platelet count of 18 x 10^9/L. Her ESR was 22 mm/h. HbsAg and AntiHCV were negative. Other investigations including ANA, renal function and CXR were normal. Skin biopsy revealed atypical lymphomatous infiltration within dermis and subcutaneous tissue in lobular pattern and showed positivity for CD3 (T cell marker) and negative for CD20(B cell marker) Bone marrow was hypocellular with no blast cells or hemophagocytosis. Unfortunately, this patient succumbed to sepsis before any specific treatment could be instituted.

Case 4

A 35 year old lady presented with eight months history of nodules and plaques on the face, trunk and arms and swelling of fingers, associated with fever. She had a huge, firm indurated swelling over her right cheek. Elsewhwere in the limbs and body were multiple subcutaneous nodules. She was febrile with hepatomegaly. (Figure 7 and 8)

Differential diagnoses of Lepromatous Hansen, Lupus panniculitis, erythema nodosum and SPTL were entertained. Complete blood count showed white cell count of 2.4 x 10^9 /L hemoglobin level of 12.4g/dl, and a platelet count of 126 10^9/L. Her ESR was 122 mm/h. Slit skin smear was negative excluding Lepromatous Hansen. Her ANA, renal, liver functions and CXR were normal. A skin biopsy confirmed SPTL with positive LCA (Leucocyte common antigen) and CD3 (T cell marker) and negative for CD20(B cell marker) CT Scan showed hepatomegaly and preaortic lymph nodes.She refused bone marrow examination and treatment and defaulted follow up.

Case 5
A 16 year old girl presented with periorbital and facial swelling for three months associated with fever. She also had subcutaneous nodules on her arms for two weeks which were better felt than seen. There was no organomegaly or lymphadenopathy (Figure 9).

A differential diagnosis of hypothyroidism, acute dermatomyositis and SPTLwere entertained. Complete blood count showed white cell count of 2.3 x 10^9/L hemoglobin level of 10.1g/dl, and a platelet count of 186 10^9/L . Her ESR and LDH were raised at 50 mm/h and1600IU/L respectively. Her ANA, renal and liver functions, CXR, serum T4,TSH , creatinine kinase were normal. CT scan showed small paraaortic lymph nodes. Skin biopsy confirmed SPTL with positive CD3 and negative for CD30. She refused marrow examination and is currently in remission without any treatment.

Discussion

Recent studies suggest that at least two groups of SPTL with a different histology, phenotype, and prognosis can be distinguished[1]. Cases with an α/β^+ T-cell phenotype are usually $CD8^-$, are restricted to the subcutaneous tissue (no dermal and/or epidermal involvement), and often run an indolent clinical course. In contrast, SPTL with a γ/σ^+ T-cell phenotype[2], approximately 25% of all cases, are typically $CD4^-$, $CD8^-$, and often coexpress CD56. The neoplastic infiltrates are not confined to the subcutaneous tissue, but may involve the epidermis and/or dermis as well, and invariably have a very poor prognosis. In the WHO-EORTC classification[2] the term "SPTL"is only used for cases with an σ/β^+ T-cell phenotype, whereas cases with a γ/σ^+ T-cell phenotype are included in the category of cutaneous γ/σ^+ T-cell lymphomas.

In SPTL, histopathology reveals subcutaneous infiltrates simulating a panniculitis showing small, medium-sized, or sometimes large pleomorphic T-cells with hyperchromatic nuclei and often many macrophages[1]. The overlying epidermis and dermis are typically uninvolved. Rimming of individual fat cells by neoplastic T-cells is a helpful, though not completely specific diagnostic feature. Necrosis, karyorrhexis, and cytophagocytosis are common findings. In the early stages the neoplastic infiltrates may lack significant atypia and a heavy inflammatory infiltrate may predominate. These lymphomas show a σ/β^+, $CD3^+$,$CD4^-$, $CD8^+$ T-cell phenotype, with expression of cytotoxic proteins. CD30 and CD56 are rarely, if ever, expressed[1,2].

Patients with cutaneous γ/σ^+ T-cell lymphomas[2] generally present with disseminated plaques and/or ulceronecrotic nodules or tumors, particularly on the extremities, but other sites may be affected as well. Involvement of mucosal and other extranodal sites is frequently observed, but involvement of lymph nodes, spleen, or bone marrow is uncommon. A hemophagocytic syndrome[9] may occur in patients with

Table I: Summary of clinical data of the five patients

Patient	1	2	3	4	5
Fever	√	√	√	√	√
Subcutaneous nodules	√	√	√	√	√
Lymph node	-	-	√	√	-
Organomegaly	-	Liver + Spleen	Liver + Spleen	Liver	-
Skin biopsy	Panniculitis with atypical lymphocytes	Panniculitis with atypical lymphocytes	Panniculitis with atypical lymphocytes	Panniculitis with atypical lymphocytes	Panniculitis with atypical lymphocytes
Immunohistochem	CD8+, TIA+	CD3+, CD30+	CD3+	CD3+	CD3+
Blood count	Leucopenia	Pancytopenia	Pancytopenia	Leucopenia, ↓ Platlet	Leucopenia
Bone marrow	Hemophagocytosis	Hemophagocytosis	Hypocellular	Refused	Refused
LFT	AST	↑ AST	Normal	Normal	Normal
Treatment	Prednisolone, interferon-alpha	Prednisolone	-	Refused treatment	-
Outcome	Remission	Died of sepsis	Died of sepsis	Defaulted	Remission

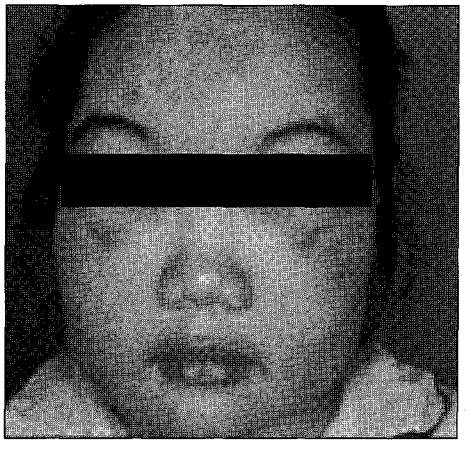

Fig 1: Facial swelling and infraorbital indurated plaques

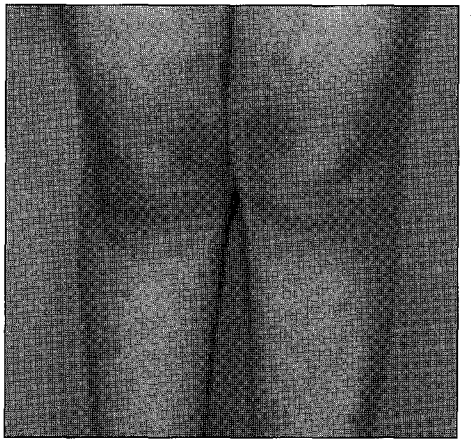

Fig 2: Subcutaneous nodules

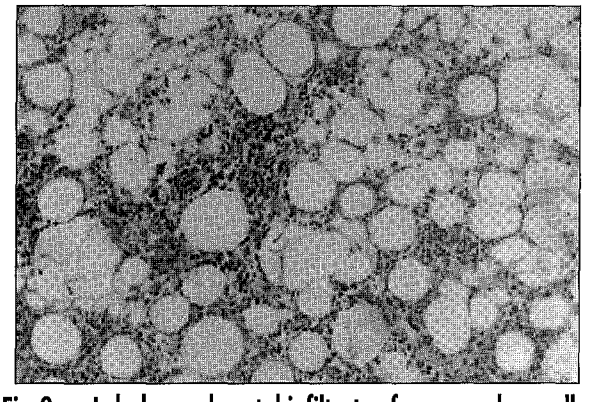

Fig 3a: Lobular and septal infiltrate of mononuclear cell

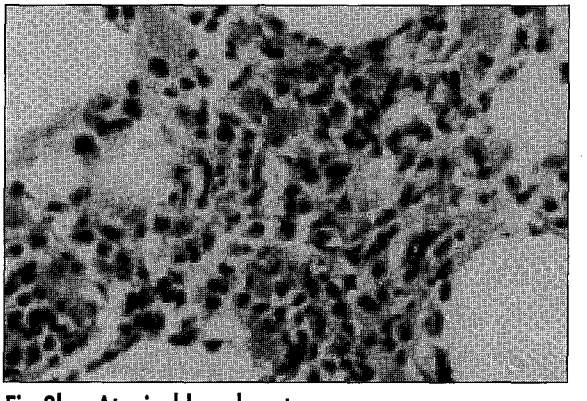

Fig 3b: Atypical lymphocytes

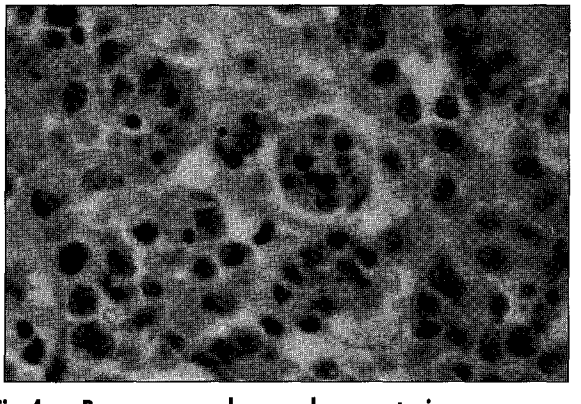

Fig 4: Bone marrow haemophaegocytosis

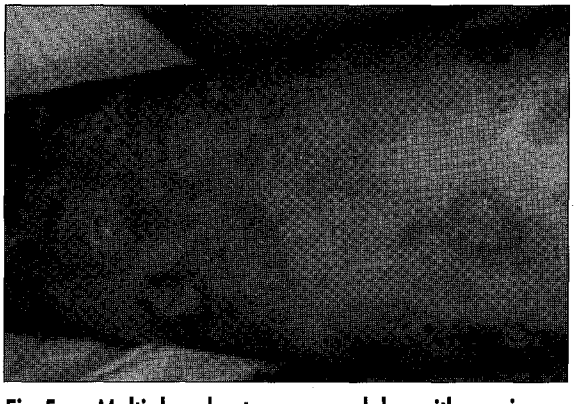

Fig 5: Multiple subcutaneous nodules with erosions

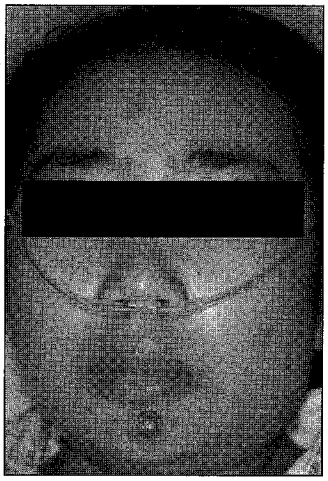

Fig 6: Erythemtous nodules with ulceration on chin

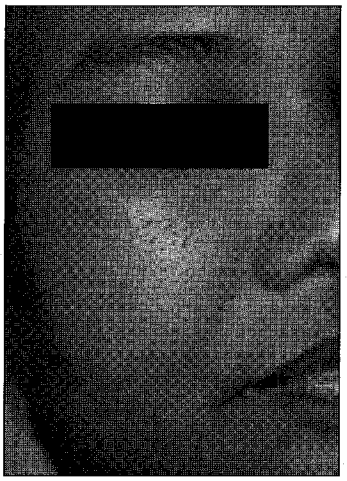

Fig 7: Indurated right cheek swelling

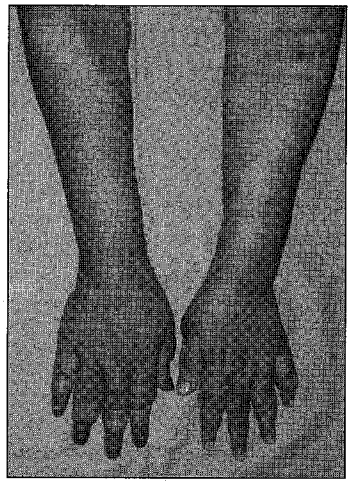

Fig 8: Multiple subcutaneous swelling on limbs

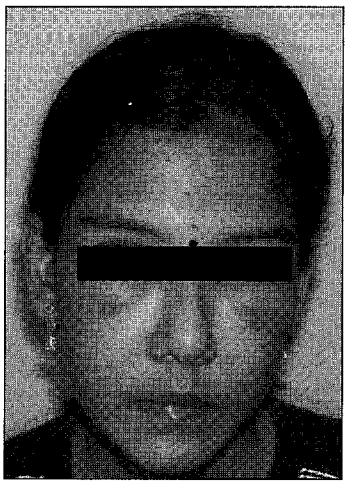

Fig 9: Periorbital and facial swelling

panniculitis-like tumors. Three major histologic patterns of involvement can be present in the skin: epidermotropic, dermal, and subcutaneous. Often more than one histologic pattern is present in the same patient in different biopsy specimens or within a single biopsy specimen. The neoplastic cells are generally medium to large in size with coarsely clumped chromatin. Large blastic cells with vesicular nuclei and prominent nucleoli are infrequent. Apoptosis and necrosis are common, often with angioinvasion. The tumor cells characteristically have a beta $F1^-$, $CD3^+$, $CD2^+$, $CD5^-$, $CD7^{+/-}$,$CD56^+$ phenotype with strong expression of cytotoxic proteins. Most cases lack both CD4 and CD8, though CD8 may be expressed in some cases.

Treatment has been used in reported cases includes, systemic corticosteroid, multidrug chemotherapy, cyclosporin, high dose chemoradiotherapy with stem cell support and total body irradiation [5,8]. It is usually treated with corticosteroid and chemotherapy (mostly but not exclusively cylophosphamide, hydroxydaunorubicin and oncovin) with or without radiotherapy. More recently, high dose regimen such as

Denileukin Diftitox[4], Fludarabine[6], mitoxantrone and dexamethasone[5] has been used successfully in the treatment of SPTL. It generally carries an unfavourable prognosis. About 45% patients have HPS which carries a mortality as high as 81%[7].

Conclusion

In our experience, SPTL is not as rare as reported in the literature. We see an average of one case per year. Our five patients seem to demonstrate the two subtypes of SPTL.SPTL should be suspected in patients with unexplained fever, recurrent subcutaneous nodules and plaques with or without ulceration. Haemophagocytosis in bone marrow and skin tissue is an important prognostic feature. In the presence of fever, pancytopenia and hepatoslenomegaly, this indicates an aggressive disease which carries a poor prognosis despite treatment as seen in our two patients.

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