Subcutaneous Panniculitis-like T-Cell Lymphoma with Hemophagocytic Syndrome: A Case Report*

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ABSTRACT

Introduction: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare disease, accounting for less than 1% of non-Hodgkin's lymphomas that is characterized by infiltration of T-cells in the subcutaneous adipose tissue.

Case presentation: A 21-year-old Filipino female presented with intermittent fever which eventually was associated with multiple eruption of cutaneous lesions. The serum antinuclear antibody (ANA) titer and pattern revealed negative results. Further clinical investigation prompted a skin lesion punch biopsy revealing atypical lymphoid infiltrates with lobular panniculitis consistent with SPTCL. Immunohistochemical studies stained strongly positive for CD3, CD8, granzyme B and negative for CD20, CD4, and CD56. The case was also compounded with the existence of hemophagocytic syndrome having fulfilled five of the eight criteria. She was given prednisone (1 mg/kg/day) with gradual resolution of cutaneous lesions leaving marked hyperpigmentation and lipoatrophy.

Discussion: SPTCL presents with a myriad of systemic symptoms but will always present with skin lesions. The biopsy for histopathological interpretation is commonly performed as a first diagnostic step followed by immunohistochemical staining. Clinical presentation, histo-pathological findings, and immunohistochemical results together clinched the diagnosis of SPTCL.

Conclusion: Patients with history of intermittent fever associated with cutaneous lesions and systemic clinical findings, SPTCL should be a differential diagnosis. However, lupus erythematosus panniculitis (LEP) must be ruled out first as its closest mimicker. This case report along with other large case series provides further evidence that monotherapy with oral prednisone can be an initial choice of therapy.

Keywords: *Subcutaneous panniculitis-like T-cell lymphoma, lupus erythematosus panniculitis*

INTRODUCTION

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare disease, accounting for less than 1% of non-Hodgkin's lymphomas. It is characterized by infiltration of T-cells in the subcutaneous adipose tissue.[1] The annual incidence of cutaneous lymphoma is estimated to be from 0.5 to 1 per 1,000,000 persons per year.[2] There is only one published case of SPTCL in the Philippines.[18]

Diagnosing SPTCL is a challenge. It presents with a myriad of symptoms that are mostly constitutional, hence, a high index of suspicion is needed for early diagnosis. A comprehensive history and physical examination complemented with proper diagnostic evaluation including biopsy and immunohistochemical are essential for the diagnosis. Currently, no standard therapeutic approach exists.

This case report aims to describe a rare case of SPTCL in a 21-year old female and the clinical challenges of arriving at a diagnosis including the diagnostic dilemmas, and differential diagnoses. Also, this report aims to supplement to the small amount of data there is as to the treatment and management of SPTCL.

CASE PROTOCOL

A 21-year-old female, single, from Samal presented with fever and multiple cutaneous lesions.

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Five months prior, the patient complained of intermittent fever with appearance of warm, erythematous, petechial, and nodular skin lesions on both lower extremities. This was associated with swelling of both lower extremities and body malaise. Consult was done and unrecalled antibiotics were given with gradual resolution of fever and skin lesions. The swelling of both legs persisted, however the skin lesions gradually resolved into hypopigmented patches.

Four months prior, cutaneous lesions recurred and progressed into pruritic skin lesions that were nodular. They were gradually enlarging in size associated with intermittent fever and body malaise. Scratching of the affected areas led to skin thickening and ulcerations. She opted application of herbal liniment. Lesions progressed in size and diameter with persistence of intermittent fever and bipedal edema.

Two weeks prior, multiple non-tender erythematous and pruritic patches appeared on her upper extremities that evolved into ulcers with serous discharges admixed with pus. Redness and swelling were noticed around the right eye. Cough productive of yellowish non-blood-streaked sputum developed. Several consultations were done where she was given unrecalled medications without resolution of her symptoms. The persistence of symptoms prompted consultation in a tertiary hospital where she was admitted.

She has no co-morbid medical conditions or prior surgeries. There were no known allergies to food and drugs. There was no history of pulmonary tuberculosis (PTB) exposure. Her family history was unremarkable. She is a non-smoker, non-alcoholic beverage drinker with no illicit drug use. She has one sexual partner with two offspring. There was no recent history of travel for the past five years. She has no exposure to chemical and industrial substances.

The patient came in awake, oriented, with generalized edema, jaundiced, and lying flat in bed. She was tachycardic at 110 bpm, tachypneic at 28 cpm,

and hypotensive at 70/50 mmHg in all extremities. There was swelling of the right eye with violaceous pigmentation on the upper and lower eyelid (Figure 1A) and icteric sclerae with pale palpebral conjunctivae.

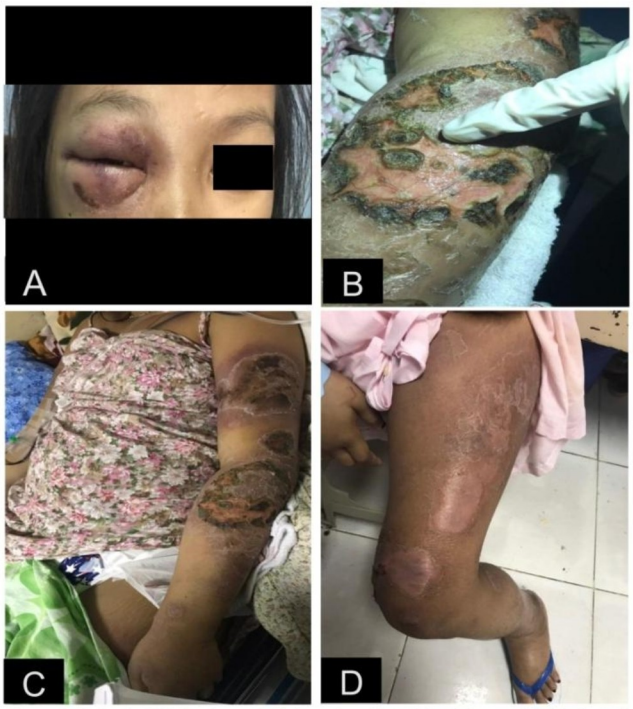

Figure 1. Patient's Skin Lesions. A. Unilateral swelling of the right eye with bipalpebral violaceous pigmentation **B.** Crusted and hyperpigmented plaques with irregular borders surrounding an ulcerated erythematous base with areas of scaling and weeping on the left forearm measuring 10 x 9 cm **C**. Upper extremity lesions **D.** Lower extremity lesions

Chest and lung examination revealed fine crackles on both basal lung fields. The abdominal girth measured 62 cm with no caput medusae and spider angiomata. She had normoactive bowel sounds. Shifting dullness with a positive fluid wave test was elicited. The abdomen was soft and non-tender. The liver span measured 16 cm and 10 cm along the midclavicular and midsternal lines, respectively. The Castell's sign – a physical exam for splenomegaly was not present. Multiple poorly circumscribed erythematous plaques topped with scales and hemorrhagic crust with areas of ulceration were seen in both upper extremities. Multiple well-circumscribed hypopigmented patches with scaly borders were found in the lower extremities. The trunk was spared. There was bipedal edema up to the level of the thighs (Figure 1D). Neurological examination was essentially normal.

She was admitted with a working impression of septic shock secondary to

community acquired pneumonia-high risk (hypotension) and infected skin lesions. Systemic lupus erythematosus and malignancy were considered.

Hematology report revealed normocytic hypochromic anemia at 76 g/L, thrombocytopenia of 97 $x10^3$, and normal WBC count at 9.04 $x10^3$. The chest x-ray revealed pulmonary congestion with bilateral pneumonia.

A liver pathology was considered due to icterisia, jaundice, anasarca, and hepatomegaly. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were both elevated at 2.8x and 8.5x from upper limit of normal (ULN), respectively. The total bilirubin was also markedly elevated at 177.31 umol/L including the direct bilirubin 90.47 umol/L and indirect bilirubin 58 umol/L. Activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalized ratio (INR) were all elevated. Severe hypoalbuminemia of 8.13 g/L was also present. Further work-up revealed markedly elevated lactate dehydrogenase (LDH) at 1,403 U/L and a peripheral blood smear with normocytic hypochromic red cells without immature leukocytes. The hepatitis profile and human immunodeficiency virus (HIV) screening were negative. Other laboratory results were unremarkable (Appendix A).

The ANA titer and pattern revealed a negative result, which made systemic lupus erythematosus less likely.

The ultrasound of the whole abdomen revealed an enlarged liver and spleen, ascites, and gallbladder wall edema. Malignancy was also entertained, hence, computed tomography (CT) scan of the whole abdomen and chest revealed bilateral pleural effusion with passive atelectasis of both lower lobes, hepatomegaly with steatosis, splenomegaly, moderate ascites, and subcutaneous edema. The blood, sputum and wound culture results were all negative.

A skin lesion punch biopsy revealed atypical lymphoid infiltrates with lobular panniculitis on Hematoxylin-Eosin (H&E) staining (Figure 2) consistent with SPTCL. On immunohistochemical staining, it revealed strongly positive for CD3, CD8, granzyme B and negative for CD20, CD4, and CD56 (Appendix C).

A distinctive associated clinical feature of SPTCL is hemophagocytic syndrome (HPS). This and the other associated clinical findings of liver injury and anemia of the patient fulfilled five of the eight criteria cytopenias (anemia, thrombocytopenia), hypertriglyceridemia (449.6 mg/dL), elevated ferritin (943 ng/mL; Normal range 13-400), fever and splenomegaly for SPTCL.

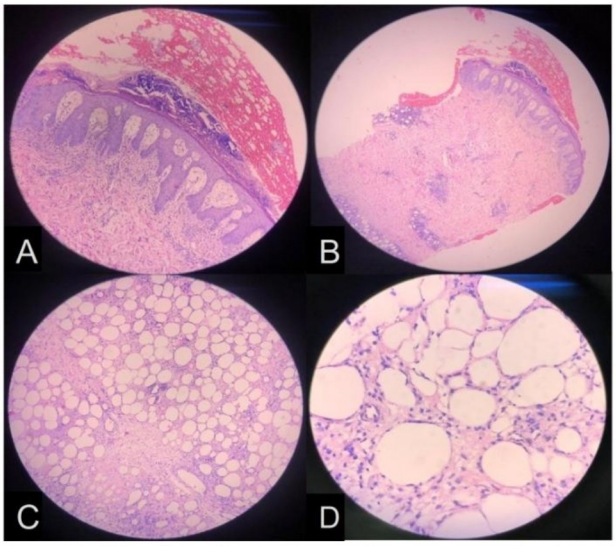

Figure 2. Final Histopathology Report: Skin punch biopsy showed **A.** epidermal necrosis overlying a mildly acanthotic and spongiotic epidermis. (x40) **B.** The dermis revealed scattered macrophages, erythrocyte extravasation, and focally dense perivascular infiltrates (mononuclear cells, neutrophils, and eosinophils) (x10). **C.** Adipocytes rimmed by lymphocytes (40x) **D.** Adipocytes rimmed by lymphocytes, disruption of adipocyte membranes, and foci of histiocytes containing cellular debris highly suggestive of subcutaneous panniculitis-like T-cell lymphoma (x100)

Cefepime and azithromycin were completed. She was clinically out of infection. Other supportive measures included albumin infusion for the severe hypoalbuminemia. Tetanus toxoid and immunoglobulin were also given for tetanus prophylaxis. Fusidic acid cream and miconazole cream were applied on the skin lesions. Essentiale, a hepatoprotectant was also started. Prednisone was started at 1 mg/kg/day with gradual resolution of ulcers, non-appearance of new skin lesions, and lysis of fever. There was marked lipoatrophy and hyperpigmentation (Figure 38) with areas of cutaneous depression.

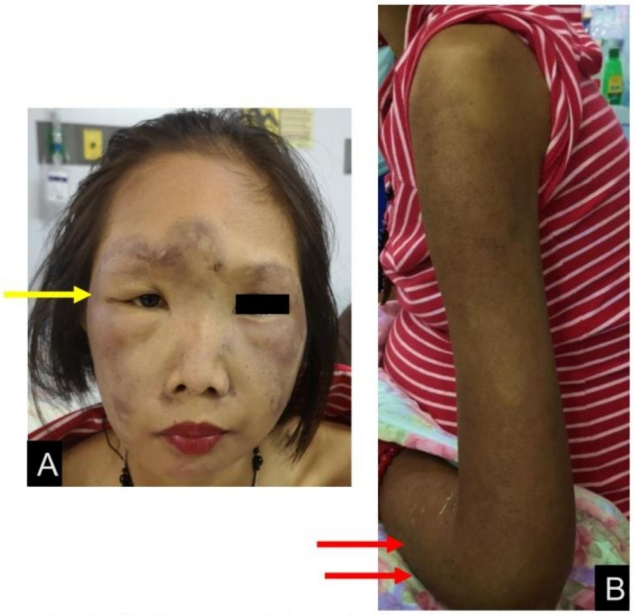

Figure 3. Patient's cutaneous lesions during steroid therapy.
A. There is a significant resolution of lesions with reduced swelling of the right eye (yellow arrow) with disappearance of violaceous pigmentation and **B.** Resolution of the plaque in the upper extremity (red arrows) leaving marked hyperpigmentation and

The patient was discharge improved with oral prednisone. She was advised close follow-up in our outpatient department. Final diagnosis was subcutaneous panniculitis, T-cell-like lymphoma with hemophagocytic syndrome.

DISCUSSION

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of disorders involving malignant monoclonal proliferation of lymphoid cells in lymphoreticular sites, including lymph nodes, bone marrow, spleen, liver, and GI tract. According to 2015 Philippine cancer Facts and Estimates3, the estimated age-standardized national incidence rates of NHLs are 3.1 per 100,000 in both sexes, 3.6 among males, and 2.7 among females. The classification of non-Hodgkin lymphoma is complex and ever-evolving, with more than 50 different subtypes listed in the latest World Health Organization classification[4].

Cutaneous T-cell lymphoma (cTcLs), cancers of the T lymphocytes, is a rare group of NHLs that arise primarily in the skin. They account for four percent of all cases of NHL.[5] It has various signs and symptoms, outcomes, and treatment options.[5] Mycosis fungoides (MF) and Sezary syndrome (SS) are the two most common subtype of cTcLs, which are still considered rare disorders.

SPTcL is classified under cTcLs with indolent clinical behavior.[10] It is also one of the rarer subtypes of cTcLs, comprising less than 1% of the entire NHL.[1] It is a cytotoxic T-cell lymphoma that preferentially infiltrates the subcutaneous adipose tissue. The exact prevalence and incidence of this disease is unknown globally. The largest case series from eight European cutaneous lymphoma centers reported 83 cases. Another 10-year retrospective study from different centers listed less than 20 cases. [8,12]

We are presented with a 21-year-old female with a history of intermittent fever associated with waxing and waning of skin indurations. It mostly occurs in females with a median age of 29 years old based on four Asian case series on SPTcL.[12,19,20,21] There has been no published data for any racial predilection.

The associated clinical sign and symptoms in SPTcL are nonspecific. Sixty percent of patients with SPTcL may have systemic symptoms such as fever, chills, night sweats, and weight loss.[1,2,9] Other clinical findings include hepatomegaly and/or splenomegaly, abdominal abnormalities (tenderness, distension), and serosal effusions.[1,7] Facial swelling has also been reported in some cases.[10] All of these systemic findings are seen in our patient. These non-specific signs and symptoms of SPTcL more often presents as a diagnostic dilemma to clinicians.

Despite the myriad of systemic symptoms of SPTcL, skin lesions will always be present.[10,12,17,18,19] They are classically indurated, poorly circumscribed, cutaneous nodules and plaques, often multifocal, and mostly involving the limbs.[6,7] Most patients presented with generalized skin lesions involving the legs (45 cases), the arms (39 cases), and/or the trunk (35 cases), and less commonly the face (16 cases). Fourteen patients presented with solitary or localized skin lesions.[10] They remain discrete or coalesce to form large indurated plaques up to 20 cm in diameter and with varying skin color.[7,8,10] Ulcerations can occur but are significantly uncommon.[9,10] Facial involvement is rare [10] and orbital involvement is even lesser.[10,24] It is interesting to note that this patient initially

had fever followed by the appearance of skin lesions after two weeks. However, it only included the lower extremities, and eventually resolved leaving hypopigmented patches. It then re-appeared in the upper extremities with more prominent indurations including a right eye swelling.

Approximately 14-17% of SPTcL have hemophagoyctic syndrome.[25] This is a rare feature in certain cases of SPTcL. However, cases are sporadic and less dueto its rarity. These patients have cytopenias and elevated liver enzymes.[9] These laboratory findings, along with hypertriglyceridemia, elevated ferritin, presence of fever, hepatomegaly, and/or splenomegaly support the diagnosis of HPS (Appendix8). All patients with HPS show hepatosplenomegaly, high serum ferritin, and high LDH level. The presence of HPS harbors a poorer prognosis. However in the case series by Willhemze, this statement was contradicting.[10] Patients with HPS were not associated with mortality. Interesting to note that upper extremity involvement portends a poorer prognosis.[10]

The biopsy for histopathological interpretation is commonly the first step for diagnosis.[10] All cases show a predominantly subcutaneous atypical lymphoid infiltrate resembling lobular panniculitis. It exhibits adipotropism where individual fat cells are rimmed by lymphocytes. This is very characteristic of SPTcL.[1,9,10,12] However, the H&E staining is not enough to support the diagnosis of SPTcL. Lupus erythematous panniculitis (LEP) is a mimicker of SPTcL and its closest differential. Clinically distinguishing the two can be very difficult. In a large case series, some of the patients had co-existent LEP and SPTcL. Some cases were initially classified as LEP but turned out to be SPTcL. LEP and SPTcL can have overlapping features both clinically and histologically hence some describe both as a spectrum.[22]

LEP always presents with nodular lesions that could also indurate. Biopsy of LEP shows epidermal involvement, mucin depositions, presence of reactive germinal centers, clusters of 8 cells, or considerable numbers of admixed plasma cells.[23] All of which are absent for this case.

Differentials for LEP/SPTcL include squamous cell carcinoma of the skin. Polyarteritis nodosa and erythema induratum (EI) were considered based on constitutional symptoms and skin lesions. However, history and biopsy findings ruled them out. Furthermore, El shows marked septal and lobular granulomatous panniculitis which is not found in our patient. lmmunohistochemical staining is warranted to differentiate these entities.

All cases of SPTcL are positive for cD3, cD8, granzyme B and negative for cD20, and cD56 in a large case series.[10,12] One patient had positive cD4 stain but was still considered as SPTcL. Our patient demonstrated strong positivity for cD3, cD8, granzyme B and negativity for cD20, cD4, and cD56. cD8+ staining is useful in identifying neoplastic cells rimming adipocytes.[17] The diagnosis of SPcTL is based on the patient's clinicopathologic and immunohistochemical findings.

There is no standard of treatment approach in these patients due to the rarity of this condition. The patients are treated with systemic immunosuppressive alone or in combination with chemotherapy such as in cHOP regimen (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone) in one case series.[10] Initial treatment with cHOP regimen resulted in a sustained complete remission in 16 (64%) of 25 patients. However, treatment with only prednisone or other immunosuppressive agents gave similar results.[16] This observation raises the question whether such patients should be routinely treated with cHOP (-like) therapy or even more aggressive regimens. ln our patient, prednisone (1 mg/kg/day) was given alone to our patient with gradual clearing of the skin lesions with no recurrence since. Other treatment modalities include radiotherapy, stem cell transplantation, and phototherapy. However, therapies are variegated and standardized treatments have yet to be established.

The tropism of SPTcL for adipocytes answers the lipoatrophy consistent with response to steroid therapy. General reduction of fat tissue contributes to the cutaneous depression and lipoatrophy of patients after resolution of these neoplastic lymphocytes around adipocytes. Resolution of lesions result in lipoatrophy followed

by localized cutaneous depression and hyperpigmentation.[7,9,10] Our patient had significant resolution of cutaneous lesions which left lipoatrophy and marked hyperpigmentation.

SPTcL has a favorable prognosis with a 5-year survival rate of 80%.[10] However, the presence of hemophagocytic syndrome harbors a poorer prognosis, hence a close follow-up for these patients must be instilled.[10,19] Although in some large retrospective studies with systemic involvement and HPS, these were not associated with increased mortality.[12]

SUMMARY

Subcutaneous panniculitis-like T-cell lymphoma is a rare disorder. An associated hemophagocytic syndrome makes this case an even rarer one.

This is a 21-year old Filipino female who sought consultation due to intermittent fever associated with multiple eruptions of cutaneous lesions. Further clinical investigation prompted a skin lesion punch biopsy revealing atypical lymphoid infiltrates with lobular panniculitis consistent with SPTcL. Immunohistochemical studies stained strongly positive for cD3, cD8, granzyme 8 and negative for cD20, cD4, and cD56. She was given prednisone (1mg/kg/day) with gradual resolution of cutaneous lesions leaving a marked hyperpigmentation and lipoatrophy.

A step-wise approach of history and physical examination, biopsy, and immunohistochemical staining is essential to the proper diagnosis of these cases. No existing standard therapeutic approach for SPTcL exists. Patients may receive a variety of treatments. She was given prednisone at 1mg/kg/day with gradual resolution of ulcers, non-appearance of new skin lesions, and lysis of fever. Our experience will contribute to the pool of knowledge in these types of patients.

CONCLUSION

Malignancy particularly lymphoma should be a differential diagnosis in patients with recurrent intermittent fever and constitutional symptoms. SPTcL should be considered when malignancy is associated with recurrent cutaneous lesions. A step-wise approach involving thorough history and physical examination followed by skin biopsy and immunohistochemical staining is essential in diagnosing these patients. Additional laboratory work up may disclose possible associations leading to diagnosis of syndromes such as hemophagocytic syndrome in our case. No standard therapeutic regimen exists. cHOP and cHOP-like regimens are successful in treating the disease. However, monotherapy with oral prednisone has been shown to work as well and was seen in our case.

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Appendix A
Laboratory Results

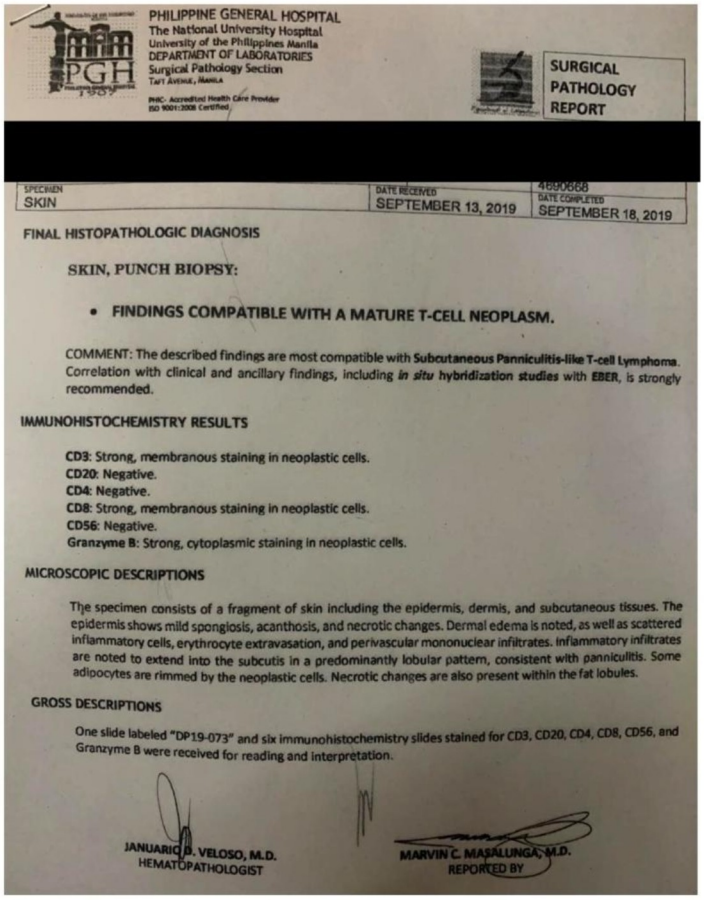
	Result	Normal range
Creatinine	48.24 umol/L	39-91 umol/L
Potassium	3.7 mmol/L	3.6-5.1 mmol/L
Sodium	138 mmol/L	136-144 mmol/L
Reticulocyte count	1.9%	0.5-1.5%
Anti HcV	Non-reactive	
HbSAg	Non-reactive	
calcium	1.81 mmol/L	2.23-2.58 mmol/L
Magnesium	0.75 mmol/L	0.74-1.03 mmol/L
cRP	1.320	cut off: 1
Anti streptolysin 0	Negative	<200
Ferritin	943 ng/mL	13-400 ng/mL
Triglycerides	449.6 mg/dL	
Anti-dsDNA	negative	

Appendix B
Diagnostic Criteria of Hematophagocytic Syndrome

Clinical features	Laboratory features
Fever*	Cytopenias of at least two lineages in the peripheral blood*
Hepatomegaly and/ or Splenomegaly*	Hemoglobin* <90 g/L Platelets <100 x 10^9/L Neutrophils <1.0 x 10^9/L Hypertriglyceridemia* and/or hypofibrinogenemia
	Fasting triglycerides ≥265 mg/dl *
	Fibrinogen ≤1.5 g/l Hemophagocytosis in bone marrow, spleen, or lymph nodes
	Low/absent natural killer-cell activity
	Hyperferritinemia (>500 mg/L)*
	High soluble interleukin 2 receptor (scD25) (>2,400 U/mL)

[a]Adapted from Jordan et al. [11]Five of eight features are required for the diagnosis
*present in the patient

Appendix C
Skin Punch Biopsy Results



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SURGICAL PATHOLOGY REPORT

[redacted]

SPECIMEN: SKIN | DATE RECEIVED: SEPTEMBER 13, 2019 | DATE COMPLETED: SEPTEMBER 18, 2019

FINAL HISTOPATHOLOGIC DIAGNOSIS

SKIN, PUNCH BIOPSY:

- FINDINGS COMPATIBLE WITH A MATURE T-CELL NEOPLASM.

COMMENT: The described findings are most compatible with **Subcutaneous Panniculitis-like T-cell Lymphoma**. Correlation with clinical and ancillary findings, including ***in situ* hybridization studies** with **EBER**, is strongly recommended.

IMMUNOHISTOCHEMISTRY RESULTS

CD3: Strong, membranous staining in neoplastic cells.
CD20: Negative.
CD4: Negative.
CD8: Strong, membranous staining in neoplastic cells.
CD56: Negative.
Granzyme B: Strong, cytoplasmic staining in neoplastic cells.

MICROSCOPIC DESCRIPTIONS

The specimen consists of a fragment of skin including the epidermis, dermis, and subcutaneous tissues. The epidermis shows mild spongiosis, acanthosis, and necrotic changes. Dermal edema is noted, as well as scattered inflammatory cells, erythrocyte extravasation, and perivascular mononuclear infiltrates. Inflammatory infiltrates are noted to extend into the subcutis in a predominantly lobular pattern, consistent with panniculitis. Some adipocytes are rimmed by the neoplastic cells. Necrotic changes are also present within the fat lobules.

GROSS DESCRIPTIONS

One slide labeled "DP19-073" and six immunohistochemistry slides stained for CD3, CD20, CD4, CD8, CD56, and Granzyme B were received for reading and interpretation.

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