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Case report

Recurrent episodes of hemophagocytic lymphohistiocytosis preceding the diagnosis of subcutaneous panniculitis-like T-cell lymphoma

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease caused by cytokine storm-induced severe inflammation, and malignant lymphoma is the leading cause of HLH in adults. We herein have reported the case of a 28-year-old man afflicted with subcutaneous panniculitis-like T cell lymphoma who presented to our facility complaining of fever, cough and myalgia for one week. Following an examination, the patient was diagnosed with hemophagocytic lymphohistiocytosis according to the diagnostic criteria of HLH 1994 protocol published in 1997. Treatment with the HLH 1994 protocol (chemotherapy with etoposide combined with steroid based regimen) was initiated and the patient recovered well. However, subcutaneous panniculitis-like T cell lymphoma was diagnosed by neck soft tissue biopsy nine months later. Thereafter, this patient then received chemotherapy using the ESHAP regimen for one cycle (etoposide 40 mg/m² BSA, cisplatin 25 mg/m² BSA and methylprednisolone 500 mg at day 1 to day 4, and cytarabine 2000 mg/m² at day 5). Currently, this patient continues his regular follow-up at our hematologic outpatient department.

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1. Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome (HPS), is a life-threatening disease caused by extreme inflammation. It is believed that uncontrolled activated lymphocytes and macrophages proliferation result in a cytokine storm, which is responsible for this critical clinical scenario. Etiologies of HLH are different in pediatric and adult patients. Primary HLH (as observed in familial HLH), X-linked lymphoproliferative syndrome, and Chediak–Higashi syndrome or viral infections, are common causes of HLH in pediatric patients.¹

On the other hand, malignancies are the leading causes of HLH in adults, particularly malignant lymphoma.² The most common-place presenting signs and symptoms of HLH are fever, hepatosplenomegaly, and cytopenias. This immune dysregulatory disorder is prominently associated with cytopenias and clinical signs and symptoms of extreme inflammation. Prompt initiation of immunochemotherapy is essential for survival, but timely diagnosis may be challenging.³ Among all the possible etiologies, malignant lymphoma is the predominant cause of HLH in adults. In 1991, Gonzalez et al⁴ described a new type of T-cell lymphoma with clinicopathological features simulating panniculitis. This new type of T-cell lymphoma had an aggressive clinical course and was often presenting with HLH. Herein, we reported a patient with subcutaneous panniculitis-like T cell lymphoma-associated HLH, although his underlying lymphoma was not diagnosed until nine months later.

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2. Case report

A 28-year-old man visited our emergency department because of intermittent fever, dry cough, and myalgia for one week. According to the patient, he had a generally unremarkable prior health history, and denied history of hepatitis or any other systemic diseases; he also denied alcohol drinking. In addition to the complained of fever and cough, the patient also described night sweating and body weight loss. However, local clinical information revealed the patient suffered from leukopenia and impaired liver function. Furthermore, our hospital laboratory data revealed leukopenia (leukocyte: 1600/ μ L; normal range: 3900–10,600), anemia (hemoglobin: 12.4 g/dL; normal range: 13.5–17.5), and thrombocytopenia (platelet: 108×10^3 / μ L; normal range: 150–400). Liver function tests showed elevated GOT (aspartate aminotransferase): 364 U/L; normal range: 8–38, and GPT (alanine aminotransferase): 235 U/L; normal range: 10–50. Abnormal LDH (lactate dehydrogenase) (2212 U/L; normal range: 120–240) was also found. The patient's abdominal computed tomography scan indicated only splenomegaly, with normal liver and gallbladder appearance (Fig. 1). In addition, hyperferritinemia: 59,384 ng/ml, low fibrinogen: 139.3 mg/dl and increased cell free IL-2R (interleukin-2 receptor): 1155.4 pg/ml were noted. A Gallium-67 scan revealed no evidence of gallium-avid tumor. The possible causes of fever were evaluation, including EBV infection, HSV, CMV or HIV and rheumatologic disease, but all of the above generated negative results. With a preliminary diagnosis of HLH, the patient then received a bone marrow examination which showed hypercellular marrow with increased infiltration of histiocytes and profound hemophagocytosis (Fig. 2). After treatment by HLH 1994 protocol (chemotherapy with etoposide combined with steroid based regimen),⁵ the patient's fever subsided and liver function improved. After that, the patient further underwent three cycles of chemotherapy with weekly etoposide.

However, 10 days after he completed the last chemotherapy round with etoposide, the patient again visited our emergency department manifesting a fever. Lab data reported leukopenia, anemia, and elevated LDH (leukocyte:3600/ μ L, hemoglobin:10.9 g/dL, platelet: 168×10^3 / μ L, and LDH:498 U/L). Thereafter,

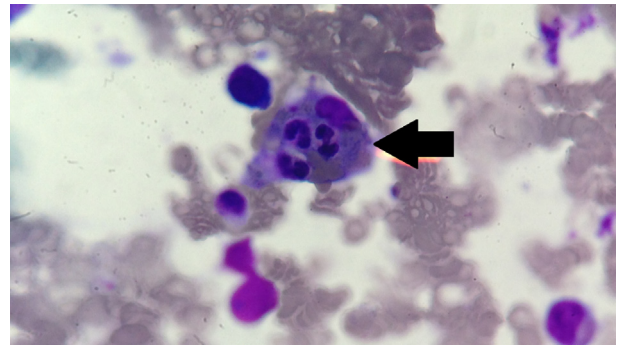


Fig. 2. Bone marrow aspiration (at initial diagnosis). Bone marrow smear showed that neutrophils are found within the cytoplasm of histiocyte (arrow), indicating hemophagocytosis.

pneumocystis jirovecii pneumonia was strongly suspected due to the patient's chest X-ray and clinical presentation. After the antibiotic Sevatrim was administered (Trimethoprim 80 mg/Sulfamethoxazole 400 mg), the patient's fever subsided. At the same time, steroid medication was discontinued to avoid occult infection.

Six weeks later, the patient's fever recurred, and subsequent examination again noted progressive leukopenia, thrombocytopenia, and elevated LDH. Repeated bone marrow examination further revealed hypocellular marrow with hemophagocytosis. Therefore, the patient received two cycles of weekly etoposide. Follow-up lab data showed improved leukopenia and decreased LDH, after which he then received another five cycles of weekly etoposide. Unfortunately, induration over the bilateral cheek with skin erythematous change and progressive facial swelling was found. Lab data indicated recurrent leukopenia (1700/ μ L) and elevated LDH (729 U/L). A CT scan of the nasopharynx reported an increased infiltration and swelling over the bilateral face, sub-mandibular region and submental region. Furthermore, several neck lymph nodes were noted, and PET (positron emission

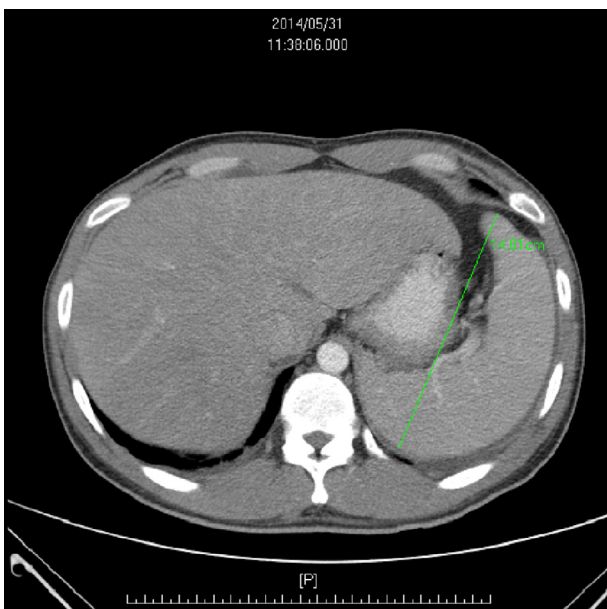


Fig. 1. CT, Abdomen (at initial diagnosis). 1. Mild splenomegaly. 2. No abnormal lymphadenopathy in retroperitoneum or pelvis.

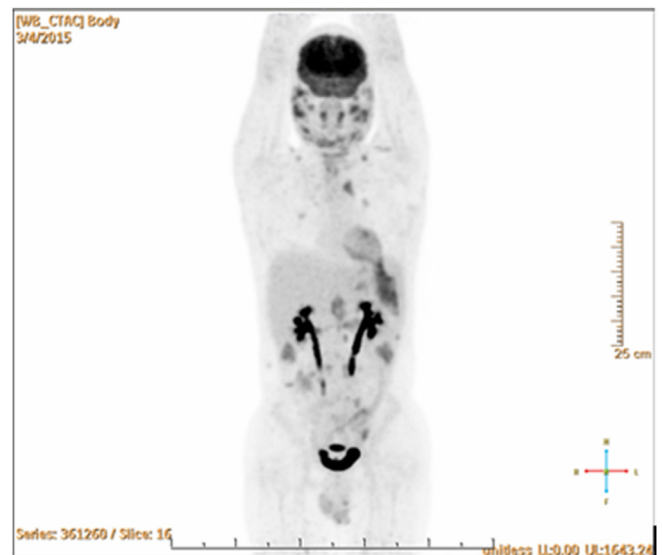


Fig. 3. Pet whole body scan (9 months after diagnosis of HLH). 1. Tumor involvement at the bilateral upper neck (level II), posterior portion of the bilateral lower neck (level V), left upper mediastinum, abdomen (mesentery), left para-aortic region, left iliac region and left deep inguinal region (Grade 3). 2. The increased FDG uptake at the superficial soft tissue of the face, anterior neck, posterior neck, bilateral upper chest wall, left upper back, right lateral abdominal wall and bilateral flank, the posterior portion of the bilateral abdominal wall (Grade 2).

tomography) scan revealed tumor involvement at the bilateral upper neck and posterior portion of the bilateral lower neck (Fig. 3). Thus, the patient received an incisional biopsy of the upper neck soft tissue, which showed panniculitis-like (Fig. 3) T-cell lymphoma and immunohistochemistry stain and showed CD3(+), CD20(–), CD56(–), CD4(–), CD8(+), TIA-1(+) and EBER(–) in-situ hybridization stain. Repeated bone marrow biopsy revealed no evidence of lymphoma bone marrow involvement. After treatment with chemotherapy using an ESHAP regimen (etoposide 40 mg/m² BSA, cisplatin 25 mg/m² BSA and methylprednisolone 500 mg at day 1 to day 4 and cytarabine 2000 mg/m² at day 5), his symptoms and ferritin level improved (Fig. 4). However, the lymphoma response requires additional image evaluation at a later date.

3. Discussion

Hemophagocytic lymphohistiocytosis (HLH) occurring as a primary or acquired disorder is a condition of uncontrolled immune system stimulation. Clinical manifestations include fever, organ enlargement, and weight loss. Additionally, laboratory tests customarily show bicytopenia or pancytopenia, cytolytic and cholestasis, serum ferritin elevation, and clotting disorders.⁶ Inherited forms of HLH produce symptoms in early childhood and can be fatal in the absence of specific treatment. In adults, the clinical spectrum ranges from mild and self-limited hemophagocytic lymphohistiocytosis to rapidly fatal multi-organ failure. However, many questions remain unresolved regarding the diagnosis and treatment in adults. Hematologic malignancies may be the main disease associated with hemophagocytic syndrome in adults. These patients have elevated early mortality, and the underlying diseases profoundly influenced the outcome.⁷

According to the HLH-2004 trial, HLH is diagnosed if five of the following eight findings are present: fever ≥ 38.5 °C, splenomegaly, peripheral blood cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen, lymph node, or liver, low or absent NK cell activity, elevated ferritin, and elevated soluble CD25 (soluble IL-2 receptor alpha).^{7,8} Our patient had fever, splenomegaly, cytopenia, hypertriglyceridemia and hypofibrinogenemia, hemophagocytosis in bone marrow, elevated ferritin and elevated soluble IL-2 receptor alpha. Initially, there was no evidence of malignancy according to both the lymphadenopathy and the initial bone marrow involvement. Thus, only HLH was diagnosed.

Regarding the treatment of HLH with HLH-1994, the estimated 3-year probability of survival overall was 55%.⁹ According to a previous comprehensive review study, ferritin level may provide a prognostic marker, and regular ferritin measurements may be useful in predicting outcomes in HLH patients.¹⁰ Our patient was treated with HLH-1994 protocol, and his ferritin dosage decreased from 59384 ng/ml to 3653 ng/ml. More importantly, his fever and cytopenia improved after the treatment.

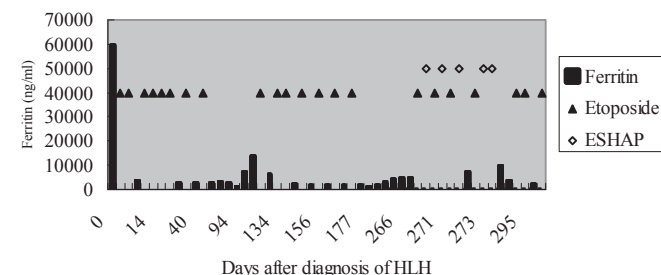


Fig. 4. Ferritin level during treatment course.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is an uncommon type of skin lymphoma. The natural history, optimal treatment strategy, and prognostic factors associated with this malignancy are not well-defined. Rein Willemze et al identified one hundred fifty-six patients with SPTCL.¹¹ Hemophagocytic syndrome (HPS) was a presenting feature in 37% of patients, and >90% of patients required treatment at diagnosis. In our patient, he was finally diagnosed as panniculitis-like T cell lymphoma confirmed by a soft tissue incisional biopsy in which immunohistochemistry stain showed CD3(+), CD20(–), CD56(–), CD4(–), CD8(+), TIA-1(+) nine months after initial diagnosis of HLH. However, according to the recent World Health Organization–European Organization for Research and Treatment of Cancer classification (WHO-EORTC), there has been a redefinition of the diagnostic criteria of subcutaneous panniculitis-like T-cell lymphoma to primary cutaneous T-cell lymphoma expressing α/β T-cell receptor (TCR) phenotype. We were limited in our ability to make further differential diagnosis of α/β or γ/δ TCR phenotype of primary cutaneous T-cell lymphoma because there were no available tests for TCR gene rearrangement.¹² Thus, this patient's final diagnosis of subcutaneous panniculitis-like T cell lymphoma was based on the pathologic report and clinical presentation.

S.R. Hoque et al reported two subsets of SPTCL: those derived from gamma-delta T cells which carry a poor prognosis, and are usually CD56 positive, and a more indolent group derived from alpha-beta T cells.¹³ In this study, two patients were CD56 positive, and both developed the hemophagocytic syndrome. Our patient belonged to the CD56 negative.

Guenova E et al reported treatment with systemic corticosteroids induced a complete remission in patients with SPTCL.¹⁴ With our patient, he received steroid therapy using the HLH-1994 protocol, which may assist treatment of SPTCL. In addition to steroid therapy, chemotherapy can also be beneficial for SPTCL patients. Zhi Li Hu et al reported treatment with combination chemotherapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone can be efficacious for a 12-year-old Chinese boy who was diagnosed with subcutaneous panniculitis-like T-cell lymphoma who presented with multiple indolent erythematous subcutaneous nodules on both extremities.¹⁵ Avninder Singh et al reported a successful regression in skin lesions and constitutional symptoms in a 22-year-old woman diagnosed as SPTCL, who presented with variably sized multiple nodules on both legs after five cycles of a cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen.¹⁶ In addition, Yu et al reported that allogeneic hematopoietic stem cell transplantation could possibly provide survival benefits to T-cell lymphoma-associated HLH by graft-versus-lymphoma effect.¹⁷

With our patient, owing to the initial presentation with HLH, we applied aggressive treatment with etoposide-based chemotherapy with ESHAP regimen. Currently, the patient has no fever or other constitution symptoms. His medical plan includes a regular follow-up and review of clinical presentation including skin and subcutaneous lesion and constitution symptoms and laboratory data.

In conclusion, the underlying disease leading to HLH is crucial to each patient's treatment and outcome. However, not all patients' underlying disease can be identified when hemophagocytic lymphohistiocytosis is diagnosed. Similar to our patient, subcutaneous panniculitis-like T-cell lymphoma may present initially with hemophagocytic syndrome without evidence of other etiology. While the optimal treatment of HLH remains controversial, current treatment regimens usually involve high dose corticosteroids, etoposide or cyclosporin. The HLH-1994 protocol is considered useful for treatment of hemophagocytic lymphohistiocytosis, but corticosteroid administration is often found to be a

risk factor attributed to developing PjP in these patient populations.^{18–20} The threshold of “how much for how long” regarding steroids and risk for PjP is unknown.¹⁹ Thus more specific treatment for underlying disease like SPCTL may be the most important future consideration.

Conflict of interest

None.

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