Occult Subcutaneous Panniculitis-like T-cell Lymphoma with Initial Presentations of Cellulitis-like Skin Lesion and Fulminant Hemophagocytosis

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Hemophagocytic syndrome (HPS) may be primary or secondary to malignancies, infections, autoimmune diseases, or drugs. In most cases, HPS occurs at the same time as the diagnosis of underlying malignancy or when it relapses. In rare situations, the neoplastic disease can be occult, even for more than a decade. We report the case of a 28-year-old woman admitted because of HPS. Treatment with etoposide for fulminant HPS was effective. Four months later, she was admitted again because of newly developed subcutaneous nodules and cellulitis-like skin lesions over her legs. Excisional biopsy of subcutaneous nodule showed subcutaneous panniculitis-like T-cell lymphoma. After etoposide, solumedrol, cytosine arabinoside, and cisplatin regimen chemotherapy, both skin lesions and subcutaneous nodules disappeared. In conclusion, for patients presenting with HPS and cellulitis-like skin lesions, occult lymphoma should be considered, which might not be diagnosed for months, even years. Adequate treatment, including steroid and chemotherapy against malignant lymphoma, should be started as soon as possible for patients with fulminant HPS because of its fatal course. [J Formos Med Assoc 2007;106(2 Suppl):S55–S59]

Key Words: adult onset Still’s disease, fever of unknown origin, hemophagocytic syndrome, panniculitis-like T-cell lymphoma

Hemophagocytic syndrome (HPS) is a clinicopathologic entity characterized by high-grade fever, hepatosplenomegaly, pancytopenia, hyperferritinemia, and hypertriglyceridemia.1 HPS may be primary, as observed in familial hemophagocytic lymphohistiocytosis, X-linked lymphoproliferative syndrome, and Chediak-Higashi syndrome.2 It may be secondary to malignancies, infections, autoimmune diseases, or drugs.3 Clinical histologic findings include accumulation in the reticuloendothelial system of activated macrophages showing phagocytosis of hematopoietic cells. HPS occurs in children as a familial disease, in adults in association with malignant neoplasm, and in both as a secondary event in the course of acute infection, generally of viral etiology or triggered by causes not always identified.4 We report the case of a 28-year-old woman who presented with HPS and cellulitis-like skin lesions over her lower legs. She was treated with etoposide for the fulminant HPS. Four months later, several subcutaneous nodules developed. Biopsy showed subcutaneous panniculitis-like T-cell lymphoma. This case is a rare example of occult lymphoma presenting with fulminant HPS and cellulitis-like skin lesions.
Case Report

A 28-year-old woman was admitted after having the following syndromes for 2 days: fever up to 39°C, chills, general soreness, arthralgias, and headache. Urine and blood cultures were sterile. Cerebral spinal fluid study showed initial pressure of 125 mmH\(_2\)O with no white blood cells (WBCs). Protein, glucose, and lactate dehydrogenase (LDH) in cerebral spinal fluid were 37 mg/dL (normal, 15–45), 53 mg/dL (normal, 50–75), and 56 U/L (normal, <20), respectively. Viral serology tests, including human immunodeficiency virus, Epstein–Barr virus, cytomegalovirus, and varicella zoster virus, were all negative. Epstein–Barr virus was also not detected by real-time quantitative polymerase chain reaction. Renal and liver function tests were within normal limits, except for elevated LDH (570 U/L; normal, 120–240). Her serum triglyceride level was 110 mg/dL (normal, 20–200). Both prothrombin time and activated partial thromboplastin time were not prolonged. Sonography of the abdomen showed no special infection source, except hepatosplenomegaly. No active lesions were noted on chest X-ray. Antinuclear antibody and rheumatoid factor were negative. Fever persisted despite empirical antibiotics.

During admission, fever-related evanescent skin rash appeared on her trunk. Her ferritin increased from 1371 ng/mL to 118,850 ng/mL (normal, 9–20) in 2 weeks. Her leukocyte, hemoglobin, and platelet levels dropped from \(3 \times 10^9/L\) to \(1.57 \times 10^9/L\) (normal, \(4 \times 10^9\) to \(8 \times 10^9\)), \(12.4\) g/dL to \(8.0\) g/dL (normal, \(12\) to \(14\)), and \(190 \times 10^9/L\) to \(41 \times 10^9/L\) (normal, \(140 \times 10^9\) to \(400 \times 10^9\)), respectively. Bone marrow examination showed a hypocellular marrow with hemophagocytosis (Figure 1). Skin biopsy of the evanescent rash showed peri-vascular infiltration of small lymphoid cells in the upper dermis. No evidence of vasculitis or leukemic cells was found. Serum aspartate aminotransferase, alanine aminotransferase, and LDH increased to 487 U/L, 319 U/L, and 1774 U/L, respectively. HPS was diagnosed by fulfilling the criteria of hemophagocytosis in bone marrow, fever up to 39°C, pancytopenia, elevated LDH, hyperferritinemia, and hepatosplenomegaly. Neither methylprednisolone pulse therapy (750 mg/day for 3 consecutive days) nor intravenous immunoglobulin reduced the fever. Because of the fulminant HPS, although the cause was unknown, she was treated with etoposide. Fever and skin rash subsequently subsided after the treatment. Her hemogram returned to normal. Repeated bone marrow examinations showed normal bone marrow. The patient was discharged in a stable condition 1 month after being admitted.

Four months later, she suffered from painful erythematous macupapules with local heat over
her lower legs. She also had intermittent fever. Her hemogram was normal. Two days later, multiple 1 × 1 cm subcutaneous nodules developed over her upper back, posterior neck, and left arm. The nodules were firm, well defined, and fixed. A left arm nodule was excised. Microscopic examination found subcutaneous panniculitis-like T-cell lymphoma (Figure 2). Section disclosed a tumor in a panniculitis pattern with perivascular infiltration from deep dermis to subcutaneous fat. Immunohistochemical staining for CD3 and CD8 was positive (Figure 3), but not for CD4 and CD45. In situ hybridization for Epstein–Barr virus encoded ribonucleic acid showed negative nuclear labeling of tumor cells. She was treated with etoposide, solumedrol, cytosine arabinoside, and cisplatin (ESHAP) chemotherapy regimen. The lower leg skin lesions and subcutaneous nodules diminished. She completed her five cycles of ESHAP regimen chemotherapy in the following 6 months and remained in a stable condition for another half year.

Discussion

HPS is a clinicopathologic entity characterized by high-grade fever, hepatosplenomegaly, pancytopenia, hyperferritinemia, and hypertriglyceridemia. Uncontrolled T-lymphocyte activation might play a critical role in promoting macrophage activation and the formation of a cytokine network. In patients with active HPS, serum levels of the T helper 1 lymphocyte cytokines interferon-γ, interleukin 12, and interleukin 18 are significantly higher than in the remission phase of the disease or in healthy controls. HPS has since been associated with a variety of viral, bacterial, fungal, and parasitic infections, as well as with collagen-vascular diseases and malignancies, in particular lymphoma. Takahashi et al conducted a clinical analysis of 52 adult patients with HPS to find that underlying diseases are heterogeneous. Lymphoma-associated HPS is clearly the most common etiology of adult HPS, regardless of the initial presentation. Identification of the etiologies of HPS is usually time-consuming. Delayed treatment of HPS would result in a fatal outcome due to its fulminant clinical course. According to guidelines proposed by Takahashi et al, when HPS is refractory to glucocorticoid or intravenous immunoglobulin therapy for 2 weeks, chemotherapy against malignant lymphoma is the recommended treatment. In most cases, diagnosis of HPS occurs at the same time as diagnosis of the underlying malignancy or with relapse of the malignancy. In rare situations, however, the neoplastic disease can be occult for months, and even for years. In our patient, the subcutaneous panniculitis-like T-cell

Figure 3. Immunohistochemical staining of subcutaneous nodule biopsy with (A) CD3 and (B) CD8 shows positively stained atypical lymphocyte cells (400×).
lymphoma was occult for 4 months. On the other hand, the initial presentation of subcutaneous panniculitis-like T-cell lymphoma with HPS mimics several diseases, such as cellulitis, adult onset Still’s disease, and sepsis. Moreover, viral infection-related HPS cannot be entirely ruled out by normal cultures and serology tests before pathologic evidence of malignancy. During the latent period, most skin biopsies fail when the cellulitis-like lesions are present. Repeated biopsies are usually required. Subcutaneous nodule biopsy provides a reliable diagnosis.

Subcutaneous panniculitis-like T-cell lymphoma is a post-thymic T-cell neoplasm characterized by lipotrophic lymphohistiocytic infiltrate commonly presenting as subcutaneous nodules resembling panniculitis. Two clinical courses are reportedly observed; a prolonged course of recurrent panniculitis or a rapid clinical deterioration secondary to the HPS. Low peripheral WBC count, elevated LDH, presence of HPS at diagnosis, and expression of the γ/δ T-cell receptor by tumor cells are poor prognostic factors. The mortality rate of subcutaneous panniculitis-like T-cell lymphoma is around 50% with a mean survival of 22 months. The frequency of HPS in subcutaneous panniculitis-like T-cell lymphoma is around 33%. When subcutaneous panniculitis-like T-cell lymphoma is combined with HPS, the mortality rate is even higher, about 81%.

Even though immunosuppressive therapy and radiotherapy are alternative treatments for subcutaneous panniculitis-like T-cell lymphoma, anthracycline-based chemotherapy regimens provide both better efficacy and longer remission duration. In the review by Weenig et al, one or more complete remissions were reported in 32% of cases, and 54% of the remissions lasted longer than 6 months. For subcutaneous panniculitis-like T-cell lymphoma associated HPS patients, however, conventional chemotherapy did not change the outcome. Patients treated aggressively with stem cell transplantation appeared to have an improved overall survival.

In summary, subcutaneous panniculitis-like T-cell lymphoma is a rare disease accompanied by HPS. At the beginning, the diagnosis might be confused with adult onset Still’s disease, overwhelming infection, viral infection-related HPS, or cellulitis. In rare situations, the underlying malignancy might be occult for months to years. For any suspected cases, early multiple agent chemotherapy is necessary to avoid fatal outcome from the disease’s aggressive behavior.

References

