Anaplastic T-Cell Lymphoma Associated with Hemophagocytic Syndrome: A Case Report

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ABSTRACT

Hemophagocytic syndrome (HPS) is mostly associated with malignant and infectious diseases. The causes and prognosis of this clinical syndrome depend on the underlying disease. And also treatment of this disease must be arranged according to the underlying causes. While non-Hodgkin's lymphomas (NHL) associated with HPS has been frequently observed, anaplastic T-cell NHL associated with HPS has been rarely reported. In this article we report a case of Ki-1$^+$ anaplastic T-cell lymphoma associated with HPS in a 16-year-old woman who presented with fever and lymphadenopathy.

Key Words: Anaplastic T-cell lymphoma, Hemophagocytic syndrome.

ÖZET

Bir Olgu: Hemofagositik Sendroma Eşlik Eden Anaplastik T-hücreli Lenfoma

Hemofagositik sendrom (HPS) sıklıkla malign ve infeksiyöz hastalıklara eşlik eder. Bu klinik sendromun sebep ve prognozu altta yatan hastalığa bağlıdır. Tedavi de altta yatan hastalığa göre düzenlenmelidir. HSP'ye eşlik eden non-Hodgkin lenfoma'ya sık rastlanırken, anaplastik T-hücreli lenfoma çok seyrek bildirilmiştir. Bu yazıda ateş ve lenfadenopati ile gelen 16 yaşında bir kadında Ki-1$^+$ anaplastik T-hücreli lenfomaya eşlik eden HPS sunulmaktadır.

Anahtar Kelimeler: Anaplastik T-hücreli lenfoma, Hemofagositik sendrom.

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INTRODUCTION

The term hemophagocytosis describes the pathologic finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets, and their precursor cells[1]. This phenomenon is an important finding in patients with hemophagocytic syndrome (HPS), more properly referred to as hemophagocytic lymphohistiocytosis (HLH)[2]. HLH is a distinct clinical entity characterized by fever, pancytopenia, splenomegaly, and hemophagocytosis in the bone marrow, liver, or lymph nodes. The syndrome, which has also been referred to as histiocytic medullary reticulosis, was first described in 1939[3]. HLH was initially thought to be a sporadic disease caused by neoplastic proliferation of histiocytes. Subsequently, a familial form of the disease (now referred to as familial hemophagocytic lymphohistiocytosis) was described[4-6]. HLH has since been associated with a variety of viral, bacterial, and parasitic infections, as well as collagen-vasculer diseases and malignancies, particularly lymphomas[7-10]. In 1979, Risdall et al described a virus-associated hemophagocytic syndrome (VAHS)[11]. Subsequent reports have further broadened the disease spectrum of hemophagocytic syndrome. It may be associated with infections [such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), adenovirus, *Salmonella*, and tuberculosis], hematopoietic malignancy, drugs (phenytoin), autoimmune disease, familial, various immunodeficiencies and many other conditions[12].

Most cases of lymphoma associated hemophagocytic syndrome (LAHS) are comprised of T-cell or NK-cell lymphoma[13]. However, there are some reports mentioning HPS cases secondary to B-cell lymphomas are higher than T-cell lymphomas, and it can be said that lymphoma associated hemophagocytic syndrome may originate from B, T or NK cells[14-16]. Ki-1$^+$ anaplastic T-cell lymphoma is a rare form of T-cell lymphomas and Ki-1$^+$ anaplastic T-cell lymphoma associated with HPS is much more infrequently reported[17].

We report a case diagnosed Ki-1$^+$ anaplastic T-cell lymphoma with HPS confirmed in the bone marrow and lymph node biopsy findings.

A CASE REPORT

A sixteen-year-old woman was admitted to our clinic, because of fever, chills, and general weakness. She had complaints of fever rising to 40-41 C with chills and lymphadenopathy in her right axilla for 20 days. Physical examination revealed fixed, painful lymphadenopathy of 3 x 2 cm in right axillary fossa. Physical and ultrasounographic examination showed normal size of liver and spleen.

The complete blood count showed; WBC: 1900/mm^3, haemoglobin: 9.1 g/dL, and platelet: 78.000/mm^3. Lymphocyte dominancy and activated lymphocytes with large basophilic cytoplasm and small amount of granules were detected in peripheral blood smear. Blood chemistry analysis revealed AST: 97 U/L (N: 45 U/L), ALT: 67 U/L (N:45 U/L), LDH: 1433 U/L (N: 450 U/L), urea: 29 mg/dL (N:20-40 mg/dL), creatinin: 0.94 mg/dL (N: 1 mg/dL). Coagulation profile with automatic coagulometer showed that; prothrombin time of 13.7 sec. (N: 11-13 sec.), partial thromboplastin time of 32 sec. (normal: 28-40 sec.), and fibrin degraded products (FDP) > 20 uL/mL (N < 5 uL/mL). Cultures of blood and urine were sterile. Serological tests for viral infections and connective tissue disease including ANA, ASO, Paul-Bunnel, Monospot test, Rose-Bengal, *Salmonella typhi* H, *S. typhi* O, CMV IgM, parvovirus B19 IgM were negative. PPD was negative. Ultrasound of the abdomen showed multiple lymphadenopathy with the diameter of 2 to 3 cm in paraaortic region.

Bone marrow aspiration and biopsy was performed to determine the cause of pancytopenia. Slight increase in monocyte/macrophage precursor cells, and hemophagocytosis of normoblast, erithrocyte and platelets were detected in bone marrow aspiration. Bone marrow biopsy revealed hyperplasia in three lineages and increased number of macrophages and hemophagocytosis including lymphocytes, platelets and erythroid cells.

Right axillary lymph node biopsy was performed to make a differential diagnosis of HPS. Lymph node biopsy revealed the destruction of normal structure and infiltration by histiocytes with large acidophilic cytoplasm and picnotic nuclei. Hemophagocytosis could be detected in some macrophages. A less number of seeded large neoplastic cells could be seen in lymph node biopsy specimen. These neoplastic cells contained large scanty basophilic cytoplasm and a kidney-shaped nucleus with 2 or 3 nucleolus. In immunohistochemical analyses, CD45RO, CD30, EMA and ALK-1 were

positive and CD20, cytokeratine were negative in these neoplastic cells, and, CD 68 was positive in histiocytes (Figures 1,2). According to these findings, the patient was diagnosed as anaplastic T-cell lymphoma and associated hemophagocytosis in bone marrow and lymph node.

While we were planning chemotherapy with CHOP regimen, the patient was transfered to another hospital because of social insurancy problems.

DISCUSSION

HPS frequently occurs in associated with infection or neoplasm[12]. HPS has been reported most commonly after EBV, CMV, and adenovirus infection. Bacterial and parasitic infections, as well as arthropod bites, have also preceded HPS[12].

Associated neoplasms have included gastric carcinoma, overian carcinoma, multiple myeloma, acute myelocytic leukemia, chronic myelocytic leukemia, hairy cell leukemia, Hodgkin's disease, B-cell lymphoma and T-cell neoplasms[12-17]. HPS is less common in the course of benign angioimmunoproliferative lesions, lymphoblastic lymphoma, and Lennert's lymphoma, among others[18].

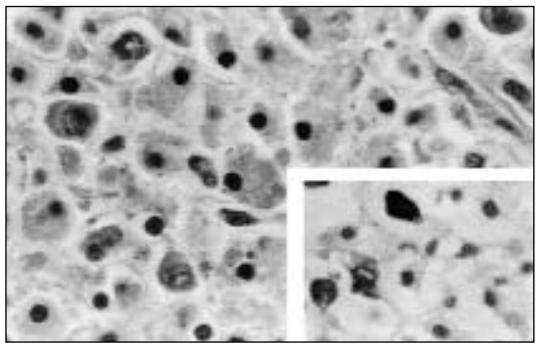

Figure 1. Histiocytosis and hemophagocytosis in lymph node (A) (HE x 1000), and, ALK-1 positivity in neoplastic cells (B) (DAB x 400).

Patient with HPS usually present with fever, sweats, weakness, lymphadenopathy, hepatosplenomegaly, pancytopenia, and extranodal involvement of marrow, lungs, central nervous system, heart, and other organs[18]. The most prominent histopathologic feature is a proliferation and infiltration of benign histiocytes, displaying a striking degree of hemophagocytosis in the bone marrow, lymph node sinuses and medullary

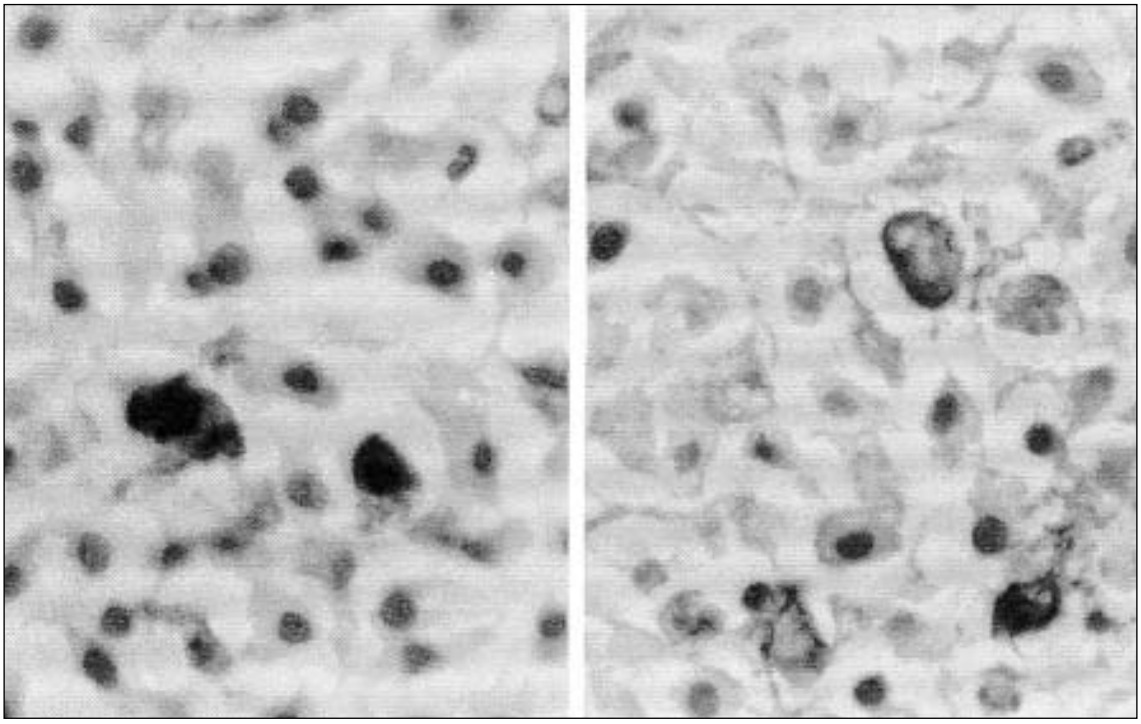

Figure 2. CD30 positivity (A) and EMA positivity (B) in neoplastic cells (DAB x 1000).

cords, the sinusoid and red pulps of the spleen, the sinusoid and portal areas of the liver and the lumina of the small vessels in the lungs and kidneys[19].

The cause of HPS is still unclear, although the possible role of cytokines produced by B-cells and T-cells and increased activity of monocyte-macrophage system have been suggested. Phagocytosis by monocytes and macrophages of blood cells is a hallmark of hemophagocytic syndrome. Nitro-blue tetrazolium reduction by monocytes from patients with HPS is approximately six times that of control monocytes and that shows hyperactivation of monocyte/macrophage system cells[20]. Activated macrophages have also increased expression of MHC class I and II molecules and M-CSF receptor expression[21]. Excessive activation of monocytes in HPS may be due to stimulation by high levels of activating cytokines. High levels of interferon-γ (IFN-γ), soluble interleukin-2 receptor, tumor necrosis factor-α (TNF-α), interleukin-1, and interleukin-6 have been demonstrated, suggesting that elaboration of the activating cytokines by T-helper cells promotes activation of macrophages in this disease[22-24]. Oversecretion of interleukin-18 and enhancement of IFN-γ and TNF-α production by interleukin-18, induction of Fas ligand expression on lymphocytes has been described recently[25]. Serum levels of soluble Fas ligand, which can trigger apoptosis in such Fas expressing tissues as the kidney, liver, and heart, also appear to be increased in HPS[26].

The exact mechanisms by which abnormal cytokine elaboration by T-lymphocytes results in HPS remain unclear. However, data from patients with EBV-associated HPS, as well as HPS associated with EBV-positive T-cell lymphomas, may be instructive. Although T-lymphocytes lack the putative EBV receptor CD21, the presence of episomal EBV genome in T-cell lymphomas and T-lymphocytes from patients with virus-associated HPS is well described[27,28]. EBV-positive T-cell lymphomas appear to elaborate TNF-α more frequently than either EBV-positive B-cell lymphomas or EBV-negative T-cell lymphomas[29]. Ki-1$^+$ anaplastic T-cell lymphoma is infrequently associated with EBV infection. The EBV genome has been detected in neoplastic cell nuclei with in situ hybridization of Epstein-Barr early RNA-1 (EBER-1) in only 12% of cases[30]. Association of EBV infection was not detected in our case either.

The familial form of HPS occurs in young children as a genetic disorder with autosomal recessive inheritance; possible loci for a responsible gene or genes have recently been mapped to the long arms of chromosome 9 and 10[31]. It has also been shown that some cases of B-cell non-Hodgkin lymphoma associated with a HPS have chromosomal abnormalities at 14q32 or 19q13[32].

Treatment of HPS should be directed to the underlying disease process. EBV-associated HPS is almost universally fatal if untreated, with death usually resulting from hemorrhage, infection, or multiorgan failure[33]. The poor prognosis of this syndrome suggests that patients should be treated initially with combination chemotherapy and immunotherapy, regardless of whether they are thought to have familial form. Chemotherapy with etoposide (which is toxic to macrophages) and dexamethasone is recommended[34]. The increasing recognition of the important role of T-lymphocytes in HPS has led to recommendation that chemotherapy be combined with cyclosporin A immunotherapy[34].

B-cell or T-cell lymphoma associated HPS can be treated with classical chemotherapy regimens like CHOP or mBACOD. But if the HPS occurs in immunocompromise hosts before treatment, therapy must be focused on malignancy. If it develops during chemotherapy, association with an infection must be considered. Usually anti-infectious agents and a combination of steroid and etoposide may be useful because there is cytokine storm during the acute phase of the disease[34]. If there is no response to these regimens, investigational modalities like 13-cis retinoic acid can be considered in the treatment approaches[17]. But the diagnosis procedure including excisional biopsy must be performed rapidly especially in lymphoma patients because of poor prognosis. Chemotherapy with allogeneic stem cell transplantation may be necessary for some patients[35].

HPS associated with Ki-1$^+$ anaplastic T-cell lymphoma is rarely reported in literature. Our case is very interesting with the diagnosis of Ki-1$^+$ anaplastic T-cell lymphoma associated hemophagocytic syndrome.

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