Intense myelofibrosis in a child: unusual result of EBV-associated hemophagocytic lymphohistiocytosis

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ABSTRACT

A previously healthy 12-year-old girl was admitted to the intensive care unit with severe pulmonary bleeding. Her history revealed that she had suffered from high fever, fatigue, sore throat, myalgia and generalized rash for two weeks. Physical examination revealed hepatosplenomegaly. Laboratory investigation showed pancytopenia associated with unusual high levels of serum ferritin, triglyceride and lactate dehydrogenase (LDH) and low fibrinogen levels. Apparent hemophagocytosis was seen in bone marrow aspiration. Bone marrow biopsy revealed myelofibrosis, and confirmed hemophagocytosis. IgM for Epstein-Barr virus (EBV) viral capsid antigen was found to be positive. She received chemotherapy for 10 days according to hemophagocytic lymphohistiocytosis (HLH)-2004 treatment protocol, since the symptoms persisted despite supportive therapy and intravenous immunoglobulin (IVIG) administration. However, the clinical status and laboratory findings did not respond to treatment and she died from severe pulmonary bleeding associated with prolonged ventilator support and sepsis. Intense myelofibrosis, which is reported rarely, particularly in patients with EBV-related HLH, contributed to this fatal prognosis.

Key Words: Myelofibrosis, EBV, hemophagocytic lymphohistiocytosis, child, pancytopenia

ÖZET

Çocukta ileri derecede miyelofibrosis: EBV ilişkili hemofagositik lenfohistiositozun nadir bir sonucu


Anahtar Sözcükler: Miyelofibrosis, hemofagositik lenfohistiosit, EBV, çocuk, pansitopeni
INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder characterized by high fever persisting more than seven days, hepatosplenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia and histopathological evidence of hemophagocytosis in bone marrow, spleen or lymph nodes. It may occur in primary (familial) or secondary (reactive) form. The latter can develop secondary to viral, bacterial and parasitic infections in previously healthy children as well as malignancy or collagen vascular disease; affects children at any age; and usually shows a better outcome than the primary form \[1,2\]. Some of the Epstein-Barr virus (EBV)-associated reactive HLH may be fatal if untreated, with death usually resulting from hemorrhage, infection or multiorgan failure. Despite current intensive chemotherapeutic options, it still carries unfavorable prognosis \[3,4\].

Myelofibrosis is a rare disorder during childhood and may be either idiopathic or secondary. Both are characterized by reticulin fibrosis in marrow and pancytopenia.

In this article we present the case of a patient who died from EBV-associated reactive HLH whose bone marrow biopsy showed myelofibrosis.

CASE REPORT

A previously healthy 12-year-old girl was admitted to the hospital with high fever, fatigue and sore throat for two days. She was given ampicillin and three days later was readmitted to the hospital with a generalized maculopapular skin rash, arthralgia and persistent fever above 39°C.

There was no family history of immune deficiency or early death. There was no consanguinity described between the parents and she had a healthy 20-year-old sister.

In her physical examination, hepato- and splenomegaly were detected 3 and 4 cm below costal margins, respectively. There was no palpable peripheral lymph node.

Her laboratory investigation revealed Hb: 9.6 g/dl, Hct: 30%, WBC: 18100/mm³, absolute neutrophil count: 16290/mm³, PLT: 251,000/mm³, SGOT: 36 U/L (Normal: 5-45 U/L), SGPT: 27 U/L (Normal: 5-45 U/L), ESR: 69 mm/h, CRP: 30 mg/dl (Normal <0.8 mg/dl), ASO: 195 Todd unit (Normal <200 Todd unit), negative rheumatoid factor and antinuclear antibody, C3: 99 mg/dl (Normal: 77-195 mg/dl), and C4: 36 mg/dl (Normal: 15-45 mg/dl).

Her fever persisted above 38°C and none of the blood, urine or throat cultures gave a positive result throughout the hospital course. On the 7th day of her hospitalization, her blood counts started to decrease and liver function tests were elevated. At the end of the 2nd week of her hospitalization, the results of blood count revealed Hb: 8 g/dl, Hct: 25%, WBC: 1250/mm³, absolute neutrophil count: 650/mm³, PLT: 21,000/mm³, SGOT: 1170 U/L, SGPT: 724 U/L, total protein: 4.7 g/dl, and albumin: 2.3 g/dl. Bone marrow aspiration showed mild hypocellularity, increased number of histiocytes and hemophagocytosis of red and white blood cells by macrophages. After this observation, additional laboratory tests were done, which revealed: ferritin: 11,471 ng/ml (Normal: 30-400 ng/ml), triglyceride: 387 mg/dl (Normal: 41-138 mg/dl), HDL: 17 mg/dl (Normal: 35-84 mg/dl), LDL: 42 mg/dl (Normal: 50-170 mg/dl), fibrinogen: <70 mg/dl (Normal: 200-400 mg/dl), and normal levels of IgG, IgM and IgA.

The results of serologic tests for hepatitis A, B, Parvovirus and cytomegalovirus (CMV) were not indicative for current infection. ELISA assay for human immunodeficiency virus (HIV) 1+2 and tests for anti HCV IgG, Salmonella and Brucella agglutinations were found to be negative.

She was treated with pulse methylprednisolone and intravenous immunoglobulin (IVIG) 0.5 g/kg/d for five days. Two days after completion of treatment she developed tachypnea, respiratory distress and hypoxia. Thorax computed tomography (CT) showed diffuse pulmonary hemorrhage. She was transferred to the Pediatric Intensive Care Unit (PICU) of our hospital. A very severe hemorrhage from endotracheal intubation tube was seen during her intubation. At that time, hypofibrinogenemia (100 mg/dl), prolonged PT (16.8 sec, INR: 2.1) and aPTT (44.1 sec), and thrombocytopenia (6000/mm³) were the detected risk factors for pulmonary hemorrhage. She received intensive and emergency support with erythrocyte, platelet and fresh frozen plasma transfusions, fibrinogen and factor VIIa concentrates, and following intubation, ventilation was initiated.
After she was stabilized, bone marrow aspiration was performed with biopsy. In aspiration smear markedly decreased bone marrow cellularity was seen. Bone marrow biopsy revealed 10% cellularity and myelofibrosis with grade IV reticulin fibrosis. There was no blastic infiltration, and the percentages of the cells positive for MPO, CD3 and CD79 were in the normal ranges. She was given etoposide, cyclosporine and dexamethasone according to HLH-2004 treatment protocol. EBV serology showed a clear evidence of current EBV infection. Serum EBV viral capsid antigen IgM was positive while IgG was found to be negative. She continued to receive chemotherapy. Her blood count showed a progressive decrease in all three lineages with ANC of 50/mm$^3$ and WBC of 200. She was supported with erythrocyte and platelet transfusions. She developed signs and symptoms of sepsis and Pseudomonas aeruginosa was grown from deep trans-tracheal aspirate and blood at the 13th day of hospitalization; chemotherapy was discontinued at the 10th day of the protocol. She was given broad spectrum antibiotics and regular supportive treatment with fresh frozen plasma, platelet and erythrocyte transfusions throughout her stay in PICU. During the hospitalization period, pancytopenia persisted. She experienced gastrointestinal bleeding with melena and re-bleeding from lungs despite factor VIIa and fibrinogen concentrates being used in addition to the transfusion treatment. Although intensive and dynamic support was supplied she expired at the 12th day of her hospitalization in PICU with pulmonary hemorrhage and sepsis while still on mechanical ventilation.

Parents did not give consent for autopsy but agreed to sampling for necropsy. Samples from liver, lung, spleen and kidney were taken, and were not consistent with any type of malignancies.

**DISCUSSION**

HLH and related hemophagocytic syndromes are rare but severe clinical pictures have occurred with a variety of infectious agents, as well as genetic, neoplastic and autoimmune diseases. HLH in the context of infection is best described as part of a spectrum of EBV-associated illness [1-3]. Our patient presented with symptoms, physical examination findings and laboratory results of secondary HLH, specifically EBV-associated HLH.

Since severe EBV-associated disease has a poor prognosis, it is suggested that those patients should be treated with a combined chemotherapy consisting of etoposide, dexamethasone and cyclosporine regardless of whether they are thought to have familial HLH [1,4,5]. In our patient, HLH-2004 treatment protocol was started. Treatment did not cause resolution of the symptoms and laboratory findings during the hospitalization course, and she died from sepsis.

EBV-associated pancytopenia results from autoimmune origin, rarely hypersplenism or HLH. In our patient, bone marrow aspiration revealed hemophagocytosis at the presentation of clinical findings, which was consistent with the clinical picture. However, later bone marrow biopsy showed myelofibrosis in addition to HLH as a significant cause for pancytopenia.

Myelofibrosis is a rare disorder in children. It may be idiopathic or secondary. The idiopathic form is a myeloproliferative syndrome characterized by reticulin fibrosis in the bone marrow, severe pancytopenia and in children hepatosplenomegaly. The clinical course is aggressive and without treatment rapidly fatal. Secondary myelofibrosis is also rare but occurs in children with chronic renal disease, exposure to toxins, collagen vascular disease, rickets and malignancies [6-8]. It has been commonly reported at presentation of acute megakaryoblastic leukemia [8], and less frequently Hodgkin disease [9], non Hodgkin lymphoma [6], myeloproliferative disorders [6] and leukemias [7]. It may be characterized by reticulin or collagen fibrosis in the marrow and usually with hepatosplenomegaly, various degrees of cytopenia and myeloid metaplasia. In most cases, treatment of the underlying disease or malignancy causes reversal of myelofibrosis. A transient myelofibrosis may also be seen in patients with Down syndrome in the absence of any malignancy.

This patient was doing well until clinical findings of EBV infection developed. Bone marrow aspiration/biopsy did not reveal acute leukemia or lymphoma. Neither clinical presentation nor physical and radiological investigations which she had during the course of her illness were indicative of any kind of malignancy.

Elevation in inflammatory cytokines including tumor necrosis factor-α, interferon-γ and interleukin 1α released from the activated lymphoid cells and macrophages has been reported
to play an important role in the pathogenesis of HLH\footnote{Lay JD, Tsao CJ, Chen JY, Kadin ME, Su IJ. Upregulation of tumor necrosis alpha- gene by Epstein-Barr virus and activation of macrophages in Epstein-Barr virus- infected T cells in the pathogenesis of hemophagocytic syndrome. J Clin Investig 1997;100:1969-79.}. A very significant elevation of serum ferritin and CRP levels was observed in our patient, which suggests the presence of hypercytokinemia. These observations led us to speculate that in this patient bone marrow fibrosis might be related to acute very severe inflammation secondary to HLH associated with EBV infection, in which hypercytokinemia plays a significant role.

Patients with HLH usually show the clinical and laboratory findings of disseminated intravascular coagulation (DIC). In our patient, pulmonary and gastrointestinal hemorrhage together with laboratory findings including elevated PT and aPTT, and low fibrinogen and platelet levels suggested that DIC was present. We think DIC contributed to our patient’s death.

Although it was reported that severe HLH may cause myelofibrosis\footnote{Masutani K, Fujimaru M, Tsubata Y, Natsui N, Okamura T. Double negative adult T cell leukemia with hemophagocytic syndrome. Rinsho Ketsueki 1997;1199-205.}, there is no pediatric case in the literature with myelofibrosis secondary to virus-associated HLH. As far as we know, this is the first case in the current literature who presented with EBV-associated HLH followed by severe myelofibrosis.

References