Infectious Mononucleosis with Hemophagocytosis

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ABSTRACT

We reported a case of 23-year-old Thai female with infectious mononucleosis, complicated with hemophagocytic lymphohistiocytosis (HLH). The patient presented with fever, rash, and hepatitis 2 weeks prior to admission. Physical examination revealed anemia, jaundice, splenomegaly, and maculopapular erythematous rash on trunk and all extremities. Complete blood count showed anemia with atypical lymphocytosis. Chest X-ray was unremarkable. The computed tomography of abdomen revealed splenomegaly with parenchymal liver disease. Serology was positive for Anti-EBV IgM and IgG, and also EBNA IgG with viral load of 7,500 copies/mL. Bone marrow study revealed atypical lymphoid cells, with increased histiocytes and hemophagocytic activity. Immunohistochemistry of the bone marrow specimen was positive for EBER. She was treated with dexamethasone for 1 week before admission, and was continued on dexamethasone during this admission. However, we added IVIG as the part of the treatment for 5 days. Essentially, she was clinically improved without the addition of any immunosuppressive agent. She was discharged with oral dexamethasone, and successfully tapered off without recurrence. EBV viral load was followed before discharge and it had decreased to less than 1,000 copies/mL. (J Infect Dis Antimicrob Agents 2014;31:167-71.)

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease, also known as hemophagocytic syndrome (HPS), characterized by impaired or absent activity of NK cells and cytotoxic T cells resulting in cytokine dysregulation and proliferation of histiocytes. HPS was first described by Scott and Robb Smith in 1939. Then virus-associated HPS was described in 1979 by Risdall. The incidence is difficult to estimate because of underdiagnosis. HLH has been divided into genetic HLH, which is associated with genetic abnormalities and acquired HLH. Acquired HLH can occur at any age group, and is subdivided based on its triggered conditions such as infection, malignancy, and autoimmune disease. Infection-associated hemophagocytic syndrome (IAHS) may be caused by bacteria, virus, fungus, and protozoa. The most common agents in IAHS are viruses in Herpesviridae family, particularly Epstein-Barr virus and cytomegalovirus.

Here, we reported a case of infectious mononucleosis caused by EBV, complicated with...
HLH in a young previously healthy female.

**CASE REPORT**

A 23-year-old Thai female, environmental scientist, lives in Bangkok who was previously healthy, came to an outside hospital due to prolonged fever for 2 weeks. Initially she felt feverish but no other localized symptoms observed. Four days later, she developed myalgia, nausea, and malaise that brought her to a private hospital. She was hospitalized and routine investigation was done. Complete blood count showed thrombocytopenia and atypical lymphocytosis. The physician made a presumptive diagnosis of dengue fever; however serologic testings for dengue infection including NS1 antigen were all negative. After two days of admission, she began to vomit accompanied with jaundice and epigastric pain without radiation. Liver function test showed direct hyperbilirubinemia and elevated liver enzymes. Serology for scrub typhus, viral hepatitis and peripheral blood smear for malaria were all negative. She was given intravenous dexamethasone and antibiotics (ciprofloxacin, doxycycline, and azithromycin). She continued to have progressive jaundice and computed tomography of abdomen demonstrated findings of mild splenomegaly with parenchymal liver disease without mass lesion and intra-abdominal lymph node enlargement. During admission, her hemoglobin dropped from 14.3 to 9.5 g/dL without evidence of visible bleeding. Although her appetite and jaundice had improved, erythematous rash developed on her face, extended down to her trunk and extremities as shown in Figure 1. She remained febrile and decided to come to our hospital for further evaluation.

At King Chulalongkorn Memorial Hospital, she was noted to have fever with body temperature of 38°C, regular heart rate at 110 beats per minute, blood pressure of 110/70 mmHg, and respiratory rate of 18 breaths per minute. Her skin lesion was also shown in Figure 1. She had pale and icteric conjunctivae. Oral examination showed mildly injected pharynx, swelling of tonsils with white patches coated bilaterally. Multiple subcentimeter lymph node enlargement at cervical, axilla, and groin regions were observed. Examinations of pulmonary and cardiovascular systems were normal. Abdominal examination was positive for splenic dullness. Neurological examination was within normal limit. Her complete blood count values were as follows; hemoglobin 7 g/dL, hematocrit 15.4%, white blood cells of 8,030 cells/mm³ with the differential count of 50% neutrophil, 36% lymphocyte, 3% atypical lymphocyte (monocytoid) and 9% monocyte, platelet count of 263,000 cells/mm³. Liver function tests were as follows; total bilirubin 13.19 mg/dL, direct bilirubin 10.86 mg/dL, SGOT 99 U/L, SGPT 271 U/L, ALP 169 U/L, INR 0.98. Chest X-ray was unremarkable.

The presumptive diagnosis was infectious mononucleosis, so serology for EBV and CMV (cytomegalovirus) were investigated. Anti-EBV IgG and IgM were both positive. Anti-EBNA IgG was negative. Serum EBV viral load was 7,500 copies/mL. Anti-CMV IgG and IgM were also positive, but viral load was undetectable.

Although infectious mononucleosis was diagnosed, anemia cannot be explained solely from such a condition. Bone marrow study was performed. Bone marrow aspiration demonstrated atypical lymphoid cells with increased histiocytes with hemophagocytic activity (Figure 2), that was also compatible with bone marrow biopsy findings. Immunohistochemistry was positive for CD3, and negative for CD20 as well as CD56. In situ
Figure 1. Skin lesion on her extremities.

Figure 2. Hemophagocytic activity in bone marrow.
hybridization was positive for EBV-encoded RNA (EBER). Therefore, a diagnosis of infectious mononucleosis caused by EBV infection complicated with hemophagocytosis was made.

Other blood chemistries were also tested and results were as follow; triglyceride 670 mg/dL, ferritin 13,194 ng/mL, fibrinogen 2.08 g/L in which fit the diagnostic criteria of hemophagocytosis.

On day 1 of admission, a total of 20 mg of dexamethasone was given. However her anemia continued to worsen and the team decided to start intravenous immunoglobulin (IVIG) at a dosage of 0.4 mg/kg for a total of 5 days. We did not proceed with chemotherapy given the relatively good response to IVIG administration. EBV viral load in serum at discharge fell below 1,000 copies/mL. She was discharged with oral dexamethasone as her home medications, and after several outpatient visits, EBV viral load has remained undetectable.

**DISCUSSION**

We diagnosed the patient based on revised diagnostic guidelines for HLH 2004 for the following criteria; fever, splenomegaly, cytopenia (anemia and thrombocytopenia), hyperferritinemia, hypertriglyceridemia, evidence of hemophagocytosis in bone marrow, and absence of NK cell activity. And we concluded that her HLH condition was triggered by EBV infection, which presented with infectious mononucleosis syndrome and confirmed by positive EBER in the bone marrow from in situ hybridization study.

This EBV infection most likely is the primary infection because of positive Anti-EBNA IgG. The patient was initially treated with high dose corticosteroid, but did not achieve satisfactory results. Thus, IVIG was initiated for a short course. She was gradually clinically and laboratory improved.

There was a retrospective cohort study to compare outcome of treatment with IVIG therapy and dexamethasone versus HLH-2004 protocol (etoposide-based regimen) in children with HLH. The result showed equal effectiveness between IVIG and HLH-2004 protocol. We opted to use IVIG first to avoid the risk of possible adverse events from chemotherapy, etoposide.

For evaluating treatment outcome, there were some studies suggesting a use of rapid reduction in triglyceride or ferritin as the laboratory parameters. Moreover, for EBV-associated HLH, quantitative analysis of EBV genome copy number after 4 months of therapy may be beneficial to further assess the treatment response and has more prognostic value. Our patient had favorable virological response, reduction in EBV viral load, after only 10 days of treatment, and persistent virological suppression at 4 months after treatment.

The interesting point of this case is awareness of HLH complication in patients who present with mononucleosis syndrome without improvement on supportive therapy or worsening of symptoms. When this specific condition is suspected and raised, conducting appropriate investigations, making early diagnosis, and providing treatment would bring dramatic benefits to the patient.

In conclusion, we reported the young female patient presented with infectious mononucleosis syndrome complicated with HLH. Diagnosis was made by both clinical and investigations including bone marrow study. The patient responded well to IVIG and dexamethasone therapy, confirmed by a
Reduction in EBV viral load and improvement of anemia.

References