Case Report

Epstein–Barr virus infection–Related hemophagocytic lymphohistiocytosis

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Abstract

We report a case of 27-year-old female diagnosed with hemophagocytic lymphohistiocytosis (HLH) following a recent Epstein–Barr virus (EBV) infection. A known case of relapsing remitting multiple sclerosis on corticosteroids for last 6 months presented to the critical care unit with fever, maculopapular rash and difficulty in breathing. A rapid and correct diagnosis with the precise treatment led to complete recovery of this patient. The HLH is a rare complication of primary EBV infection.

Keywords: Epstein–Barr virus, hemophagocytic lymphohistiocytosis, relapsing-remitting multiple sclerosis

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Introduction

The hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome that occurs due to unregulated activation of lymphohistiocytic cells and results in hemophagocytosis, hypercytokinemia, and multiorgan system dysfunction.[1] The diagnostic criteria for HLH are shown in Table 1, established by the histiocyte society.[2]

The HLH has been classified into two forms: Primary or familial and secondary or acquired. Primary HLH is an autosomal recessive condition linked to mutations in the gene coding perforin. More than 70% of patients with familial HLH develop the disease at 1-year of age. The secondary HLH is most commonly associated with viral infections, including Epstein–Barr virus (EBV), cytomegalovirus (CMV), varicella zoster virus (VZV), herpes simplex virus (HSV), parvovirus, and human immunodeficiency virus (HIV).[2,3,4] Secondary HLH has also been associated with malignancies, bacterial, or parasitic infections. EBV-associated HLH has relatively high incidence in Asian countries.[3] Here, we present a case of EBV-associated HLH in a young women who recovered successfully due to early recognition and prompt therapy.

Case Report

A 27-year-old female admitted to Intensive Care Unit (ICU) of our hospital with fever and back pain for 5 days, widespread maculopapular rash for 2 days and difficulty in breathing for 1-day. The patient was a known case of relapsing remitting multiple sclerosis with five relapses. After her last relapse, she has received oral corticosteroids for 6 months.

On admission, the patient was drowsy but arousable and responding to verbal commands. She subsequently developed respiratory distress and required endotracheal intubation and mechanical ventilation. Laboratory evaluation on critical care admission revealed a low

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white blood cell count, severe pancytopenia, low hemoglobin, elevated lactate dehydrogenase, ferritin and triglycerides level [Table 2]. The clotting test revealed hypofibrinogenemia with a normal value of international normalized ratio and activated partial thromboplastin time [Table 2]. The ultrasound of the abdomen showed mild ascites with hepatosplenomegaly.

Magnetic resonance imaging (MRI) brain with contrast revealed findings consistent with multiple sclerosis. There was no postcontrast enhancement to suggest activity. No acute ischemic changes and no evidence of hemorrhage seen. There were no MRI findings suggestive of encephalitis.

Based on the clinical features and laboratory results, a provisional diagnosis of the macrophage activation syndrome was made. Bone marrow aspiration and additional serology tests were performed. In bone marrow aspiration, macrophages showed evidence of hemophagocytosis. Hepatitis (B and C) as well as HIV serology were found to be negative. The CMV, parvovirus, VZV and rubella IgM antibody tests were also negative. Blood and urine cultures were negative at the time of admission and throughout her hospitalization. The cerebrospinal fluid (CSF) biochemistry was normal, and its aerobic culture was negative. HSV and mycobacterium tuberculosis polymerase chain reaction (PCR) on CSF were negative.

The EBV visceral capsid antigen IgM and IgG were positive while Epstein–Barr nuclear antigen IgG was negative. This serological pattern indicates a recent EBV infection. The rheumatoid factor test was negative. This was included solely as a check for the source of false positive IgM reaction. The EBV DNA quantitative PCR performed on plasma was positive with a viral load of 22,959 DNA copies/ml.

The patient was subsequently started on high doses of corticosteroids and immunoglobulin. As the clinical condition did not improve, etoposide was also started according to HLH-2004 protocol.[2] Etoposide was administered in a dose of 150 mg/m^2 on day 4 and day 7. The patient showed a good response to this treatment. She was extubated on day 7 of her ICU admission, her rashes start to resolve and she became afebrile. The EBV DNA copies number decreased, platelets count improved significantly, and hyperferritinemia also showed improvement. She was shifted to the ward on day 10, and later discharged on day 21. At discharge from the hospital, she was advised to come for her regular follow-up in the neurology clinic.

Table 1: Diagnostic criteria for HLH

The diagnosis of HLH may be established by presence of one of the two criteria
Molecular diagnosis of familial hemophagocytosis (pathologic mutations of perforin [PRF1], SH2D1A/SAP, UNC13D, syntaxin 11 [STX11], MUNC18-2, Ras-related protein Rab27a [RAB27a]) or
Five out of eight diagnostic criteria listed below are fulfilled
Fever ≥38.5°C
Splenomegaly
Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin <9 g/dL (in infants <4 weeks: hemoglobin <10 g/dL)
Platelets $<100\times10^3$/mL
Neutrophils $<1\times10^3$/mL
Hypertriglyceridemia (fasting, >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
Hemophagocytosis in bone marrow or spleen or lymph nodes or liver
Low or absent NK-cell activity
Ferritin >500 ng/mL
Elevated soluble CD25 (alpha chain of soluble IL-2 receptor)

HLH: Hemophagocytic lymphohistiocytosis; NK: Natural killer; IL-2: Interleukin-2

Table 2: Laboratory results of the patient

Blood parameters	Patient's value	Normal range
White blood cell count (×10^3/μL)	2.96	4-10
Hemoglobin (g/dL)	8.9	12.0-15.0
Platelets count (×10^3/μL)	30	150-410
Biochemistry		
AST (U/L)	706	14-36
ALT (U/L)	293	9-52
Lactate dehydrogenase (U/L)	10,055	313-618
Ferritin (ng/mL)	1250	6.24-137
Triglycerides (mg/dL)	286	0-150
Coagulation tests		
Activated partial thromboplastin time (s)	25.1	24.4-32.2
Prothrombin time (s)	11.2	8.8-12.3
INR	1.11	0.8-1.2
Fibrinogen (mg/dL)	119.6	200-400

AST: Aminotransferase; ALT: Alanine aminotransferase; INR: International normalized ratio

Discussion

EBV-induced HLH can affect any age group, ranging from infant to young adult and tends to occur in apparently immunocompetent individuals. Although associated with substantial morbidity and mortality, early diagnosis and precise therapy may result in successful treatment of this condition.

The treatment is aimed at controlling the lymphocyte/macrophage activation and proliferation. In addition to corticosteroids and immunoglobulin, treatment of EBV-associated HLH often requires administration of etoposide.[1]

One of the biggest challenges of HLH is the correct diagnosis. The signs and symptoms can mimic infection, tumor and rheumatic diseases.[5,6] The HLH should be included in the differential diagnosis of clinical

conditions such as fever of unknown origin, hepatitis with coagulopathy (30% of the HLH patients present with transaminases above 100 U/L), sepsis with multiple organ failure and lymphocytic encephalitis. The HLH can present with neurological symptoms due to CNS infiltration by activated macrophages.[6] Any severe or unusual progression of symptoms in a common disease should raise the suspicion of an HLH complicating the underlying condition.

EBV induced hemophagocytosis can occur in patients with underlying multiple sclerosis on prolonged steroid therapy. Our case highlights that HLH should be included in differential diagnosis of a patient admitted in critical care with atypical and severe febrile syndrome. This will enable early diagnosis with the establishment of the cause. It will also help in initiating specific treatment for improved survival. The EBV DNA quantitative PCR helps in diagnosis and monitoring of EBV-associated secondary HLH patient.

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Conflicts of interest

There are no conflicts of interest.

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