

Epstein-Barr Virus (EBV)-Induced Hemophagocytic Lymphohistiocytosis in the Course of Metamphetamine Abuse

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal disorder characterized by abnormal activation of macrophages and occurring in many conditions in all age group. It is also characterized by hemophagocytosis in the bone marrow and in the reticuloendothelial system (RES). The underlying mechanism of acquired HLH is associated with uncontrolled inflammatory reaction which in most cases is triggered by infection or malignancy [1].

Case Report

A 47-year-old man gave a history of night sweats, unremitting fever and uncontrolled weight loss 3 months prior his first visit to our institution. Treatment with antibiotics, anti-viral and anti-fungal agents failed. He had a 10-year history of metamphetamine abuse. On admission a physical examination found a massive splenomegaly and mild hepatomegaly. Hematology showed a hemoglobin of 10.8 g/dL, WBC of $0.57 \times 10^9/L$ and PLT of $33 \times 10^9/L$. Blood smear was dominated by lymphocytes and monocytes with only small proportion of mature neutrophils. No blast cells were found. Laboratory tests detected hyponatremia (126 mmol/L), hypoproteinemia (4.5 g/dL) and hypertriglyceridemia (3.06 mmol/L). Transaminases were elevated (max. AST=622 IU/L and max. ALT=462 IU/L) as well as alkaline phosphatase (max 339 IU/L). Ferritin level was markedly increased to 40.000 ng/mL (normal 21.8-274.6) and fibrinogen level was decreased to 0.65 g/L (normal 1.7-4.2). Initial evaluation excluded the common causes of pancytopenia as there were no vitamin B₁₂, folic acid and iron deficiencies. No bacteria or fungi were isolated from the blood, urine and stool samples. All results of virological findings (HBV, HCV, CMV, HIV, parvovirus B19, HHV-6) were negative except for EBV. The level of EBV DNAemia was 875 copies/mL. A decreased number of CD4+ and NK cells were demonstrated in blood by flow cytometry. Imaging studies were negative. Review of the bone marrow examination found a markedly hypercellular bone marrow with estimated cellularity of 80-90%; erythroid and myeloid precursors were quantitatively increased but with normal morphology. Megakaryocytes were also normal. More than 5 histiocytes per slide with hemophagocytosis on bone marrow cytology aspiration have been found. Erythrocytes engulfed by a huge histiocyte was shown on Figure 1. The diagnosis of EBV-induced hemophagocytic lymphohistiocytosis (HLH) was eventually determined. The patient received the treatment according to the HLH-2004 protocol consisting of etoposide, cyclosporine and dexamethasone. The patient's status improved with normalization of laboratory parameters.

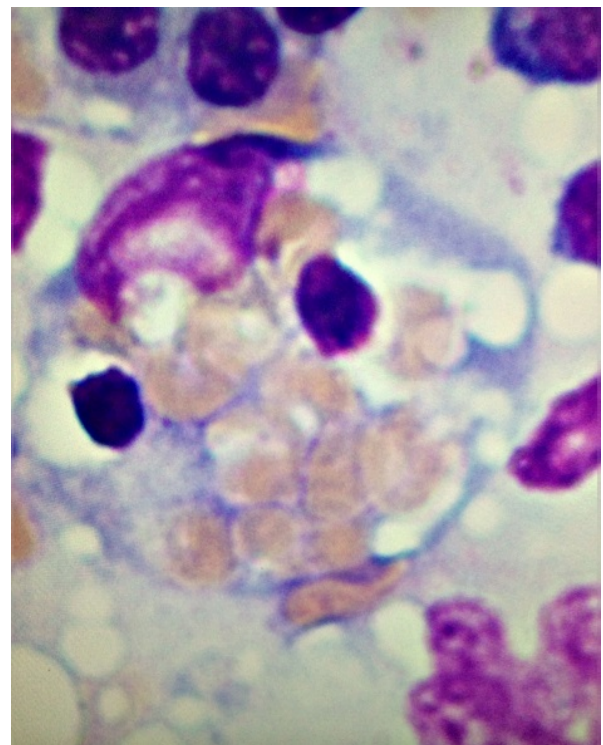


Figure 1: Bone marrow aspiration cytology showing a large histiocyte with engulfed erythrocytes (MGG staining).

Discussion

HLH is a rare clinical entity characterized by multi-system hyperinflammatory process resulting from excessive activation of histiocytes and CD8+ T cells associated with abnormal function of natural killer cells. The characteristic clinical findings include hectic fever, cytopenia, hepatitis and splenomegaly [2]. EBV remains the main trigger of acquired HLH which may develop both in immunocompetent and immunocompromised patients. It was demonstrated that EBV infected B cells stimulate CD8+ T cells leading to hypercytokinemia and activation of histiocytes [3]. One may speculate on a potential pathogenic link between metamphetamine abuse and HLH development as the drug may have a detrimental effect on immune system increasing the susceptibility to viral infection. It was demonstrated that methamphetamine abuse may decrease CD4+ T-cell population and alter cytokine profile in rat model [4].

References

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