

Case Report

Hodgkin lymphoma presenting as Hemophagocytic Lymphohistiocytosis: A case report and review of published cases

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a serious syndrome that occurs in association with malignancy, infections and autoimmune diseases.

Case presentation: A 30 years old female patient presented with fever, splenomegaly, pancytopenia, hyperferritinemia, hypertriglyceridemia and hemophagocytosis in bone marrow aspirate. She was initially diagnosed as HLH. Bone marrow biopsy revealed the presence of Hodgkin lymphoma.

Discussion: The most common HLH associated-malignancy is T/natural killer cell lymphoma and less commonly diffuse large B-cell lymphoma. The combination of HLH and Hodgkin lymphoma is rare. A strong association between Hodgkin lymphoma associated HLH and Epstein Barr virus (EBV) infection has been discussed in published case reports. Hodgkin lymphoma may be a cause of HLH and their relation with EBV has to be investigated.

Key words: Hemophagocytic lymphohistiocytosis (HLH); Hodgkin lymphoma; Epstein Barr virus (EBV).

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INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a life threatening syndrome resulting from over stimulation of the immune system leading to uncontrolled production of cytokines (hypercytokinemia or cytokine storm) with subsequent macrophages proliferation and hemophagocytosis¹. Based on the underlying etiology, HLH can be classified into either primary (genetic) or secondary (acquired). Primary HLH occurs in patients with genetic abnormalities that alter the cytotoxic function of natural killer (NK) cells and T lymphocytes². While, the secondary HLH occurs in association with infections (particularly viral infection), autoimmune diseases and malignancy.

Lymphomas are the most common cause of malignancy associated HLH particularly non-Hodgkin lymphoma (NHL). HLH associated with Hodgkin lymphoma has been rarely reported.¹

Guidelines currently available for diagnosis of HLH are those provided by the Histiocyte Society in 2004³, upon which patients should have at least 5 out of 8 criteria to be diagnosed as HLH. These criteria

include fever, splenomegaly, bi or pancytopenia in the peripheral blood, elevated ferritin level ($\geq 500\mu\text{g/L}$), hypertriglyceridemia and/ or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen, or lymph nodes, low/or absent NK-cell activity and high levels of soluble CD25.

We herein report a case of HLH that is found to be the initial manifestation of Hodgkin lymphoma.

CASE REPORT

A 30-years old female patient admitted to the Hospital of Kasr Al-Ainy School of Medicine, in May, 2016. She was complaining of high fever for 2 weeks, easy fatigability, weight loss and night sweating. Pan-computerized tomography revealed huge splenomegaly together with bilateral axillary and cervical lymphadenopathy.

Laboratory data of the patient at admission are shown in Table 1. The patient had high ferritin and high triglyceride levels. Complete blood count (CBC) revealed pancytopenia, upon which bone marrow aspirate/

biopsy (BMA/B) was done. BMA was normocellular. The myeloid series showed toxic granulations and mild eosinophilia, while the erythroid series revealed megaloblastoid changes. Megakaryocytes were increased in number with normal morphology and platelet budding. Plasma cells were increased by scanning.

Macrophages were increased in number with signs of hemophagocytosis (Figure 1). Taken together, our patient fulfilled 6 out of 8 criteria for diagnosis of HLH. A few-days later, BMB was examined and revealed the presence of a granuloma formed of macrophages, plasma cells and eosinophils with large immature cells with evident nucleoli within. These cells were positive for CD30 by immunohistochemistry.

Based on the aforementioned findings, our patient was diagnosed as stage IV Hodgkin lymphoma complicated with HLH.

Table 1: Laboratory data of our patient at admission

Parameter	Value	Reference range
TLC (μL)	1500	4000-10000
Hemoglobin (g/dL)	5.8	12-14.5
Platelets ($\text{X}10^3/\mu\text{L}$)	111	150-450
Total bilirubin (mg/dL)	0.3	0.3-1.3
AST (U/L)	26	10-40
ALT (U/L)	10	7-56
LDH (U/L)	481	140-280
Urea (mg/dL)	32	8-20
Creatinine (mg/dL)	0.4	0.4-0.8
Triglyceride (mg/dL)	216	< 150
Ferritin ($\mu\text{g/L}$)	15140	11-307
Fibrinogen (mg/dL)	658	150-400
Na (mmol/L)	127	135-145
K (mmol/L)	3.1	3.5-5
Protein (g/dL)	7	6.4-8
Albumin (g/dL)	2.6	3.5-5

TLC: total leukocyte count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, Na: Sodium, K: Potassium.

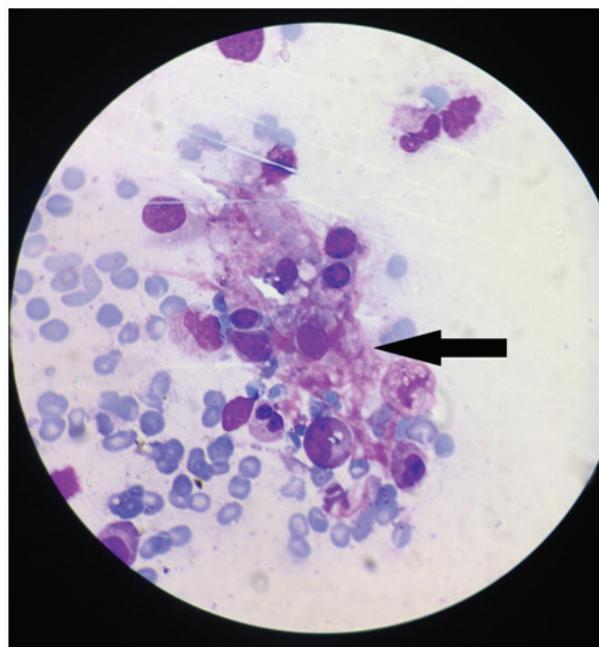


Figure 1: Bone marrow aspirate smear showing macrophages with hemophagocytosis (Giemsa stain, $\times 1000$).

DISCUSSION

HLH is a potentially fatal disease. Thus main challenge for treatment of HLH patients is making prompt diagnosis together with search for the underlying cause to initiate a specific therapy.

Malignancy is the most common cause of secondary HLH particularly hematological malignancy. Because it has an aggressive fatal course, proper investigation and treatment of the underlying cause could save patient's life.

Lymphoma-associated HLH has been reported with T/NK-cell lymphoma and diffuse large B-cell lymphoma⁴. A cohort study of 264 patients with hemophagocytosis revealed that malignancy was the underlying cause in 64% of cases, of which 96% had hematological malignancy, whereas, non Hodgkin lymphomas were the most common (54% T/NK cell and 32% B cell) and no case of Hodgkin lymphoma associated with HLH⁵.

Although Hodgkin lymphoma-associated HLH (HL-HLH) is less common, several case reports have been published. In a case series of 34 patients with HL-HLH, one of the main features of this disease is its strong association with Epstein-Barr virus (EBV) infection. Viral proteins were detected in tumor cells

(Hodgkin cells or Reed-Sternberg cells) among 32 out of 34 patients (94%)⁶. On the other hand, EBV was detected in only 40% of cases of Hodgkin lymphoma not associated with HLH⁷.

The association between EBV and HL-HLH was evident in other published case reports⁸⁻¹⁷. Besides, EBV infection has been considered as the most common cause of infection induced HLH¹⁸. About one third of adult patients with secondary HLH have more than one underlying cause¹⁹. This may explain the occurrence of HLH in association with both Hodgkin lymphoma and EBV that is assumed to be due to viral protein expression by infected tumor cells which result in the production of large amounts of cytokines with subsequent HLH⁶.

Conclusion: This case emphasizes the importance of considering Hodgkin lymphoma as an underlying cause of HLH. The causative relation between EBV infection and HL-HLH needs to be properly investigated.

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