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Secondary Hemophagocytic Lymphohistiocytosis in a Patient with Miliary Tuberculosis: A Case Report

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Introduction

Hemophagocytic Lymphohistiocytosis (HLH) also known as hemophagocytic syndrome is a life-threatening hyper inflammatory syndrome characterized by excessive activation of macrophages and T cell along with impaired ability of Natural Killer (NK) cells and cytotoxic T lymphocytes to kill the target cells [1]. HLH was first reported by the Scottish pediatricians James Farquhar and Albert Clarieaux in 1952, where two infants presented with cytopenia's, unremitting fever and hepatosplenomegaly. However, both infants died after few weeks of initial presentation. There was evidence of widespread infiltration of benign appearing histiocytes with hemophagocytosis in the lymphoreticular system on autopsy. They defined this syndrome as familial hemophagocytic reticulosis, which is currently known as HLH. The estimated incidence is approximately 1.2 cases per 1,000,000 individuals per year [2].

HLH is due to various pathophysiological pathways: 1) Hyperactivation of cytotoxic T lymphocytes and macrophages; 2) proliferation and infiltration of macrophages into various organs; and 3) elevated levels of various cytokines, resulting in progressive organ dysfunction [2]. More researches have shown down regulation of proapoptotic signals and genes related to innate and adaptive immune responses as well as up regulation of genes coding for proinflammatory cytokines and antiapoptotic factors to be important pathological mechanism [2].

HLH can be primary (congenital) or secondary (acquired). Mostly, secondary HLH is arbitrarily divided into three groups depending on the diseases. A-HLH denotes autoimmune disease-associated HLH, whereas HLH triggered by malignancy and infection is denoted by M-HLH and I-HLH, respectively [3]. HLH associated with miliary tuberculosis is rare with higher mortality rates [4].

Pathogenetic mechanism of primary HLH is associated with genetic mutations of perforin and vesicle trafficking genes. It is commonly found in children and adults with primary immunodeficiencies like Chediak-Higashi. The clinical outcome of primary HLH is fatal if immunosuppressive chemotherapy not initiated at an early stage [3]. Acquired HLH in otherwise healthy persons is also associated with infections like Epstein-Barr Virus (EBV), Herpes Simplex virus and tuberculosis bacterium [5,6].

Amongst infections, EBV is reported to be most common cause of HLH however; TB-HLH is less commonly reported. Incidence rate of TB is very high in Southeast Asian and developing countries like India [7]. Since, diagnosis of HLH is commonly missed; high degree of suspicion is required for its diagnosis, particularly with conditions like TB which can have varied clinical manifestations [8].

Thus, understanding the prognosis and characteristics of secondary TB-HLH in order to achieve early recognition and treatment is extremely necessary to prevent irreversible tissue damage. Thereby, in this manuscript we describe a patient of tuberculosis complicated with HLH.

Case Presentation

A 44 years old male was admitted with complaints of high-grade fever, cough with expectoration, worsening breathlessness for one week and tachypnea for last 2 months. Patient also complained of low-grade febrile illness (not documented) with night sweats and weight loss. On examination he was thin built, febrile (oral temperature: 103°F), had bilateral sub-centimetric cervical and axillary lymphadenopathy, hepatosplenomegaly (liver 2 cm, spleen 4 cm below the costal margin), bilateral coarse crepitation (anterior and midaxillary lines). There was no pallor, edema, raised jugular

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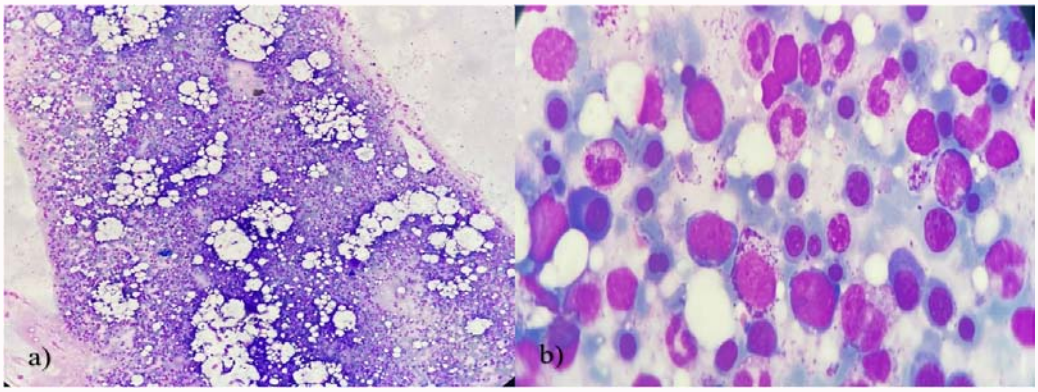

Figure 1: A: Leishman-stained bone marrow imprint showing cellular marrow with fat spaces and normal maturing myeloid series. B: Erythroid and megakaryocytic series (100x and 1000x).

Table 1: Diagnostic criteria for hemophagocytic lymphohistiocytosis according to the HLH-2004 protocol [2].

A diagnosis of HLH can be made if either criteria 1 or 2 is met:
1. Molecular diagnosis consistent with HLH
2. Clinical and laboratory criteria (at least 5/8 criteria should be fulfilled)
a. Fever
b. Splenomegaly
c. Cytopenia ≥ 2–3 cell lines in peripheral blood (hemoglobin <9 g/100 mL, platelets<100 × 10^9 /L, neutrophils <1.0 × 10^9 /L)
d. Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥ 3.0 mmol/L, fibrinogen ≤ 1.5 g/L)
e. Hemophagocytosis in bone marrow, spleen, CSF, or lymph nodes. No sign of malignancy
f. Decreased or absent NK-cell activity (according to local laboratory reference)
g. Ferritin ≥ 500 µg/L
h. sCD25 (soluble IL-2–receptor) ≥ 2,400 U/mL
Supportive evidence includes:
• Cerebral symptoms with moderate pleocytosis and/or elevated protein
• Elevated transaminases
• Elevated bilirubin
• Elevated LDH

CSF: Cerebrospinal Fluid; HLH: Hemophagocytic Lymphohistiocytosis; IL: Interleukin; LDH: Lactate Dehydrogenase; NK: Natural Killer

venous pressure or ascites. Clinical diagnosis of miliary tuberculosis was suspected based on history and examination.

Radiological evaluation showed grade I fatty liver and hepatosplenomegaly on ultrasonography. Routine hematological laboratory evaluation revealed normocytic normochromic anemia [hemoglobin: 119 g/L (120-140 g/L), Mean Corpuscular Volume (MCV): 93.4 fL], leukopenia [leukocyte count: 2.3 ×10^9/L, Absolute Neutrophil Count (ANC): 1740/cumm] and thrombocytopenia (platelet count: 15 × 10^9/L). Biochemical investigations revealed total bilirubin: 0.7 mg/dL (direct 0.2 mg/dL), raised liver transaminases (3 times the upper limit of normal), reduced total protein levels (5.1 gm/dl) with albumin (2.2 gm/dl) and globulin (2.9 gm/dl).

Coagulation profile depicted prolonged prothrombin time [27 sec, control 12 sec, activated partial thromboplastin time (35 sec, control 26 sec), INR 1.2 and high levels of D-dimer >5250 ng/ml. Microbiological and serological work up were negative for Human Immunodeficiency Virus (HIV), hepatitis B and C viruses, dengue, malaria; and microbial cultures of blood, urine, sputum were sterile.

Bone marrow aspiration and biopsy were sent for evaluation of miliary tuberculosis. Peripheral smear examined showed leucopenia and thrombocytopenia. Bone marrow aspirate smears were partly diluted with peripheral blood and showed no particle.

Bone marrow imprint showed particle with highly cellular trails. Erythroid series showed normoblastic reaction, myeloid showed normal maturation with increased eosinophilic precursors. Megakaryocytes were adequate. There was slight increase in number of mature plasma cells and histiocytes with some showing hemophagocytosis. No atypical cells/parasite or granuloma was identified on imprint smear (Figure 1).

Bone marrow core measuring 1.3 cm in length was examined by Hematoxylin and Eosin staining showed bony trabeculae enclosing marrow spaces with normally maturing myeloid series cells. Erythroid series showed predominantly normoblastic reaction with adequate number of megakaryocytes. A non-caseating epithelioid cell granuloma was seen, however no Langhans type giant cells seen (Figure 2a, 2b). Furthermore, there was increased number of histiocytes with some showing evidence of hemophagocytosis (Figure 2c, 2d). However, Ziehl Neelson staining for acid fast bacilli was negative. Thereafter, further investigations and workup for tuberculosis associated HLH was done.

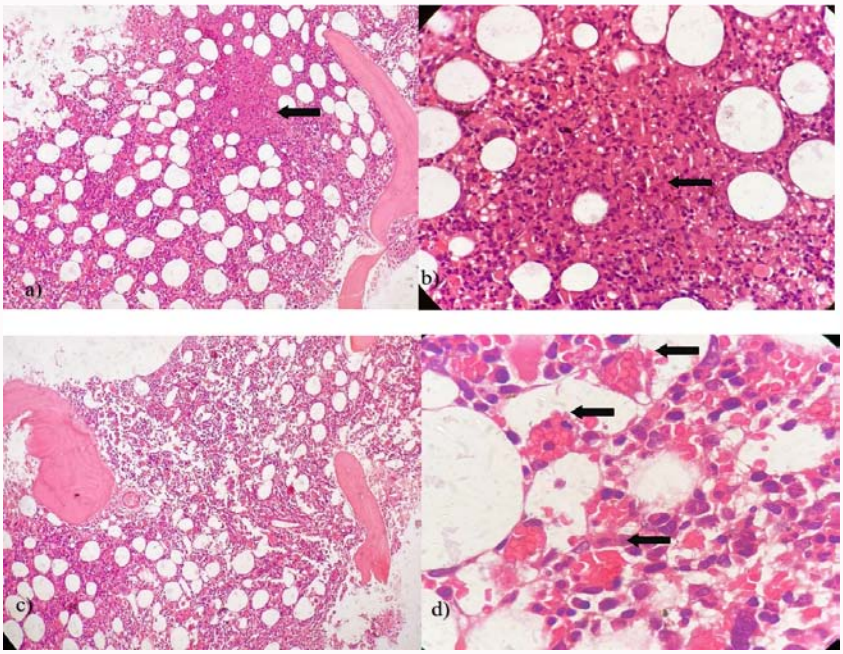

Figure 2: A, B: Hematoxylin and Eosin-stained bone marrow biopsy shows presence of non-caseating epithelioid cell granuloma in the marrow spaces (100x, 400x). C, D: Depict presence of many hemophagocytic histiocytes in the marrow spaces (400x, 1000x).

Plasma fibrinogen was within normal levels (233 mg/dl) whereas lipid profile showed raised serum triglyceride levels (193 mg/dl). Hyponatremia and hyperkalemia were present along with raised urea and creatinine. Hyperferritinemia (>1800 ng/mL), raised lactate dehydrogenase (920 IU/L) and elevated ESR (50 mm in 1st h) was also present. The Mantoux test was negative. However, real time PCR test with sputum sample was reported to be positive for tuberculosis.

Thus, as per HLH-2004 Protocol (Table 1) and after correlating with clinical details, radiological and real time PCR positivity on sputum sample, diagnosis of tuberculosis with secondary hemophagocytic lymphohistiocytosis was made.

The patient was managed with supportive measures. Later on, he was started on Anti-Tubercular Therapy (ATT) along with steroids. He was discharged in a stable condition but patient did not come for follow up.

Discussion

TB-HLH is a type of severe tuberculosis, diagnostically challenging for clinicians as its most common clinical presentation is Pyrexia of Unknown Origin (PUO). This condition was first reported in the 1980s but since last few years there are many cases reported in literature on TB-HLH [6].

Here, we report a rare case of TB associated HLH in an adult male diagnosed using PCR performed on sputum sample and bone marrow examination. The patient was successfully treated with ATT and corticosteroids. In this case, clinical suspicion of miliary TB was made with the help of history and physical examination. TB is widespread in Asian countries, including India, and is one of the important causes of but due to lack of precise diagnosis and non-specificity of clinical manifestations, early detection is quite difficult [7,9].

Mycobacterium TB is an obligate intracellular pathogen which exacerbate macrophage over activity as well as Th1 cell mediated cytotoxicity thereby resulting in HLH. It is evidenced by increased serum levels of IFN-γ, M CSF, and TNF-α in patients with tuberculosis [8]. Therefore, high TNF-α and IFN-γ results in hematopoiesis suppression along with apoptosis thus, resulting in cytopenia. Inhibition of lipoprotein lipase results in hypertriglyceridemia and macrophage over activity leading to excess release of ferritin (an acute phase reactant) in response to inflammatory cytokines; tissue infiltration causes organomegaly, and fever is secondary to release of cytokines like IL 1, IL 6 [8].

Literature shows that in patients diagnosed with TB complicated with HLH, there is 100% mortality if they did not receive ATT, whereas there is 40% to 60% reduction in mortality rate by combination of ATT and immunotherapy. Suppression of cytokine storm is of utmost importance in patients with HLH for long-term efficacy of ATT and needs to be done by induction of immunotherapy at an early stage of treatment. Thus, it was observed that patients who received immunotherapy alone also experienced significantly higher overall survival rates than patients who did not receive [7,10,11].

Highly elevated level of ferritin is an important prognostic marker and is strongly associated with HLH. Lin et al. concluded in a study that a rapid rate of fall in ferritin levels following therapy initiation was directly proportionate to overall survival and thereby associated with decreased mortality [12]. However, Park et al. in their 23 patients of secondary HLH found that the rate of decline in ferritin was not associated with survival whereas high fibrinogen at the time of diagnosis was significantly associated with decreased mortality [13]. Similarly, Padhi et al. found that high serum ferritin (>1000 ng/mL) was an important indicator of disease severity and was associated with decreased survival, but the results were statistically insignificant on univariate analysis [1].

In our case, patient was clinically suspected as miliary tuberculosis, having fever with organomegaly. Evidence of cytopenia and hemophagocytosis on bone marrow examination led to suspicion

of TB-HLH which was confirmed by further biochemical results including hyperferritinemia, hypertriglyceridemia and elevated liver enzymes.

In conclusion, this case illustrates early diagnostic challenges of both HLH and miliary tuberculosis. It provides the need for deep understanding of possible triggers of HLH, with more attention on TB-associated HLH since TB is most common infection in developing countries. In patients with tuberculosis who present with cytopenia(s), coagulopathy, high triglyceride levels, HLH should be considered as a differential diagnosis. Till date literature highlights the fact that TB HLH have an unpredictable and/or poor outcome with or without ATT. Thus, early diagnosis and initiation of ATT, even in the presence of disseminated disease might alter the final outcome towards favorable in such cases.

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