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Case Report

DISSEMINATED TUBERCULOSIS PRESENTING AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

ARINDAM KARGUPTA, INDRANI DAS, ANANYA SENGUPTA, ABHISHEK CHAKRABORTI, SHOUNAK GHOSH

Department of General Medicine, Medical College & Hospital, Kolkata - 700 073, West Bengal, India. Email: dr_indranidas@rediffmail.com

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an immune dysregulation syndrome which is characterized by widespread but ineffective activation of immune system of our body. This activation leads to release of a large pool of cytokines from the activated lymphocytes and macrophages. This hypercytokinemia leads to the development of characteristic features of HLH such as fever, cytopenias, hepatosplenomegaly, raised serum ferritin level, hemophagocytosis in marrow/spleen/lymph nodes, low fibrinogen and or hypertriglyceridemia, low natural killer cell activity, and high-soluble CD25 [1]. Five out of the above eight features are required for the diagnosis. There are 2 variants of HLH, primary HLH; where the defect in the immune system is hereditary and secondary HLH; where it is caused by other secondary diseases such as infections, hematological malignancies, autoimmune and auto-inflammatory diseases. In this article, we have reported a case of HLH, which was secondary to disseminated tuberculosis. There are only few case reports of HLH secondary to disseminated tuberculosis. Mortality may be as high as 50%. Although tuberculosis has various manifestations, our patient presented with fever, skin rash, cytopenias, splenomegaly, and very high ferritin. Marrow examination showed epithelioid granuloma, hemophagocytosis, and positive Ziehl–Neelsen staining. At present, no definite treatment guidelines have been formulated because of multiple drug interactions and toxicities. We treated our patient with non-hepatotoxic anti-tubercular drugs and steroids, followed by addition of isoniazid, rifampicin, and pyrazinamide on improvement of hepatic profile. Thus, high index of clinical suspicion, prompt diagnosis, and early management may reduce the mortality in this devastating disease. Moreover, this is more common in immunocompromised patients, but here, we have diagnosed this case in an immunocompetent man.

Keywords: Erythematous rash, Fever, Disseminated tuberculosis.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an immune dysregulation syndrome in which activated macrophages cause phagocytosis in various organs. It is characterized by fever, cytopenias, splenomegaly, hypofibrinogenemia and or hypertriglyceridemia, hemophagocytosis in bone marrow/spleen/lymph nodes, ferritin >500 ug/L, soluble CD25 >2400 U/L, and low natural killer cell activity. 5 out of these 8 criteria are required for the diagnosis. It may be primary/genetic or secondary. Secondary causes include infections such as Epstein bar virus, tuberculosis, rheumatological disorders, and malignancy. Here, we report a case secondary to disseminated tuberculosis. Although tuberculosis has various manifestations, it presenting as HLH is very rare.

CASE REPORT

A 42-year-old male patient presented to us with fever of 2 weeks duration. Fever was of moderate grade and was associated with appearance of erythematous papulonodular skin lesions on the trunk and upper extremities. Fever was not associated with any cough, expectoration, hemoptysis, dysuria, weight loss, sweating, joint pain, photosensitive rash, or any yellowish discoloration of his eyes. There was no history of tuberculosis or drug abuse or any promiscuous sexual behavior. The patient is an electrician by occupation.

On general examination, the patient had mild pallor and tachycardia. In the oral cavity, there were multiple ulcers with erythematous margin (Fig. 1). Few were tiny and some were fairly large. In addition, there were multiple erythematous papulonodular lesions on the anterior chest wall, abdomen, and back. The lesions had no central hemorrhage (Fig. 2). On examination of abdomen, there was firm and non-tender hepatosplenomegaly. Respiratory, cardiovascular, and the nervous system examinations were normal.

On investigating, routine hemogram showed pancytopenia (hemoglobin - 7.3 g/dl, total count - 2.9 × 10^9/L [N60 L35 M5], and platelet - 60 × 10^9/L). The liver enzymes were elevated (alanine aminotransferase - 310 U/L [7-56 U/L] and aspartate aminotransferase - 295 U/L [10-40 U/L]). His blood glucose and renal function were normal. Among others, malarial double antigen, dengue immunoglobulin M, sputum Gram-stain/culture/acid-fast bacillus (AFB), urine routine examination/culture, and blood culture were all negative. The autoimmune marker antinuclear antibody was also negative. Ultrasound of the whole abdomen showed hepatosplenomegaly. Chest skiagram, echocardiography, and computed tomography scan of chest did not reveal any abnormality.

Broad-spectrum antibiotic, piperacillin - tazobactam was started. However, since fever persisted despite antibiotic therapy, we went for bone marrow aspiration and biopsy in consultation with the Department of Hematology. Marrow samples were also sent for fungal culture and TB BACTEC culture.

Thus, we now had a patient with pancytopenia, hepatosplenomegaly, erythematous maculopapular skin lesions, and fever persisting despite therapy. Hence, we thought of the possibility of HLH and sent serum fibrinogen, triglyceride, and ferritin. Serum fibrinogen was below normal 1.38 g/L (normal 2.33-4.96 g/L), serum triglyceride was 390 mg/dl, and serum ferritin was 18892.6 ug/L (normal 24-336 ug/L in males). Bone marrow study showed increased number of macrophages with significantly high hemophagocytic activity. It also showed the presence of a single epithelioid granuloma (Fig. 3) along with some large binucleated cells. Marrow AFB staining was positive. Punch biopsy from the skin lesions failed to show any significance.

Hence, a diagnosis of HLH with disseminated tuberculosis was made.

We started non-hepatotoxic anti-tubercular drugs (ethambutol, levofloxacin, and streptomycin) due to his elevated liver enzymes along

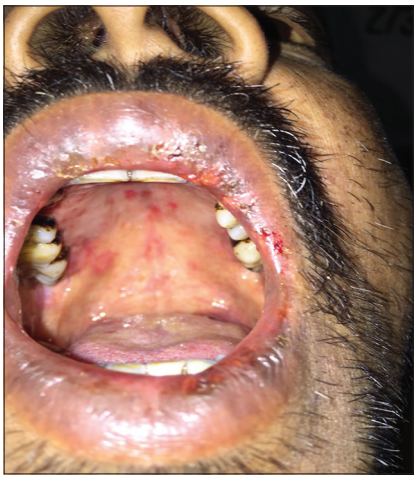

Fig. 1: Oral ulcers

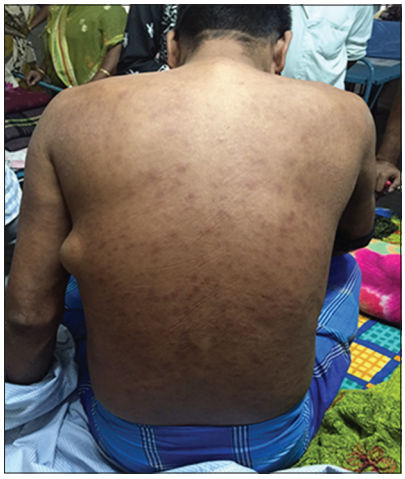

Fig. 2: Multiple erythematous maculopapular lesions

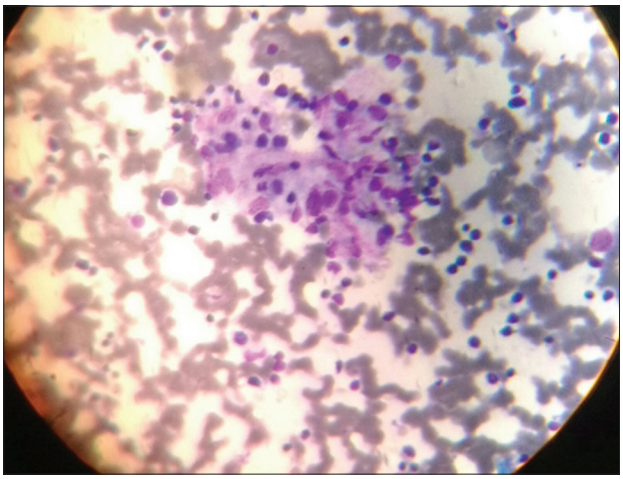

Fig. 3: Marrow slide showing epithelioid granuloma and hemophagocytosis

with injection dexamethasone 10 mg/m^2. Within few days of therapy, the patient became afebrile and his skin lesions gradually started to resolve. The patient was discharged in an afebrile and stable condition. The liver enzymes declined gradually and isoniazid, rifampicin, and pyrazinamide were added during his follow-up visit.

DISCUSSION

Scottish pediatricians Farquhar and Claireaux first reported a case of HLH in 1952 when they noticed rapid death of their patients despite the use of antibiotics and steroid [2]. HLH is a hyperinflammatory immune dysregulated state that is triggered by various stimuli. All these pathways ultimately lead to widespread activation of macrophages and cytotoxic T-lymphocytes, and liberation of multiple pro-inflammatory cytokines leading to prolonged fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, and high ferritin [3]. Main causes of mortality are central nervous system dysfunction, multi-organ failure, and disseminated bacterial or fungal infections due to prolonged neutropenia [4-6]. It is of two major variants – primary or genetic and secondary. Secondary causes may be either infective (Epstein bar virus, herpes, Parvovirus, Varicella Zoster, HIV, mycobacterial, fungal, leishmaniasis, toxoplasmosis, malaria, etc.), auto-immune or auto-inflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's, and systemic Juvenile idiopathic arthritis), malignancies, or iatrogenic immunosuppression. Macrophage activation syndrome is secondary HLH due to auto-immune diseases.

At present, guidelines have already been laid down for diagnosis of HLH and according to that, 5 out of 8 criteria shave to be present for diagnosis of HLH [7]. Among these, our patient had 5 of them, as he had fever, splenomegaly, pancytopenia, low fibrinogen, raised ferritin, and bone marrow features of hemophagocytosis.

Hemophagocytosis due to disseminated tuberculosis, i.e. AFB in bone marrow is not that much common and there are only a few case reports stating this association. Around 70 cases have been reported since 1975. As tuberculosis is very much common in our country, it can present with these atypical features, such as pancytopenia, hepatosplenomegaly, and raised serum ferritin. Majority of the case reports state high mortality of 50% in HLH associated with TB [8]. Recently, an association of HLH with choroid tubercles has been shown by Rathnayake *et al.* [9]. Poor prognosis markers are age, high ferritin, delay in treatment, disseminated intravascular coagulation, etc. It is treated with anti-tubercular and immunosuppressive drugs. As rightly pointed out by Park *et al*., in the patients with severe disease and/or associated sepsis or multiple organ failure at the time of diagnosis, it may be difficult to use cytotoxic agents such as etoposide. In such circumstances, immunosuppression with corticosteroids and/or cyclosporine remains the foundation of early management as it can control systemic inflammation [10]. First-line anti-tuberculous drugs such as rifampicin have enzyme-inducing activity, which can lower the efficacy of drugs such as cyclosporine and etoposide used in the HLH 2004 protocol. Besides, HLH *per se* leads to significant derangement of liver functions, making the administration of anti-tubercular treatment as well as etoposide difficult. Moreover, HLH may even be exacerbated after initiation of anti-tubercular drugs, which may be challenging to treat [11]. Our patient has been successfully treated with non-hepatotoxic anti-tubercular drugs and steroids followed by isoniazid, rifampicin, and pyrazinamide and his symptoms subsided gradually. This indicates the importance of an early detection and timely management.

CONCLUSION

Tuberculosis, a common disease in our country, but with varied manifestations can also present as HLH. Prompt diagnosis and early initiation of therapy can reduce the high mortality of this disease.

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