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Teaching Case

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A rare initial presentation in Extra Pulmonary Tuberculosis- Hemophagocytic Lymphohistiocytosis as a differential diagnosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder characterized by excessive activation of the immune system leading to tissue damage and organ dysfunction.
We present a case of HLH Like initial presentation secondary to extrapulmonary tuberculosis (TB) in a young male who presented with fever, constitutional symptoms and generalized lymphadenopathy.
Initial presentation of this case there were no much evidence to suggest extrapulmonary tuberculosis, but few months later he presented with a lymphocytic exudative pleural effusion with high Adenosine Deaminase (ADA) level and patient improved with antituberculosis treatment(ATT).
Initial presentation of this case there are some features favouring HLH but not fulfilling the required criteria for diagnosis based on our Sri Lankan setting, but HLH can be considered as the most probable differential diagnosis while discussing others.
This presentation emphasizes importance of high degree of suspicion of tuberculosis as the underlying etiology for Pyrexia of Unknown Origin (PUO) with atypical clinical findings with high inflammatory response.

Keywords: HLH, TB, ATT

INTRODUCTION

HLH characterized by hyperactivated benign macrophages or histiocytes engulfing white blood cells, red blood cells, platelets, and their precursors in the reticuloendothelial system [1].

Apart from the hereditary form of HLH, there are a variety of etiologies which can trigger this clinical phenomenon, known as secondary or reactive HLH, such as infections, autoimmune diseases [2], drugs [3], or immunosuppressive conditions [4].

In this case report we are discussing about a male who presented for evaluation of fever of unknown origin and who was shown to have tuberculosis-induced atypical clinical presentation with some features resembling HLH.

CASE PRESENTATION

26year old unmarried previously healthy male presented with evening pyrexia, loss of appetite and weight loss for 4-weeks duration. On examination he had non tender matted

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lymphadenopathy in the left posterior cervical region. The examination of the cardiovascular, respiratory, and abdominal systems was normal.

Investigations revealed a hemoglobin (Hb) level of 12.4g/dL (mean corpuscular volume (MCV) 84 fL), white blood cell count (WBC) of 9.8 × 103 /µL (granulocytes 85.1 %, lymphocytes 8.1), platelets 290 × 103 /µL, erythrocyte sedimentation rate (ESR) of 110mm/1st hour, C-reactive protein (CRP) of 70 mg/dL, aspartate transaminase (AST) of 492 U/L, alanine transaminase (ALT) of 659 U/L, serum albumin of 32mg/dL, serum bilirubin (total) of 18µmol/L, alkaline phosphatase of 146U/L, gamma-glutamyl transferase of 23 U/L, international normalized ratio (INR) of 1.01, serum creatinine of 90micromol/L, serum sodium of 139 mmol/L, and serum potassium of 4.3 mmol/L.

A septic screen including blood and urine cultures were negative and the sputum culture was positive for coliform species. Sputum Gene-Expert test was negative. Mantoux test showed an induration of 14 mm. Chest X-ray and electrocardiogram (ECG) were normal. 2D Echo revealed good biventricular function. The blood picture revealed moderate rouleaux formation and Neutrophil predominance with left shift and reactive lymphocytes suggestive of infective or inflammatory process. Serum ferritin was 12500microgrm/L, LDH was 1183U/L and serum triglyceride level was 160mg/dl. Ultrasound scan of abdomen did not reveal an organomegaly. CECT Chest, Abdomen and Pelvis showed low attenuated lymph nodes in right supraclavicular, mediastinal and mesenteric region. ANA titre showed 1:100 and DsDNA was negative, Hepatitis screening, retroviral studies, CMV and EBV antibodies were negative.

Lymph node biopsy revealed infiltration of numerous histiocytes showing erythrophagocytosis and reported as the overall picture favor HLH.

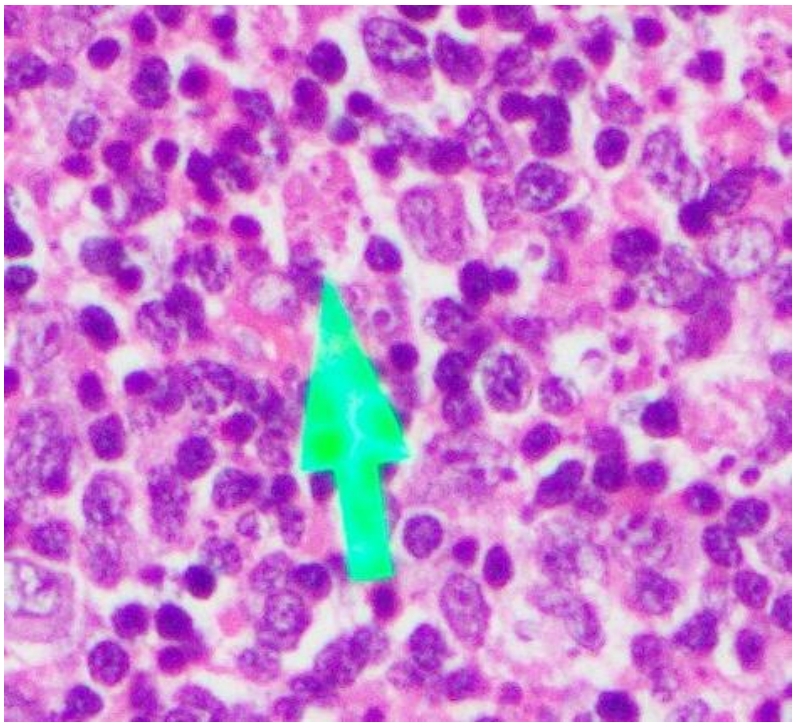

Figure 1. The arrow points a histiocyte which has engulfed erythrocytes.

Bone marrow aspiration showed normocellular marrow with proportionately active haemopoiesis and reactive changes without granuloma formation or necrosis, there was no evidence of marrow infiltration. Bone marrow aspirate TB PCR was negative.

A presumptive diagnosis of possible Systemic Lupus Erythematosus(SLE) with respiratory infection was made and was treated with IV Ceftriaxone 1g 12 hourly and prednisolone 60mg daily. After 10 days of treatment his ESR and CRP improved to 20mm/1st hour and 24mg/L respectively and he was discharged from the hospital with Hydroxychloroquine sulphate 200mg daily with a plan to monitor his progress in the outpatient clinic**.** Three days later he developed a low-grade intermittent fever. Three weeks later he developed breathlessness and was re admitted to the hospital where he was found to have a left sided moderate pleural effusion. Pleural fluid analysis shows turbid fluid with 66g/l proteins with a differential count of 93% lymphocytes and 7% of polymorphs and pleural fluid LDH /serum LDH ratio of 0.7, suggestive of a lymphocyte predominant exudative effusion with high Adenosine Deaminase (ADA)value of 89 IU/L. Pleural fluid cytology report was negative for malignant cells and bacterial culture. Full blood count, liver, renal function tests, were normal and the ESR 95mm/1st hour and a CRP value of 65mg/Dl.

Based on the results of pleural fluid analysis showing lymphocytic to neutrophil ratio>0.75 and ADA>40, and presence of supraclavicular, mediastinal, and mesenteric lymph nodes, a diagnosis of extrapulmonary tuberculosis was considered while awaiting TB culture report. A presumptive anti TB therapy is usually acceptable even without a confirmatory test for patients with epidemiological risk factors for TB and supportive diagnostic studies in the absence of alternative diagnosis. [1] The patient was started on a 4 drug standard anti-tuberculosis therapy (ATT). After one month follow up he became asymptomatic and ESR had reduced to 15mm/1st hour.

Although pleural fluid TB culture became negative, due to good clinical and biochemical response the ATT was continued. After six months of treatment, he noticed a tender neck lump in the posterior cervical region. This was found to be an abscess and was tested positive for TB PCR. The ATT was therefore extended for further 3 more months.

DISCUSSION

Tuberculosis is a leading cause of morbidity and mortality in developing countries which shows diverse range of clinical presentations. Therefore, tuberculosis is known as “a great mimicker” which make early diagnosis difficult and may even result in misdiagnosis. [7] Atypical presentation of TB causes a diagnostic challenge and thereby can delay the initiation of treatment.

HLH is a life threatening aggressive syndrome caused by excessive immune activation. [1] HLH can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis like infection, inflammatory conditions, autoimmune diseases and malignancy. Cell types involved in the pathogenesis of HLH include macrophages, natural killer (NK) cells and cytotoxic lymphocytes(CTL). [1]

The hyperinflammatory or dysregulated immune reaction observed in HLH is thought to be due to absence of normal downregulation by activated macrophages and lymphocytes due to natural killer and cytotoxic T cell dysfunction. The NK/ T cells or cytotoxic T cells depend on cytolytic enzymes, perforin and granzymes, to kill pathogens. These cytolytic enzymes are defective in HLH [7–9]. This defective innate immune system results in uncontrolled infectious processes; on the other hand, it leads to persistent activation of the phagocytotic cells by increased cytokine release. The dysregulated histiocytes and T lymphocytes secrete pro-inflammatory cytokines (especially Th1 cytokines) [5, 6], such as tumor necrosis factor-a, interferon-c, IL-1, IL-6, IL-8, and IL-18.

Also, the increased expression of adhesion molecules enhances the phagocytic activity of macrophages or histiocytes [4]. The overall clinical picture can be attributed to this so-called hypercytokinemia [5], and all clinical features can be explained by this cytokine storm [1]. Among the various groups of infectious pathogens that give rise to reactive HLH, Mycobacterium tuberculosis is an important cause, especially in endemic areas and in immunocompromised individuals. [8]

As described above the pathophysiology of HLH involves excessive immune activation and cytokine

storm, but the exact underlying mechanism of TB-HLH remains unclear, although TB infection is known to disrupt immune homeostasis leading to secondary HLH. [2] In patients with TB, the levels of interferon-g, tumor necrosis factor-a, and granulocyte/monocyte colony-stimulating factor are higher than those in a healthy population. [7] Meanwhile, Mycobacterium tuberculosis can induce migration of monocytes and macrophages to regional lymph nodes through a mechanism mediated by IL-12 and IL-15, leading to antigen-specific T-cell expansion, stimulation of persistent cytokine release, followed by subsequent activation and proliferation of macrophages. [3-6] The initial presentation of this case is very atypical and not conclusive for any diagnosis.

We considered several differential diagnoses including HLH, Stills disease, Systemic Lupus Erythematosus and prolonged systemic sepsis. Even though the lymph nodes show hemophagocytes, bone marrow is negative for hemophagocytes, and only three clinical criteria are there in this presentation according to HLH diagnostic criteria(Table 1).

There are two investigations that we are unable to perform due to limited facilities includes soluble CD 25 level (soluble IL2 receptor alpha) and natural killer cell activity level.

These investigations are crucial to confirm the diagnosis of HLH.

H score is another method used in the diagnosis of HLH, however it only considers hemophagocytes in the bone marrow, not in the lymph nodes.

When considering other differential diagnoses, it can include inflammatory reaction like Stills disease. But necessary Yamaguchi criteria is not fulfilled in this case. Other conditions give rise to HLH like presentation include prolonged sepsis, but this presentation patient was not in a state of sepsis and inflammatory markers were not that high and initial septic screening was negative.

SLE can be a differential diagnosis for the above presentation. His ANA is positive but other criteria are not fulfilling.

As such, only condition that comes closer to the above presentation is HLH rather than other differential diagnoses. However due to limited investigating capacity we are unable to confirm the diagnosis.

During the second hospital admission with breathlessness, he had clinical and laboratory evidence of extrapulmonary tuberculosis which we believe had probably caused this initial atypical presentation.

Table 01: HLH diagnosis criteria (2004) [11]

Table 1

Diagnostic criteria of HLH-2004.

Molecular identification of an HLH-associated gene mutation (ie, PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A, or BIRC4). Children require documentation of homozygosity or compound heterozygosity of HLH-associated gene mutations. By comparison, heterozygosity may be sufficient for adults if they have clinical findings associated with HLH.
OR
Five of the following 8 findings
Fever ≥38.5°C
Splenomegaly
Peripheral blood cytopenia, with at least 2 of the following: hemoglobin <9 g/dL (for infants <4 wks, hemoglobin <10 g/dL); platelets <100,000/μL; or absolute neutrophil count <1000/μL
Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
Hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver
Low or absent NK cell activity
Ferritin >500 ng/mL (the authors prefer to consider ferritin >3000 ng/mL as indicative of HLH)
Elevated soluble CD25 (soluble IL-2 receptor alpha) that measures 2 standard deviations above age-adjusted laboratory-specific norms

CONCLUSION

HLH is an uncommon clinical manifestation and, if not suspected early, it can be fatal. It can rarely complicate a Tuberculous infection [10]. In patients with Pyrexia of Unknown Origin clinical manifestations of HLH can sometimes precede the diagnosis of Tuberculosis.

It is very important to follow these patients as the underlying triggers such as bacterial infections, connective tissue disorders or malignancies which may even take months to develop as in this case.

Author declaration
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Author Contributions
UPE: Wrote the case report, drafted and edited the manuscript
JI: Analyzed and edited the manuscript

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No funds were needed in writing this case report.

Ethics approval and consent to participate
Informed written consent was obtained from the patient for publication of this case report.

Competing interests
The authors declare that there are no conflicts of interest.

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