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Hemophagocytic lymphohistiocytosis: An unusual presentation of disseminated tuberculosis: A case report and literature review

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome associated with cytokine storm. Here, we present a patient with acquired HLH associated with *Mycobacterial tuberculosis* infection.

Case presentation: We report a 66-year-old hypertensive and diabetic male patient who presented with four days history of fever and abdominal pain. Denied history of cough and weight loss. Laboratory investigation showed: elevated ferritin, C-reactive protein, and triglyceride. Bone marrow examination showed > 50% hemophagocytosis (RBCs and platelets ingested by macrophages), positive acid-fast bacillus for *Mycobacterium tuberculosis* bacilli, and no evidence of malignancy. Complete blood count showed anemia and thrombocytopenia. The patient fulfilled six out of eight clinical criterions of the acquired Hemophagocytic lymphohistiocytosis (HLH). The patient was managed with anti-tuberculous medications with adjuvant steroid. On the subsequent days, the patient showed significant clinical improvement and discharged home. However, the patient passed away a week after home discharge.

Conclusion: The present case highlights on the importance of early diagnosis and treatment of acquired HLH associated with tuberculous infection to improve the clinical outcome of the patient.

1. Background

Hemophagocytic lymphohistiocytosis (HLH) is characterized by aggressive activation of macrophages and cytotoxic T cells and natural killer (NK) cells, resulting in hypercytokinemia and subsequent cytokine storm and immune-mediated injury of multiple organ systems [1]. The incidence of HLH from bone marrow studies of critically ill patients with cytopenia was 0.8 to 4% [1]. HLH is relatively rare condition which is almost uniformly fatal unless promptly recognized and treated [2]. According to the HLH-2004 diagnostic guidelines [3], acquired HLH is defined as the presence of at least five out of eight of the diagnostic criteria which includes: fever, splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis evident on pathological examination (bone marrow, spleen, or lymph node tissue), low or absent natural killer cell activity, hyperferritinemia, and high serum levels of soluble CD25 [3]. In two-thirds of the case, HLH may present as an acquired hyperinflammatory disorder, often triggered by infectious, autoimmune, or neoplastic conditions. The most common infectious etiologies associated with HLH are viral infections, followed by tuberculosis (3%) [1]. Considering high prevalence of tuberculous infection in low and middle income countries (LMIC), it's vital to have high index of suspicion towards tuberculosis among patients presenting with features of HLH. HLH-associated with tuberculous infection may lead to fatal outcomes, if not identified and treated timely [3-7].

2. Case presentation

We report a 66-year old hypertensive and diabetic male patient, who presented with fever,abdominal painand nausea of four days duration. The patient reported generalized weakness,fatigue and decreased

Abbreviations: **CT**, Computed tomography; **CRP**, C reactive protein; **HIV**, Human immune deficiency virus; **HLH**, Hemophagocytic lymphohistiocytosis; **TB**, Tuberculosis.

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appetite of 1 month prior to the onset of fever. The patient has no history of cough, weight loss, or excessive sweating. Vital signs showed blood pressure: 80/50 mmHg, pulse rate: 120 beats per minute, respiratory rate: 34 breathe per minute, temperature: 103 ^{0}F, and Oxygen saturation of 84% on room air. He had mild pallor and scleral icterus. Abdominal examination was remarkable for tender hepatomegaly. The respiratory exam showed bilateral basal course crepitation, the rest of the physical examination was unremarkable. All laboratory investigations are summarized in the table below (Table 1). Chest X-ray showed bilateral lower lung haziness, and the abdominal ultrasound examination showed spleenomegally and hepatomegaly. The abdominal CT scan showed thickening of intestinal wall, sub mucosal edema in the caecum, ascending colon till hepatic flexure, and enlarged liver and spleen (Fig. 1).

Subsequently, the patient was admitted to the medical ICU and started with fluid replacement and parenteral antibiotics. However, the patient become delirious and acidotic and continued to experience a persistent fever, cytopenia and elevated serum ferritin, thus, bone marrow aspiration and biopsy were performed. Bone marrow aspiration showed increased macrophage activity with approximately 50% showing hemophagocytosis (Fig. 2), while bone marrow biopsy showed cellular marrow with few epithelioid granulomas with no evidence of malignancy (Fig. 3), alerting the treating physician to consider HLH. In an effort to look for secondary etiology for HLH, AFB staining was done from bone marrow aspirate, which was positive for acid-fast bacilli (Fig. 4). Following the diagnosis of tuberculosis associated with HLH, the patient was started on a modified anti-tubercular regimen (Rifampicin, Isoniazid, Ethambutol, and Levofloxacin) with an adjuvant corticosteroid. The anti-tubercular drugs were modified because the patient had a deranged liver function. During the subsequent days after initiation of treatment, the patient showed clinical improvement. Laboratory parameters also showed improvement with serial increase in hemoglobin and platelet counts and improved liver function. After 2 weeks in the medical ICU, the family requested discharge and transfer to a nearby hospital due to social reasons and hence the patient was referred to a nearby hospital. However upon phone call follow-up, we learned that the patient died one week after he was discharged from our hospital.

Table 1
Patient's Laboratory test, results and laboratory reference ranges.

Laboratory test	Results	Reference range
WBC	11,700 cells/mm^3 (N% 79%)	4,500–10,000 cells/mm^3
Platelet count	120x10^9 / cells/mm^3	150,000 to 450,000 cells/mm^3
Hemoglobin	10.6gm/dL	14.0 to 17.5 gm/dL
Urea	71 mg/dL	4.3–22.4
Creatinine	2.29 mg/dL	5.1 – 14
SGOT	140 U/L	0–35 U/L
SGPT	80 U/L	0–35 U/L
Total bilirubin	7.6 mg/dL	0.3–1.0 mg/dL
Direct bilirubin	6.4 mg/dL	0.1–0.3 mg/dL
Alkaline phosphatase	110 U/L	30–120 U/L
GGT	60 U/L	9–50 U/L
Sodium	140 mEq/L	136–145 mEq/L
Potassium	3.87 mEq/L	3.5–5.0 mEq/L
Lactate	38 mmol/L	0.7–2.1 mmol/L
HIV 1/2, HBSAg and anti HCV	Negative	
ANA	Negative	
Fasting blood glucose	90 mg/dL	70–99 mg/dL
CRP	31 mg/L	0.3–10 mg/L
Ferritin	2028 ng/mL	20–250 ng/mL
Triglyceride	375 mg/dL	< 150 mg/dL
ESR	40 mm/Hr	1– 13 mm/Hr
Fibrinogen	262 mg/L	200 – 400 mg/L

3. Discussion

The present case reported HLH associated with *Mycobacterial tuberculosis* infection in a 66-year-old diabetic and hypertensive man. The patient fulfilled six out of eight clinical and laboratory evidences suggestive of acquired Hemophagocytic lymphohistocytosis [8-12]. Acquired HLH is associated with the production of high levels of activating cytokines by host lymphocytes and monocytes in response to variety of factors such as tuberculous infection [13]. In this case, other risk factors such as HIV infection were absent. Furthermore, histopathological examination from the bone marrow sample revealed acid fast bacilli, suggesting disseminated *Mycobacterium tuberculosis* infection. The following criterions of HLH were present in this case: fever, splenomegaly, hyperferritinemia (8 times elevated), hemophagocytosis, elevated triglyceride, and bicytopenia (Table 1). Clinical manifestations of HLH are due to hyperactivation of CD8 + T lymphocytes and macrophages proliferation, ectopic migration, and infiltration of these cells into various organs. Thus, massive macrophage activation will result in hypercytokinemia with persistently elevated levels of multiple proinflammatory cytokines resulting in progressive organ dysfunction that may lead to death [19-21].

Tuberculosis, being a chronic disease, remains a common health problem in underdeveloped countries, posing significant morbidity and mortality. The causative organism *Mycobacterium tuberculosis (MTB)* is known as a "great mimicker" and has a diverse range of clinical manifestations. Tuberculosis may rarely present with clinical features of HLH (Table 2). Because of these, diagnosing HLH associated with TB infection is highly challenging. However, any degree of delay in the diagnosis and treatment TB-HLH will always associated with significant morbidity and mortality. HLH associated disseminated TB is uncommon and to date only a few cases have been reported (Table 2). A systematic literature review (January 1975–March 2014) found that HLH complicated the clinical course of 63 tuberculosis patients with a high mortality rate of 49%. The mean serum ferritin level was 5963 ng/mL (range 500–38,539 ng/mL); and a higher proportion (54.2%) of patients had pancytopenia at presentation. A high proportion (65%) of patients had underlying comorbidities [22].

The main causes of mortality include, central nervous system dysfunction, multiorgan failure, and disseminated bacterial or fungal infections due to prolonged neutropenia. HLH causes cytokine overproduction, which will always be associated with disseminated intravascular coagulation, hypoxemia, hemostatic imbalance, vasodilator shock, and death. Lactic acidosis is the most common cause of anion gap metabolic acidosis and is associated with high morbidity and mortality in hospitalized patients [23]. Poor prognostic markers include, age above 30, high ferritin, disseminated intravascular coagulation, multiple comorbidities, severe form of tuberculosis, and delay in treatment [14-18]. Thus, the present case possesses several poor prognostic factors which likely explain the death of the patient. These poor prognostic factors includes: age above 65 years, multiple comorbidities (diabetes and hypertension), and 8x elevated ferritin level. Furthermore, the present case also suffered from severe and disseminated tuberculosis; which will further worsen the clinical outcome.

The histopathological hallmark of HLH-associated disseminated TB involving bone marrow is an abnormal excessive accumulation of white blood cells and hemophagocytosis. These histopathological features are absent in non-HLH bone marrow tuberculosis, which is characterized by hypercellular marrow with well-formed epithelioid granulomas with central caseating necrosis [23]. HLH associated with TB (Table 2) is often treated with anti-tubercular therapy. In patients with severe disease and/or associated sepsis or multiple organ failure, treatment is challenging. The management of HLH secondary to tuberculosis, also includes immunosuppressive medications such as *Tocilizumab*, a monoclonal antibody targeting the interleukin-6 receptor [23]. The present case presented with fever of unknown origin, cytopenia and raised ferritin; prompting workup for HLH. However, he did not have classical

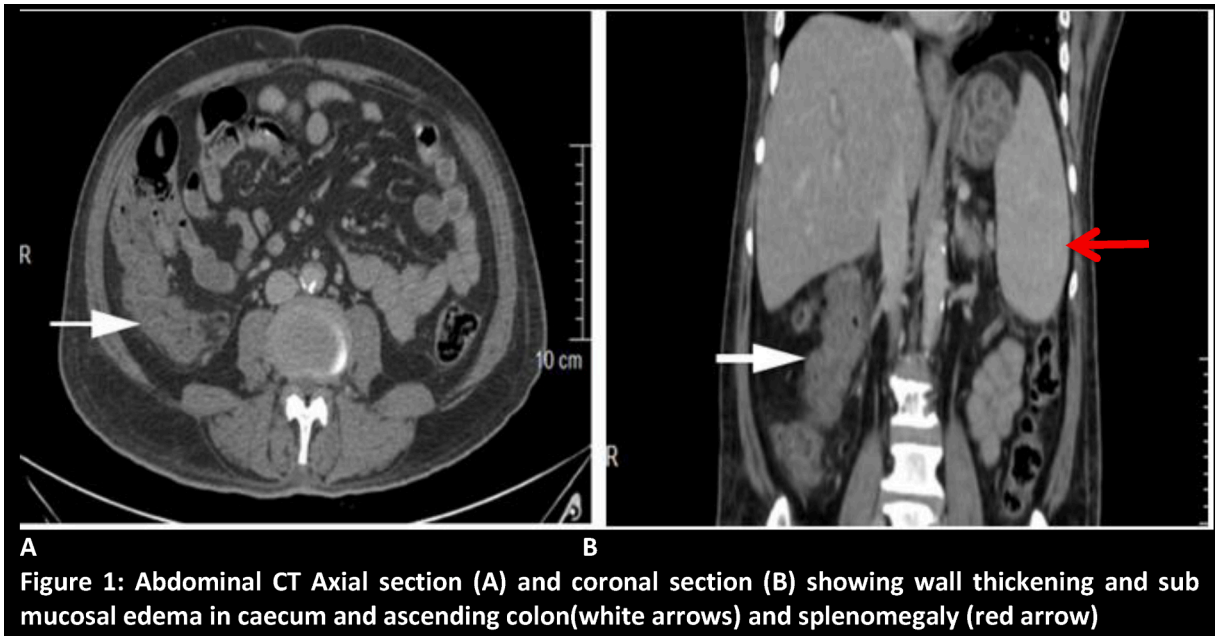

Fig. 1. Abdominal CT Axial section (A) and coronal section (B) showing wall thickening and sub mucosal edema in caecum and ascending colon(white arrows) and splenomegaly (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

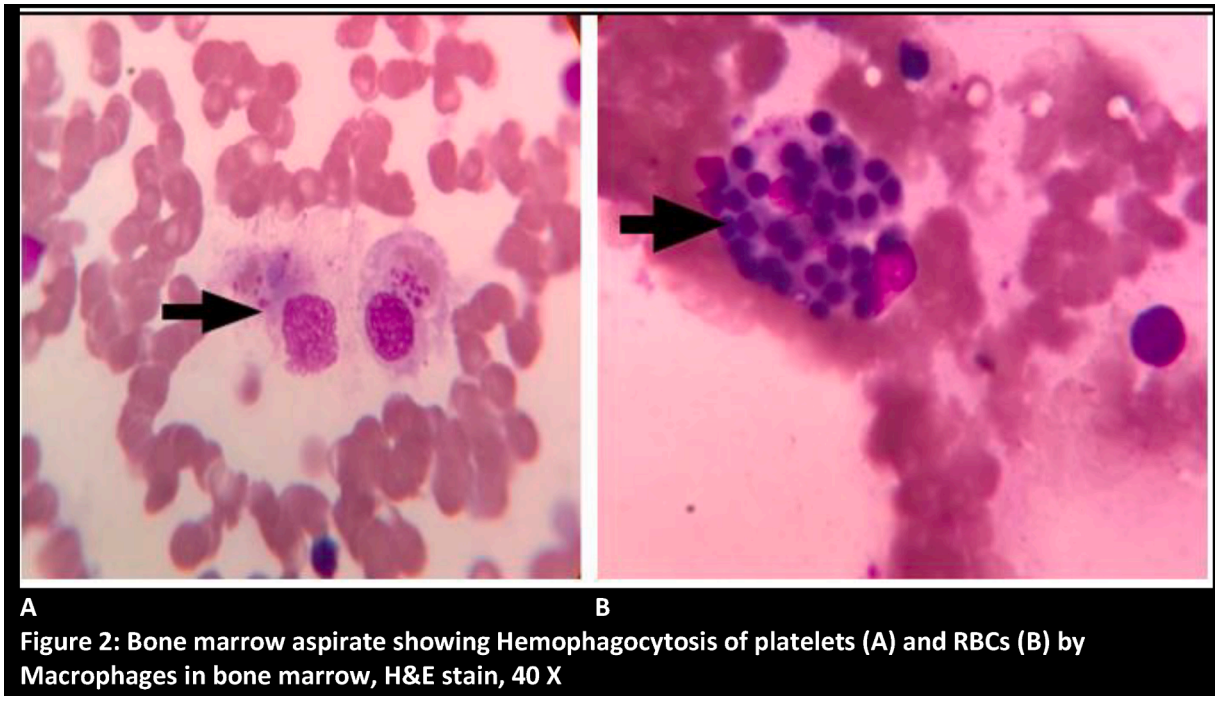

Fig. 2. Bone marrow aspirate showing Hemophagocytosis of platelets (A) and RBCs (B) by Macrophages in bone marrow, H&E stain, 40 X.

signs and symptoms of pulmonary TB or obvious signs of TB involvement in other organs. Tuberculosis with HLH often present with unusual features such as, fever of unknown origin and cytopenia [24]. Recent studies have supported the role of tocilizumab in patients infected with COVID 19 which developed hemophagocytic lymphohistiocytosis [25], [34,35]. Needless to say, it's of a timely importance to investigate the role of tocilizumab in patients with tuberculosis induced HLH. Tuberculosis is a common disease in developing countries with varied manifestations including presenting as a secondary HLH. Furthermore, tuberculosis infection with secondary HLH may be associated with high mortality. Patients with Tuberculosis complicating with HLH mostly lack typical signs and symptoms of TB and often present with fever of unknown origin and hematologic derangements, leading to delayed diagnosis.

4. Conclusion

In summary, the present case describes an immunocompetent patient with HLH-associated with disseminated tuberculosis. This case also highlights on the relevance of early diagnosis and treatment to improve the clinical outcome.

Ethics approval and consent to participate

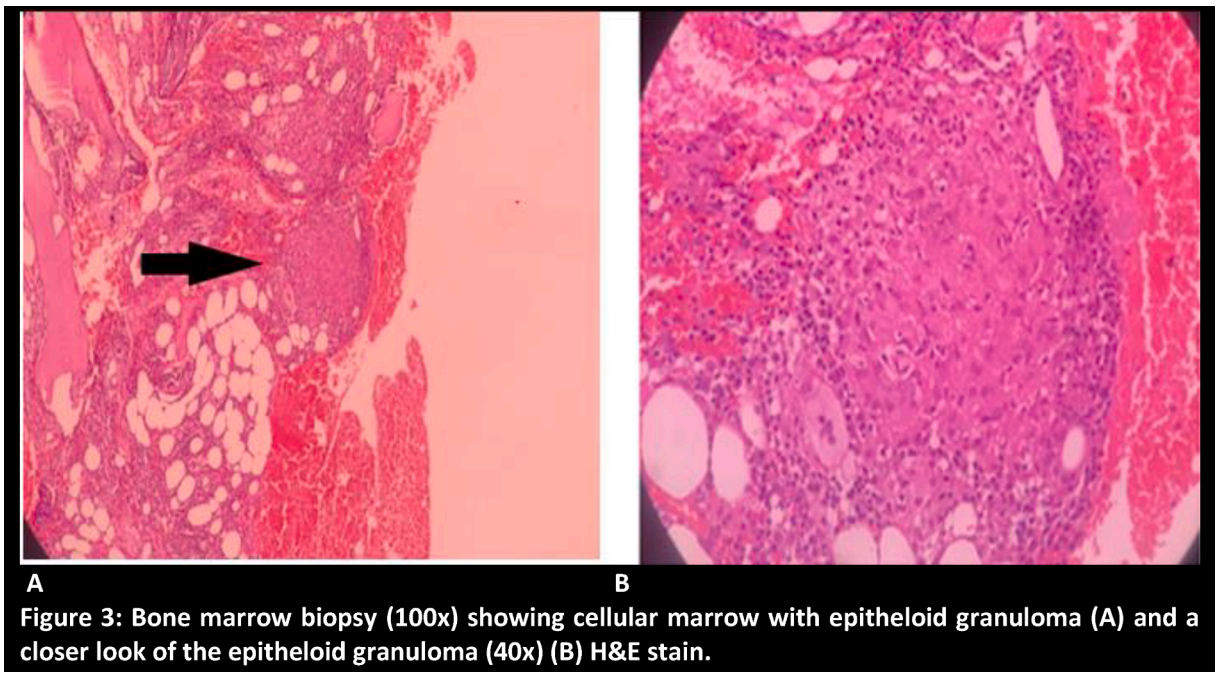

Fig. 3. Bone marrow biopsy (100x) showing cellular marrow with epitheloid granuloma (A) and a closer look of the epitheloid granuloma (40x) (B) H&E stain.

Fig. 4. Ziehl-Neelsen stain of bone marrow aspirates showing single acid-fast bacilli (red arrows). Magnification × 100. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The authors' institution does not require ethical approval for the publication of a single case report.

Consent to publication:

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials:

All data sets on which the conclusions of the case report based, to be available as spreadsheets documents and available from the corresponding author on reasonable request from the editors.

Table 2
Summary of published case reports on HLH associated with tuberculosis.

#	Authors	Age/ Sex	Presenting symptoms	Treatment	Outcome
1	Hashmi et al. 2017	58/F	Sepsis of pulmonary origin	Antibiotics	Died
2	Martínez-Pillado et al. 2019	27/F	Fever and splenic abscess	Antibiotics + Anti-tuberculous drugs	Improved
3	Shiu et al. 2019	74/F	Intermittent fever for one month	Anti-tuberculous drug + steroid	Improved
4	Rathnayake et al. 2015	40/F	High-grade fever of 2 weeks duration	Anti-tuberculous drug + steroid	Improved
5	Mbizvo et al. 2019	54/F	Fever and continuous, stereotyped, right-sided facial contractions	Antiepileptic + antituberculous drugs + steroid	Improved
6	Seo et al. 2016	14/F	Constitutional symptoms for one month	Anti-tuberculous drug + steroid	Improved
7	Parsi and Dargan et al. 2020	28/ M	Constitutional symptoms for one month	Anti-tuberculous drug + steroid	Died

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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