Case Report

An uncommon scenario from a common burden

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an infrequent disorder occurring as a result of unrestrained immune activation. Tuberculosis (TB) is a catastrophic cause of secondary HLH if not treated appropriately. Here, we report an unusual case of secondary HLH associated with abdominal TB. Although rare, secondary HLH should be ruled out in patients with TB, especially in the presence of pancytopenia.

Key words: Hemophagocytic lymphohistiocytosis, *Mycobacterium tuberculosis*, pancytopenia, tuberculosis

INTRODUCTION

South-east Asia is one of the world's largest tuberculosis (TB) endemic region with an estimated five million people affected, accounting to 40% of the global burden. Five of the eleven countries in this region are among the top 22 countries with the highest burden in the world as of 2012.[1] In Asia, the highest numbers of infected persons are in India (4.58 million) followed by Thailand, Myanmar, and Vietnam. Hemophagocytic lymphohistiocytosis (HLH) is rare, potentially a life-threatening condition which occurs as a result of unchecked immune activation and tissue damage. TB is an uncommon and usually a fatal cause of secondary HLH if not treated appropriately. Here, we report an unusual case of secondary HLH associated with abdominal TB.

CASE REPORT

A 50-year-old female with an unremarkable past or family history presented with fever for 20 days, abdominal pain, distention and jaundice for 2 weeks. On examination, she was pale and icteric with bilateral pitting pedal edema. She had distended abdomen with diffuse tenderness, her liver was enlarged with a span of 18 cm. Her spleen was also enlarged 12 cm along its long axis. Laboratory investigations revealed hemoglobin of 6.6 g/dL, white cell count of 2550 cells/mm^3, platelet count was 1.05 lakhs/cumm, and erythrocyte sedimentation rate was 34 mm at 1st h. Her liver function test showed total bilirubin of 11.41 mg/dL and direct bilirubin 9.59 mg/dL, alkaline phosphatase of 928 U/L, gamma-glutamyl transferase 247 U/L, serum glutamic oxaloacetic transaminase of 210 U/L, partial thromboplastin time of 39.6 s, prothrombin time of 22.6 s, and international normalized ratio was 2.24.

Workup for etiology including dengue, malaria, enteric fever; leptospirosis, scrub typhus, and viral markers like HIV, hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus and Epstein–Barr virus (EBV), rheumatological disorders including rheumatic factor and antinuclear antibodies were negative. Her blood and urine culture were sterile. Her serum ferritin and lactate dehydrogenase

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were 9934.2 ng/dL and 1261 U/L respectively. Ultrasound abdomen showed hepatosplenomegaly and moderate ascites.

In view of persistent fever and cytopenias with hyperferritinemia, she was worked up for HLH. Further investigations showed low fibrinogen 67.5 mg/dL and high fasting triglycerides - 756 mg/dL. Bone marrow biopsy showed normocellular marrow with mild increase in megakaryocytes and reticulin fibers. Given the constellation of fever, pancytopenia, hypertriglyceridemia, hyperferritinemia, and hypofibrinogenemia the diagnosis of HLH was entertained although hemophagocytes in the bone marrow biopsy could not be proven. Ascitic fluid analysis was done which was exudative in nature, and acid-fast bacilli (AFB) were present. Ascitic fluid cytology showed reactive mesothelial cells with increased number of neutrophils suggestive of the acute inflammatory process. Diagnostic laparoscopic peritoneal biopsy showed extensive peritoneal fibrosis with the evidence of granuloma together with AFB confirmed the underlying cause of HLH as abdominal TB.

The patient was started on antituberculous therapy (ATT) along with steroids. The patient improved dramatically with fall in ferritin levels, deranged blood parameters were normalized, and she was discharged with ATT and steroids. She defaulted the medication and came back with the deterioration of all the symptoms and signs and could not be revived.

DISCUSSION

TB is well known to cause a diverse range of clinical presentations. One of its rare but fatal manifestations is secondary HLH, which is universally fatal in the absence of antituberculous treatment.[2] HLH is rare condition which is characterized by highly stimulated but an inactive immune response. Primary HLH is a genetic disorder and secondary HLH is associated with secondary infections, autoimmune disorders, and malignancy.[3] While a broad range of infections has been linked with HLH, most frequently with EBV. Other implicated pathogens include cytomegalovirus, HIV, parasites such as *Leishmania*, fungi such as *Candida* and *Bacteria* such as *Mycobacterium tuberculosis*. TB is an uncommon but important cause of secondary HLH, accounting for about 3% of all cases, and affects all age groups.[2]

Review of various case reports related to mycobacterium associated HLH has been published but the actual incidence of HLH has not been estimated.[4,5] In a national survey of HLH in Japan between 2002 and 2005, two patients had HLH with TB out of the 799 identified.[6] In another report of TB associated with HLH, 37 cases were identified. 15 out of all reported cases had no clinical evidence of pulmonary TB, which possibly increased the diagnostic difficulty.[5] Another report of TB in Taiwan documented hemophagocytosis in seven patients out of 833 with culture-positive TB.[7]

Familial HLH in an adult patient homozygous for A91V in the perforin gene in association with TB infection has also been reported.[8] Underlying comorbid conditions such as end-stage renal disease receiving hemodialysis or had undergone renal transplantation, malignancy, AIDS, and sarcoidosis were found to be associated with TB-causing HLH.[5]

The pathological hallmark of HLH is an aggressive proliferation of macrophages and histiocytes which phagocytose other blood cells leading to the clinical symptoms. Although the exact pathogenesis of TB associated HLH is not known clearly, it is likely to be related to immune dysregulation. TB normally induces a Th1 response, in which cytotoxic.

Th1 cells and macrophages cooperate to increase the efficiency of cytotoxic lymphocytes and the capacity of macrophages to proliferate. In any secondary HLH, defective cytotoxic T cells and natural killer cells produce a disordered and inadequately regulated immune response that may result in the survival and proliferation of *Bacteria* with ongoing immunological stimulation.[2,4]

The aim of treatment of HLH is to suppress the severe hyperinflammation and also to control the infection which has triggered the syndrome. HLH associated with infectious illnesses such as TB may resolve with treatment of the underlying infection. Data from systematic reviews suggest that HLH secondary to infections such as TB may recover with early anti-microbial therapy and steroids alone.[9] However, some have added immunotherapies in addition to the ATT such as high-dose steroids, intravenous immunoglobulin, chemotherapy (e.g., etoposide or vincristine), splenectomy, and plasma exchange. Despite the availability of various regimens, HLH nevertheless carries a high death rate. One series reported overall mortality as 44%.[4] Brastianos *et al.* reviewed 36 cases of TB-associated HLH wherein, patients who did not receive either antitubercular or immunomodulatory treatment uniformly succumbed, emphasizing the deadly nature of this disease.[5]

Indeed, the major correlate with mortality is the time to diagnosis. Further, the coexisting organ dysfunction due to HLH may also complicate drug administration for TB. Poor prognostic factors include age more than 30, disseminated intravascular coagulation, hyperferritinemia, and increased beta 2-microglobulin levels.[5,10]

CONCLUSION

Involvement of multiple organs and especially the reticuloendothelial system can also produce a clinical presentation similar to disseminated TB; thus cases of HLH

secondary to TB can easily be missed if the entire illness is attributed to TB alone. Although unusual, secondary HLH should be ruled out in patients with disseminated TB, especially in the presence of pancytopenia.

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Conflicts of interest

There are no conflicts of interest.

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