Asian Pac. J. Health Sci., **2017; 4(3):245-248** **e-ISSN: 2349-0659, p-ISSN: 2350-0964**

Document heading **doi: 10.21276/apjhs.2017.4.3.37** **Case Report**

Hemophagocytic syndrome secondary to tuberculosis- a rare case report

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Received: 10-08-2017 / Revised: 18-08-2017 / Accepted: 03-09-2017

ABSTRACT

Hemophagocytic syndrome , also known as hemophagocytic lymphohistiocytosis (HLH) is the manifestation of immune dysregulation. It is associated with ineffective but increased response and infiltration of active lymphocytes and histiocytes in various organs. It presents with clinical and biochemical manifestations of fever, splenomegaly, pancytopenia, hypertriglyceridemia, hyperferrritinemia. It can be primary or secondary. Primary (genetic) usually presents in childhood. Secondary is due to infection by viruses or other etiologies are also important as early detection and treatment improves the survival rate in this devastating disease. Hemophagocytosis due to tuberculosis is uncommon. Few cases have been reported in literature. The present case report is of a 20 year male, diagnosed as secondary HLH due to tuberculosis, highlighting importance of early diagnosis and treatment of this devastating disease, thus reducing the mortality.

Keywords: Hemophagocytic syndrome, secondary, tuberculosis, Bone marrow

Introduction

Hemophagocytic lymphohistiocytosis /Hemophagocytic syndrome is an immune dysregulation syndrome, associated with ineffective but exaggerated immune response and infiltration of active lymphocytes and histiocytes in various organs. It was first described in 1952 by the Scottish paediatricians James Farquhar and Albert Clarieaux, who encountered 2 infants with an unrecognized complex of cytopenias, hepatosplenomegaly and unremitting fevers. Both infants died a few weeks after initial presentation. Upon autopsy, there was evidence of widespread infiltration in the lymph nodes, spleen, liver and bone marrow with lypmhocytes and benign appearing histiocytes with hemophagocytosis. They identified this syndrome as familial hemophagocyticreticulosis [1] which is now known as HLH. Its incidence is 1.2 cases per 1,000,000 individuals per year [2]. It is characterized by clinical and biochemical manifestations of fever, cytopenias, splenomegaly, hypofibrinogenemia and or hypertriglyceridemia, hemophagocytosis in bone marrow/ spleen/ lymph nodes, ferrrrtin> 500 ug/L, soluble CD 25> 2400 U/L and low natural killer cell activity, 5 out of these 8 criteria are required for the diagnosis. It can be either primary or secondary. Primary HLH usually presents in childhood. Secondary HLH occurs due to infection with Epstein bar virus, tuberculosis, malaria, rheumatological disorders, malignancy [3-5].

Hemophagocytosis due to tuberculosis is very rare [3,4]. Very few cases have been reported mostly in immunocompromised patients. We report a case of hemophagocytic syndrome secondary to tuberculosis in immunocompetent man. Early diagnosis and treatment is a demanding need in this devastating disease.

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Case report

A 20 year old male presented with high grade fever of 2-3 months duration, ascites and cervical lymphadenopathy. Patient did not respond to treatment for fever. He was subjected to cytology OPD for FNAC of cervical lymph node. Cytosmears from

cervical lymph node showed predominantly caseousnecroisis and few lymphocytes. Epithelioid granuloma were not seen on cytosmears , (Fig 1). On further investigations, S. Ferritin level was raised upto 736 ug/L (N-24-336 ug/L in males) , S. LDH level - 4000 IU/L (N- 105-333 IU/L) . Liver enzymes were raised, SGOT – 52 IU/L, SGPT- 72 IU/L, renal function and other biochemistry investigations were within normal range. USG abdomen showed mild splenomegaly, hepatomegaly, multiple lymph nodes measuring upto 1.5 cm. Ascitic fluid was tapped which showed raised ADA level upto 85 U/L. Chest X-Ray was unremarkable.

Further, Bone Marrow Aspiration was done which showed hypercellular marrow with normoblastic and megaloblastic hyperplasia. Significant increase in number of macrophages was seen with significant high hemophagocytic activity (Fig2,3). Later, biopsy of cervical lymph node was done which showed epithelioid granulomas. Hemophagocytic activity was not seen in the lymph node (Fig 4). Hence, considering all the investigation parameters, a diagnosis of Hemophagocytic lymphohistiocytosis (HLH) secondary to tuberculosis was made. Patient was put on antitubercular drugs and steroids. He responded well to the treatment within 7 days.

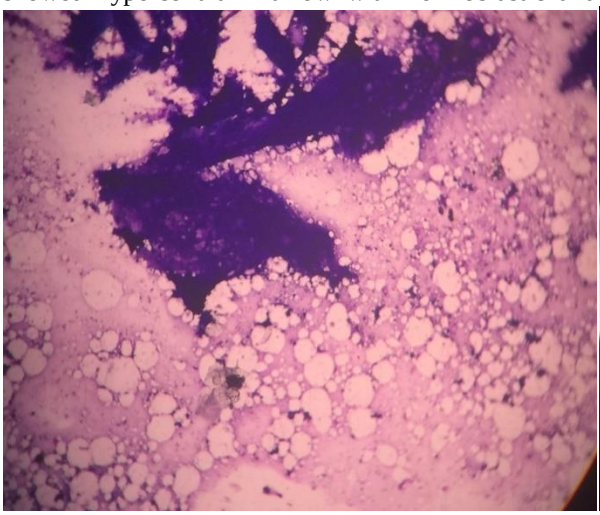

Fig 1:Cytosmears showing necrosis in cervical lymph node, MGG stain, 40 X

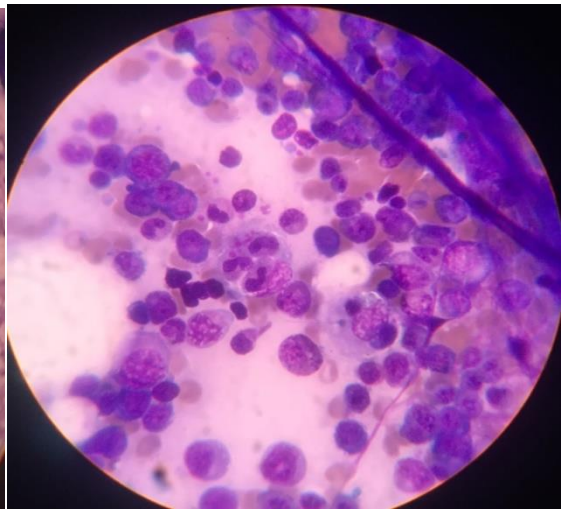

Fig 2:Hemopahgocytosis in bone marrow, MGG stain, 40 X

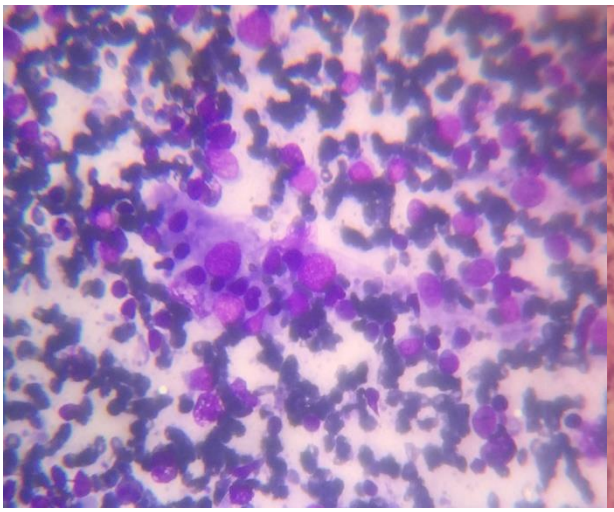

Fig 3:Hemophagocytosis in bone marrow MGG stain, 40 X

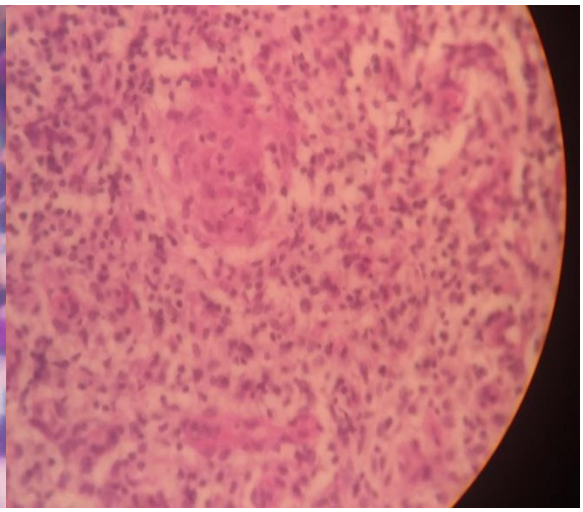

Fig 4:Epithelioid granulomas in Lymph node biopsy,H&E stain, 40 X

Discussion

Hemophagocytic syndrome / Hemophagocytic lymphohistiocytosis (HLH) is a disorder characterized by benign proliferation of the mature histiocytes and phagocytosis of the platelet, erythrocytes, lymphocytes and their hematopoetic precursors in the Bone Marrow giving rise to cytopenias [5-8].
Many patients present with fever of unknown origin [9]. The onset of systemic manifestations is abrupt, like pallor, fever, rash, lymphadenopathy, hepatosplenomegaly, neurological manifestations, raised lactate dehydrogenase (LDH) and serum bilirubin. It may take fulminant course with fatal outcome [6,7].

Hemophagocytic syndrome is a life threatening immune dysregulatory syndrome caused by severe hypercytokinemia due to stimulated but ineffective immune process. 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, hypercytokinemia with persistently elevated levels of multiple proinflammatory cytokines resulting in progressive organ dysfunction that may lead to death [3].
These interrelated factors are responsible for clinical manifestations of prolonged fever, hepatosplenomegaly, bleeding, skin rash, CNS abnormalities, jaundice and laboratory findings of bicytopenia or pancytopenia, coagulopathy, hyperlipidemia, hypofirinogenemia, hyperferritinemia , transaminitis, hyperbilirubinemia and hypoalbuminemia [10].
Main causes of mortality are central nervous system dysfunction, multiorgan failure, and disseminated bacterial or fungal infections due to prolongedneutropenia[11-13]. HLH can be primary (familial) and secondary.
Primary HLH usually present in childhood particularly < 2 years of age [14], associated with perforin mutation. Secondary HLH is associated with production of high levels of activating cytokines by host lymphocytes and monocytes. It occurs due to infection (Epstein bar virus, parvovirus, varicella zoster, HIV, mycobacterial, fungal, leishmaniasis, leptospirosis, rickettsia, 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 [4].

To diagnose HLH 5 out of 8 of the criteria set up by Histiocytic Society 2004 must be present[15], table 1.

Table 1: Diagnostic criteria for hemophagocytic lymphohistiocytosis. According to the HLH 2004 Protocol

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)
- Fever
- Splenomegaly
- Cytopenia> 2-3 cell lines in peripheral blood
- (hemoglobin < 9 g/100 ml, platelets < 100x 10 /L,Neutrophils< 1.0 x 10 /L
- Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides > 3.0 mmol/L, fibrinogen < 1.5 g/L)
- Hemophagocytosis in bone marrow, spleen, CSF, or lymph nodes. No sign of malignancy
- Decreased or absent NK-cell activity (according to local laboratory reference)
- Ferritin > 500 ug/L
- 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**

Our patient fulfilled 5 out of 8 criteria as he had fever, splenomegaly, pancytopenia, bone marrow evidence of hemophagocytosis, hyperferritinemia. Bone marrow aspiration has a sensitivity of 84 % for the diagnosis of HLH. Most studies require a number of macrophage showing signs of phagocytic activity above 2-3 % and a median of 6 histiocytes per 500 nucleated cells [17]. Hemophagocytosis due to tuberculosis is unusual.

There are only few cases reported. HLH due to tuberculosis has high mortality rate (50%). Most of case report reveals death of the patient [16]. Judicious case detection and timely management have important prognostic significance. Poor prognostic markers are age over 30 years, high ferritin, delay in treatment, disseminated intravascular coagulation, etc.

Conclusion

Tuberculosis, is a common disease in India, with varied manifestations. It can also present as HLH. Prompt diagnosis and early initiation of treatment can reduce the high mortality associated with this disease.

Acknowledgements

Patient and his relatives

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Source of Support: Nil
Conflict of Interest: Nil