
Haemophagocytic syndrome in an Infant- A rare case report**Dr. Balaji D. Baste¹, Apoorv Giri^{2*}, Dr. Ashwin K. Barsagade³, Dr. Pradeep S. Umap⁴, Dr. Anuradha V. Shrikhande⁵**¹Assistant Professor, Department of Pathology, Seth G. S. Medical College and K.E.M. Hospital, Mumbai, Maharashtra, India²Assistant Professor, Department of Pathology, Swami Ramanand Teerth Government Medical College and Hospital, Ambajogai, Dist. Beed, Maharashtra, India³Assistant Professor, Department of Pathology, Government Medical College and Hospital, Akola, Maharashtra, India⁴Professor and Head, Department of Pathology, Government Medical College and Hospital, Akola, Maharashtra, India⁵Professor and Head, Department of Pathology, Indira Gandhi Government Medical College and Hospital, Nagpur, Maharashtra, India***Corresponding author**

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Abstract: Hemophagocytic lymphohistiocytosis is a defect in the immune response leading to hypercytokinemia and an unbridled activation of lymphocytes and histiocytes with a uniformly fatal outcome in absence of treatment. We evaluated a 1.5 month old female child, who presented with clinical features of sepsis, but soon developed pancytopenia and deranged coagulation profile. Radiological investigations showed hepatosplenomegaly and bone marrow revealed hemophagocytosis by histiocytes.**Keywords:** Hemophagocytic lymphohistiocytosis, pancytopenia, fever, bone marrow, infant.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder of the lymphoid cells and histiocytes marked by an untrammled albeit non-neoplastic proliferation of abnormally active lymphocytes and mature macrophages; the spleen, liver, bone marrow, skin and meninges being the more privileged sites of such escalation. The resultant hyper-inflammation leads to a systemic illness featuring pyrexia, organomegaly, variable cytopenias, liver dysfunction and hemophagocytosis by histiocytes principally in, but not limited to, the bone marrow, spleen and lymph nodes. The disease is distinguished by a fulminant clinical course and high mortality despite adequate treatment.

CASE REPORT

A one and a half month old female infant, born out of non-cosanguineous marriage, was referred to our institution with an 8 days' history of fever, cough and cold and abdominal distension associated with excessive crying, rapid breathing and refusal of feeds since last 3 days. Her past and family history was unremarkable and her immunization history was up to date. Her birth history revealed delivery through LSCS due to deep transverse arrest however, she cried at birth and her neonatal period was uneventful.

General physical examination revealed fever, pallor, lethargy, tachycardia (PR = 168 /pm), tachypnea (RR = 72/min) and icterus. Systemic examination

showed B/L decreased breath sounds with occasional crepitations, abdominal distension and sluggish bowel sounds.

Initial hemogram showed leukocytosis (18700/cumm), thrombocytopenia (52000/ μ l); DLC revealed lymphocytosis (77%) and Hb = 8.6gm%. Peripheral smear consisted of atypical lymphoid cells, smudge cells and occasional blasts like cells (blastoid) with giant platelets and a microcytic to normocytic – RBC morphology. However, serial hemograms registered a continuous fall in the TLC and platelets, neutropenia and anemia. Patient's coagulation profile was deranged with PT>1min and APTT>2min. Reticulocyte Production Index was 1%.

Imaging studies indicated the presence of mild hepatosplenomegaly, splenic microabscess, moderate ascites and mild B/L pleural effusion on ultrasound and CT scan was additionally suggestive of early changes of liver parenchymal disease.

Ascitic fluid contained plenty of RBCs and pus cells and glucose and protein were raised (130mg/dl and 4.7gm/dl). Gram and Ziehl-Nielsen stains were non-contributory and blood culture did not show any growth. Serology for HIV, HBsAg, HAV, HCV, Dengue, Malaria and enteric fever were negative.

Serum biochemistry was remarkable for the following:

- Raised serum transaminases(SGOT = 143U/ml, SGPT = 147U/ml)
- Decreased total protein and serum albumin(5gm/dl and 2.5gm/dl respectively)
- Raised serum bilirubin(total = 2.3gm/dl; direct = 2.2gm/dl)
- Decreased serum sodium(120mEq/l)
- KFTs were within normal limits as was serum ALP and serum potassium.

Bone marrow aspiration (Figures 1 to 3) revealed a hypocellular marrow with decrease in erythropoiesis, granulopoiesis and thrombopoiesis. M/E Ratio was 3:1. The predominant feature was presence of many large histiocytes which were scattered diffusely and in small groups, showing phagocytosis of RBCs, normoblasts, myeloid series cells and lymphoid cells (Hemophagocytosis). No parasites were seen. Based on the above findings a diagnosis of hemomphagocytic lymphohistiocytosis was made. However the child's condition progressively deteriorated and she died on day 5 of admission.

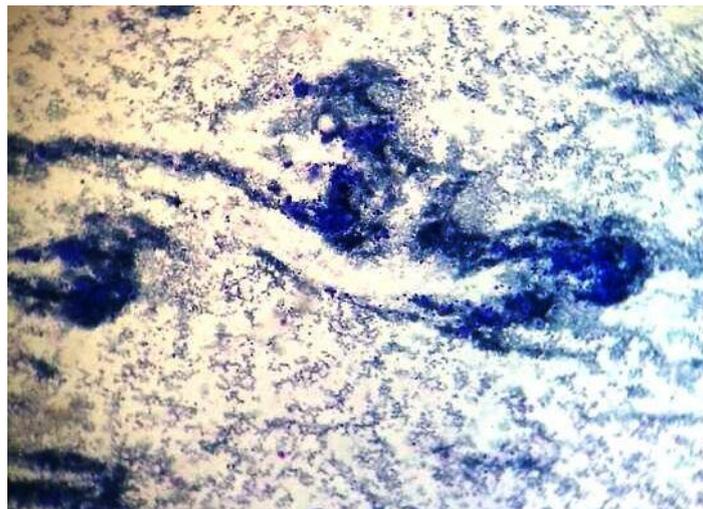


Fig-1: Photomicrograph showing a hypocellular marrow (Leishman stain, 40X)

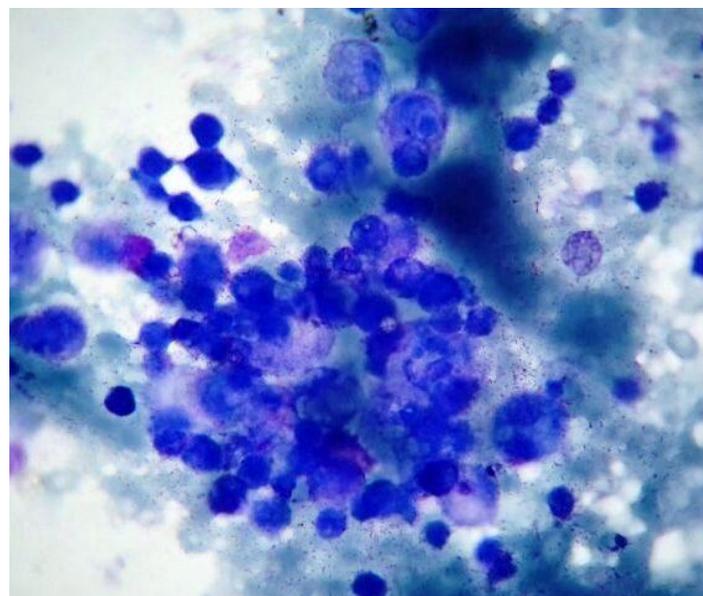


Fig-2: Photomicrograph showing predominantly dissociated histiocytes showing phagocytic activity (Leishman stain, 400X)

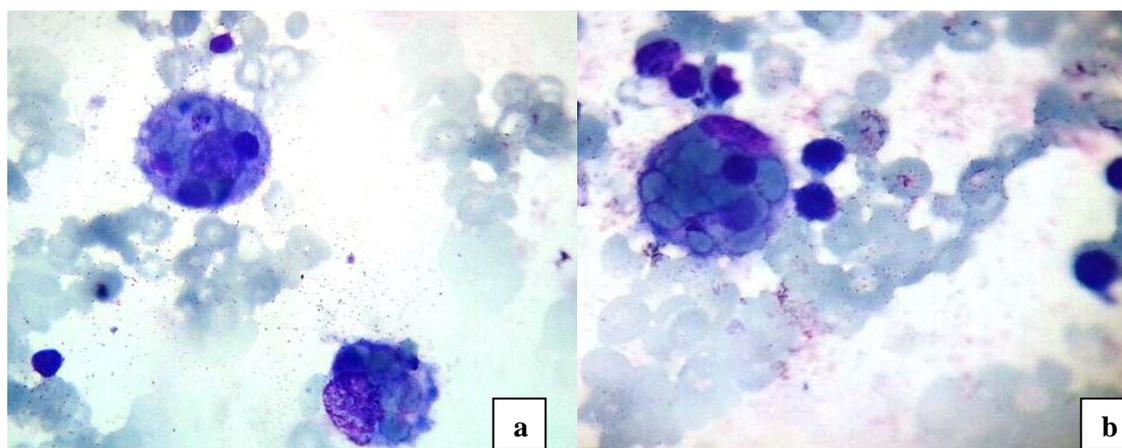


Fig-3: Photomicrographs showing histiocytes with (a) hemophagocytosis of normoblasts and a myeloid precursor and (b) normoblasts (Leishman stain, 1000X)

DISCUSSION

Primary form of HLH typically manifests in pediatric population, is an autosomal recessive or x-linked disorder and can be familial or associated with immune deficiencies. Secondary form usually occurs at an older age and is triggered by an underlying condition like infections (viral, bacterial, protozoan or fungal) or lymphoma. Macrophage activation syndrome (MAS) is a phenomenon now recognized as a form of hemophagocytic lymphohistiocytosis that is characteristically associated with autoimmune diatheses particularly, systemic juvenile rheumatoid arthritis, systemic lupus erythematosus, adult Still's disease and Sjogren syndrome [1, 2]. Immunodeficiency syndromes known to be associated with HLH include Chédiak-Higashi syndrome, Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2, and X-linked proliferative syndrome (XLP) [3, 4]. The genetic defects in HLH can occur at any age, and in cases harboring these defects, infections can also be the inciting factor [5, 6]. Hence classification of HLH into genetic and acquired is considered more appropriate [3, 4]. It is theorized that all forms of HLH are due to functional impairment of cytotoxic T lymphocytes (CTLs) and NK cells [7]. This is accompanied by uncontrolled macrophage activation and inadequate apoptosis of immunogenic cells [8]. The clinical picture and laboratory manifestations result from increased levels of inflammatory cytokines secreted by activated T cells and macrophages, particularly Th1 cytokines such as interferon- γ , IL-12 and IL-18, along with IL-1 β , IL-6 and tumor necrosis factor alpha [9, 10].

HLH should be suspected in cases of an unexplained sudden onset of a systemic inflammatory response syndrome (SIRS), including fever, malaise, hepatosplenomegaly, jaundice, generalized lymphadenopathy, and cytopenias [11]. CNS involvement (seizures, meningitis, irritability, hemiplegia etc.) is frequently seen in pediatric age group [3, 12]. Dermatological involvement in the form

of non-specific rash (often purpuric morbilliform) may also be seen in a significant number of patients [3, 13].

The diagnosis of HLH may be established [14]:

1. A molecular diagnosis consistent with HLH (for example, pathologic mutations of PRF1, UNC13D or STX11 are identified)

OR

2. Fulfillment of five out of the eight criteria listed below:

- Fever
- Splenomegaly
- Cytopenias (affecting at least two of three lineages in the peripheral blood):
- Hemoglobin <9 g/100 ml (in infants <4 weeks: hemoglobin <10 g/100 ml)
- Platelets <100 $\times 10^3$ /ml
- Neutrophils <1 $\times 10^3$ /ml
- Hypertriglyceridemia (fasting, ≥ 265 mg/100 ml) and/or hypofibrinogenemia (≤ 150 mg/100 ml)
- Hemophagocytosis in BM, spleen or lymph nodes
- Low or absent NK cell activity
- Ferritin ≥ 500 ng/ml
- Soluble CD25 (that is, soluble IL-2 receptor) >2400 U/ml (or per local reference laboratory)

The three cardinal features of HLH are fever, hepatosplenomegaly and pancytopenia [15]. Helpful but unpublished markers which support the diagnosis [16, 17] include

- Cerebrospinal fluid (CSF) pleocytosis
- Neurologic symptoms (e.g. lethargy, cranial nerve palsies, seizures)
- Conjugated hyperbilirubinemia and transaminitis

- Hypoalbuminemia
- Hyponatremia
- Elevated D-dimers

Although the present case fulfilled 4 of the 8 diagnostic criteria, the absence of any other hematological disorder and objective proof of any malignancy or infectious disease, and the presence of some of the supportive indicators, as sighted above, put the diagnosis in favour of HLH.

CONCLUSION

HLH is often missed or delayed mostly due to the overlapping clinical findings with many infectious, malignant and autoimmune disorders, lack of diagnostic tests in many facilities and also because of the physicians being incognizant of its existence. Although the present case did not fulfil all the essential criteria for the diagnosis, the presence of supportive criteria heavily pointed to the identification of HLH. Therefore, in cases of fever with hepatosplenomegaly and pancytopenia, a combination of diagnostic and supportive criteria should be employed to substantiate the diagnosis of HLH.

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