Haemophagocytic Lymphohistiocytosis (HLH): Case Series in Tertiary Referral Hospital Over Three Years

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Abstract
Haemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes that commonly appears in infancy, although it has been seen in all age groups. We are reporting a series of 5 cases of HLH in young adult and paediatric patients identified over three years.

Introduction
HLH is not only a rare entity in adults, but also has high mortality. Primary HLH is a heterogeneous autosomal recessive disorder found to be more prevalent with parental consanguinity. Secondary HLH occurs after strong immunologic activation which can occur with systemic infection, immunodeficiency or underlying malignancy. Both forms are characterised by overwhelming activation of normal T-lymphocytes and macrophages invariably leading to clinical and haematologic alterations and death in absence of treatment. Here we are reporting case series of HLH in young adult and paediatric patients.

Case 1
A 32 yr old male presented with headache, fever with rash since 15 days in OPD. He had seizures, was loaded with phosphenytoin, intubated and mechanically ventilated. He was extubated and shifted to the ward after 2 days, initial infective workup and other investigations were normal. After 1 day he was found to be drowsy and shifted back to the ICU with persistent fever. An MRI was done and it showed features suggestive of acute demyelinating encephalomyelitis, and skin biopsy showed erythema multiforme. He was started on methyeprednisolone pulse therapy, CSF analysis and initial bone marrow biopsy was normal. Patient continued to have persistent fever, all infective work up was negative, patient had deranged liver function tests and pancytopenia, repeat bone marrow biopsy showed features of haemophagocytosis (HLH). Treatment was started according to the HLH protocol which includes etoposide and dexamethasone, but patient continued to deteriorate and died after 17 days.

Case 2
A 36 yr old male treated at local hospital for fever, myalgia, vomiting, diarrhoea and altered sensorium of 3 days duration. When seen in our hospital, patient was very drowsy and not arousable requiring intubation and mechanical ventilation. Initial work up showed multiorgan failure and tested positive for IgM leptospira. He was anuric
with severe metabolic acidosis requiring dialysis. Patient continued to be comatose with persistent fever, bone marrow biopsy done as work up for fever showed features of haemophagocytosis (HLH) and treatment was started as per the protocol. On Day 6 blood and deep ET c/s showed ESBL E-coli and he was started on carbapenems, but patient continued to deteriorate and died after 10 days.

**Case 3**

A 4 yr old boy presented with fever of 1 week, abdominal pain, distension, irritability and altered sensorium since 3 days. On examination child was drowsy, had temperature, generalised rashes, hepatosplenomegaly and had tonic posturing. He received loading dose of phenytoin, was intubated and ventilated. Initial investigations showed pancytopenia, all other infective workup was negative, bone marrow biopsy done showed features of HLH. Treatment was started according to the HLH protocol, child showed improving trends and was extubated, but child had a vacant stare. EEG showed focal continuous epileptiform activity, child was shifted to another hospital on parent’s request.

**Case 4**

A 7 month old girl presented with fever, poor feeding for 4 days, child was positive for dengue NS1Ag 1 week before admission. On presentation child had high fever with respiratory distress, and was hypotensive necessitating intubation and mechanical ventilation. Initial workup showed deranged coagulation profile, severe metabolic acidosis and reactive lymphocytes on peripheral smear, bone marrow biopsy showed haemophagocytes. Treatment was initiated as per HLH protocol along with supportive management. ECHO showed LV dysfunction with severe mitral regurgitation, child continued to deteriorate and died.

**Discussion**

Haemophagocytic lymphohistiocytosis (HLH) is a syndrome characterised by fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, rash and haemophagocytosis by non-malignant macrophages. Laboratory findings characteristic of this disease includes hypertriglyceridaemia, hyperferritinaemia, hypofibrinogenaemia and deranged LFT. Symptoms of HLH are typically rapidly progressive, often resulting in death from haemorrhage, multi-system organ failure or infection. Survival from HLH requires prompt recognition of syndrome, correction of its underlying cause and HLA specific therapies.

In acquired form HLH has been associated with infections such as EBV, CMV, inflammatory diseases such as Juvenile rheumatoid arthritis and malignancies such as T-cell non-Hodgkin lymphoma and Hodgkin lymphoma. In HLH an apparent loss of restraint of function of normal histiocytic cells is
correlated with elaboration of high levels of interferon –γ by activated CD 8+ T cells and TNF-α and IL-6 by activated macrophages.5

Standard definition of HLH requires at least 5 of 8 clinical criteria to be met: fever, splenomegaly, peripheral cytopenias of 2 or 3 lineages, hypertriglyceridaemia, elevated ferritin, elevated soluble CD25, absent NK-cell activity and histological evidence of HLH in bone marrow, lymph nodes or spleen. All of the patients in the series fulfilled the criteria for HLH (Tables 1 and 2).

In our first patient diagnosis of HLH was delayed as the initial bone marrow biopsy did not show haemophagocytic cells. We did not look into other laboratory markers. Initial bone marrow biopsies are insensitive for diagnosis of HLH.2 Our first patient developed HLH after viral infection. In a series of 6 cases associated with EBV infection, all of them died within 3 months of onset of symptoms.6 In our second patient HLH is presumably secondary to leptospirosis which has not been reported in literature earlier. Since he had persistent high fever, bone marrow biopsy was done which showed hypercellular marrow with haemophagocytes (Figure 1) supported by additional laboratory findings of hypertriglyceridaemia, hyperferritinaemia, elevated LDH. He developed multi-organ failure quite early and succumbed to HLH. Similarly both of our paediatric patients had HLH following viral infection and did not respond to HLH protocol, though the outcome is relatively better in paediatrics.

Four of five patients in our series died of HLH and did not respond to treatment by HLH-2004 protocol, which we started after histological evidence from bone marrow.

**Conclusion**

We describe case series of 4 HLH patients 2 adults one following viral infection which is known entity and other one following leptospirosis which is not reported in literature and three paediatric HLH cases all of which probably following viral infection. Diagnosing HLH may be difficult and is often delayed because the clinical presentation mimics other conditions like severe sepsis, hepatic failure and malignancies,8 so we need to have high index of suspicion and look for markers to detect this syndrome in early phase of illness and start treatment according to HLH 2004 protocol for better outcome.5,7

**References**


**Fig. 1:** Microscopic picture of phagocytosis by histiocyte of leucocytes and erythrocytes