

## Case Series

# Infection associated hemophagocytic lymphohistiocytosis: a report of three cases

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## ABSTRACT

HLH (Hemophagocytic lymphohistiocytosis) is not an uncommon disorder; it is an overreaction of the immune system. It can be familial or acquired and both share one common feature of a highly stimulated and ineffective immune response. Acquired HLH is commonly seen with infection (infection associated hemophagocytic syndrome-IAHS); malignancies and rheumatic disease where it is also known as (macrophage activating syndrome). Here we are reporting three cases of secondary HLH associated with dengue, typhoid and vivax malaria.

**Keywords:** Secondary HLH, Infection, Dengue, Enteric, Malaria

## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is not an uncommon disorder; it is an overreaction of the immune system. It can be familial or acquired and both share one common feature of a highly stimulated and ineffective immune response.<sup>1,2</sup>

Acquired HLH is commonly seen with infection infection associated hemophagocytic syndrome (IAHS); malignancies and rheumatic disease where it is also known as (macrophage activating syndrome). Here we are reporting three cases of secondary HLH associated with dengue, typhoid and vivax malaria.

## CASE SERIES

### *Dengue fever associated HLH*

8 years old previously healthy girl presented with high grade intermittent fever for past 3 days associated with non-bilious vomiting with periumbilical abdominal pain and headache. Physical examination was normal. Initial

investigation showed nonstructural protein 1 (NS 1) antigen (Ag) positive, with negative immunoglobulin M (IgM)/immunoglobulin G (IgG) with hemoglobin (Hb) of 11.0 gm/dl, total counts of 4500/cmm and platelets count of 1.5 lac, with normal liver enzyme. The patient started to improve with conservative management but fever returned after 4 days, which was high grade and intermittent. Physical examination revealed pallor, tachycardia, tender hepatomegaly and splenomegaly. On investigation she had pancytopenia [Hb-8.5g/dl, thin layer chromatography (TLC)-1600/cumm, platelet (Plt)-65000/cumm], possibility of dengue associated HLH was considered and investigated accordingly (Table 2).

Diagnosis of dengue fever with virus associated hemophagocytic syndrome was made according to diagnostic criteria of the HLH protocol of histiocyte society (Table 1).

Bone marrow was planned but refused by parents. She was managed with intravenous (IV) dexamethasone followed by oral prednisolone, she responded dramatically to steroids, with normalization of peripheral blood counts noted 1 week later with complete recovery on follow up.

**Table 1: HLH diagnostic criteria 2004.**

Criteria	Diagnosis
At least 3/4	Fever
	Splenomegaly
	Hepatitis
	Cytopenias
At least 1/4	Hemophagocytosis
	Hyperferritinemia
	Increased soluble IL2 R alpha
	Absent or very decreased NK cell function
Supportive of HLH	Hypertriglyceridemia
	Hypofibrinogenemia
	Hyponatraemia

**Table 2: Investigation in infection associated HLH.**

Investigation	Dengue fever	Enteric fever	Vivax malaria
Hemoglobin (g/dl)	8.5	5.6	9.7
TLC	1600	7600	5300
DLC (N/L/M/E)	78/18/2/2	64/26/6/6	73/20/4/3
Platelet	65000	90000	85000
CRP	68	95	52
LDH (U/L)	744	656	634
SGOT (U/L)	157	146	41
SGPT (U/L)	139	121	39
Albumin (mg/dl)	3.9	3	3.5
Creatinine (mg/dl)	0.5	0.7	0.6
Sodium (meq/l)	130	132	131
Potassium (meq/l)	3.6	4.0	3.9
Chloride (meq/l)	99	98	100
Tri glycerides (mg/dl)	356	222	290
Ferritin (ng/ml)	773.5	1872	1600
Coagulation profile (PT/APTT)	Normal	Normal	Normal
Spleen size	Tip palpable	Tip palpable	2 cm palpable

**Enteric fever associated HLH**

6 year old girl presented with history of fever (high grade, intermittent) for 10 days duration. She was treated with oral antibiotics (cefexime) for last 7 days and was admitted with recurrence of fever. Fever was high grade, intermittent associated with non-bilious vomiting. On physical examination she had pallor, tachycardia for age, and hepatosplenomegaly with no lymphadenopathy. On investigation, patient had anemia [Hb-5.6), thrombocytopenia (Plt-90,000/cumm), C-reactive protein (CRP) was raised (105), typhidot IgM positive and WIDAL titer was raised (TO; TH >1:360]. She had raised liver enzymes [Serum glutamic oxaloacetic transaminase (SGOT)-146, Serum glutamic pyruvic transaminase (SGPT)-121] with normal renal function and electrolytes.

She was treated as case of complicated enteric fever with IV ceftriaxone but there was no clinical improvement then possibility of secondary HLH was considered and investigated accordingly (Table 2). She was given blood transfusion and IV dexamethasone, followed by oral prednisolone she showed dramatically improvement, complete blood count (CBC) normalized on day 4 with complete recovery on follow up.

**Vivax malaria associated HLH**

10 years old boy presented with intermittent fever with chills of 2 days. Physical examination was normal. Investigation showed normal counts and blood smear was positive for plasmodium vivax. He was treated with chloroquine followed by primaquine, and was discharge after 3 days of afebrile period with blood smear negative for Plasmodium vivax trophozoites. He was readmitted after 2 days with high fever and vomiting, his blood counts showed Hb of 6 gm%, TLC-2200/cmm and platelet count of 80,000 with no other focus of infection, possibility of secondary HLH was considered and investigated accordingly which confirm diagnosis of HLH (Table 2). Bone marrow reported as normal. He was managed with blood transfusion and steroid and showed good clinical improvement with normalization of CBC in a weak and other parameter on follow up.

**DISCUSSION**

Hemophagocytosis is the engulfment of hematopoietic cells by activated macrophages acting outside of usual immune system regulations. HLH covers a wide array of related diseases including HLH, autosomal recessive familial HLH (FHL), familial erythrophagocytic lymphohistiocytosis, viral-associated hemophagocytic syndrome, and autoimmune-associated macrophage activation syndrome (MAS).<sup>1,2</sup> It is of two types - familial and secondary hemophagocytic lymphohistiocytosis and are characterized by uncontrolled activation of T cells and macrophages, with resultant fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, marked elevation of serum proinflammatory cytokines, and macrophage hemophagocytosis. The diagnosis of HLH formulated by the histiocyte society is depicted in Table 1.

The genetic analysis for mutations is undertaken as quickly as possible, but generally requires some time to complete and should not interfere with initiation of treatment. The genetic findings and family history will determine whether the diagnosis is (autosomal recessive) primary HLH or secondary HLH.<sup>1,2</sup>

In our case series, all these patient were febrile even after adequate treatment with cytopenias which led to the suspicion of secondary HLH. The patients were further evaluated and found to satisfy the clinical criteria for diagnosing HLH. In 2 of the patients, bone marrow was not done because the parents were unwilling and in the third it was reported normal.

A number of conditions are associated with secondary HLH. By prevalence, these include viral infections (29%), other infections (20%), malignancies (27%), rheumatologic disorders (7%), and immune deficiency syndromes (6%).<sup>3</sup> Most common among the viral infections was dengue (52%).<sup>4</sup> Multiple large scale studies by Ellis et al, Raju et al and Bhattacharya et al demonstrate that HLH is a potential fatal complication of dengue and high index of suspicion should be kept so as to promptly recognize the complication and treat immediately.<sup>5-7</sup>

Enteric fever is a common disease of the tropics. HLH as a complication of typhoid is rarely reported.<sup>8,9</sup> A possibility of secondary HLH should be considered in complicated enteric fever.

Malaria-related hemophagocytic lymphohistiocytosis is a rare, potentially fatal, hyper inflammatory. It is usually associated with Plasmodium falciparum infection. It is less frequently associated with Plasmodium vivax.<sup>10</sup>

Therapy for primary HLH (autosomal recessive genetic disease or familial occurrence) consists of a combination of etoposide, corticosteroids, cyclosporine, and intrathecal methotrexate. The goal is to reach the point of initiating stem cell transplantation. In secondary HLH, the immediate aim to suppress hyperinflammation and then to eliminate pathogen activated antigen presenting cells (APC) so as to remove the stimulus for ineffective activation of T cell.<sup>1,2</sup>

## CONCLUSION

HLH is a potentially life threatening complication, which can occur in any disease and complicate the clinical scenario. The clinician must keep high index of suspicion and HLH should be considered in differential diagnosis when we have constellation of symptoms like fever, organomegaly, rapidly evolving cytopenias, LFT disturbance and coagulopathy.

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## REFERENCES

1. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. J Blood Med. 2014;5:69-86.

2. Ishii E. Hemophagocytic Lymphohistiocytosis in Children: Pathogenesis and Treatment. Front. Pediatr. 2016;4:47.
3. Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, et al. Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. Arthritis Rheum. 2003;49(5):633-9.
4. Ray U, Dutta S, Mondal S, Bandyopadhyay S. Severe dengue due to secondary hemophagocytic lymphohistiocytosis: A case study. ID Cases. 2017;8:50-3.
5. Ellis EM, Sharp TM, Pérez-Padilla J, González L, Poole-Smith BK, Lebo E, et al. Incidence and Risk Factors for Developing Dengue-Associated Hemophagocytic Lymphohistiocytosis in Puerto Rico, 2008 - 2013. PLoS Negl Trop Dis. 2016;10(8):e0004939.
6. Raju S, Kalyanaraman S, Swaminathan K, Nisha A, Praisid S. Hemophagocytic lymphohistiocytosis syndrome in Dengue hemorrhagic fever. Indian J Pediatr. 2014;81(12):1381-3.
7. Bhattacharya D, Angurana SK, Nallasamy K, Iyer R, Jayashree M. Severe Dengue and Associated Hemophagocytic Lymphohistiocytosis in PICU. Indian J Pediatr. 2019;86(12):1094-8.
8. Non LR, Patel R, Esmaeli A, Despotovic V. Typhoid Fever Complicated by Hemophagocytic Lymphohistiocytosis and Rhabdomyolysis. Am J Trop Med Hyg. 2015;93(5):1068-9.
9. George N, Sethi P, Nischal N, Kumar A, Siripurapu G, Wig N, Vyas S. A Catastrophic Presentation of Enteric Fever with Secondary Hemophagocytic Lymphohistiocytosis. J Assoc Physicians India. 2018;66(12):11-2.
10. Amireh S, Shaaban H, Guron G. Severe Plasmodium vivax cerebral malaria complicated by hemophagocytic lymphohistiocytosis treated with artesunate and doxycycline. Hematol Oncol Stem Cell Ther. 2018;11(1):34-7.

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