

Case Report

Hemophagocytic lymphohistiocytosis: a rare and fatal manifestation of dengue fever

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ABSTRACT

Authors describe a rare case of dengue fever manifesting as hemophagocytic lymphohistiocytosis. A 26-year-old man presented with acute gastroenteritis along with high grade fever, leukopenia, thrombocytopenia, acute kidney injury, liver dysfunction. Further work-up revealed elevated serum ferritin and LDH levels, and bone marrow biopsy showed hemophagocytes. As dengue fever is in rising trend all over the world, especially in Asian countries, clinicians should look out for this rare but potentially fatal complication of dengue fever.

Keywords: Dengue, Hemophagocytic lymphohistiocytosis, HLH, Pancytopenia

INTRODUCTION

Dengue fever is a common acute febrile illness in tropical countries. It is caused by Dengue virus of the Flaviviridae family, transmitted by the *Aedes aegypti* mosquito. Dengue fever can present with a wide spectrum of clinical manifestations, ranging from self-limiting febrile illness to life threatening haemorrhagic fever and shock syndrome. Rare and atypical manifestations have also been reported.¹

Hemophagocytic Lymphohistiocytosis (HLH) is a rare, life-threatening hyper inflammatory syndrome, characterized by excessive, although ineffective, stimulation of the immune system. It is classified as familial (primary), which manifests in early life and has high mortality without treatment, and acquired (secondary), associated with various infectious etiologies, autoimmune disorders and hematological malignancies.² Among the viral infections, Epstein Bar virus has been most commonly associated with HLH, although it has

also been reported with other viral infections like dengue fever.³⁻⁵

Authors describe the case of a 26-year-old man who had Dengue fever complicated by the development of hemophagocytosis. This report adds to the limited number of adult cases of dengue-associated hemophagocytic syndrome described in the literature.

CASE REPORT

A 26-year-old male presented to the medical emergency with complaints of high-grade fever since 4 days, and loose stool (10-12 episode), vomiting (10-15 episode) and reduced urine output since 1 day. On examination he was conscious, oriented and hemodynamically stable. He was diagnosed as a case of acute gastroenteritis with acute kidney injury and admitted in the ward.

On the next day he developed respiratory distress (respiratory rate of 45/min), tachycardia (heart rate-150

bpm) and a fall in Oxygen saturation (SpO₂ 88% on 15 Lt of O₂ by Non-rebreathing mask). Auscultation revealed crepitations in bilateral lung fields. The patient was intubated and shifted to ICU.

On further evaluation in ICU his laboratory values were: hemoglobin 6.7 gm/dL, total leucocyte count 3600/mm³, platelet count 29000/mm³, blood urea 136 mg/dL, serum creatinine 4.8 mg/dL, serum pro-calcitonin 10.03 ng/ml. Liver function tests revealed: albumin 2.2 g/dL, total bilirubin 3.2 mg/dL, prothrombin time International Normalized Ratio of 1.21, Alanine Aminotransferase 312 U/L, and Aspartate Aminotransferase 475 U/L. Viral markers for Human Immunodeficiency Virus, Hepatitis B and C were negative. Fever panel workup showed negative results for malaria, typhoid, leptospirosis and chikungunya, but positive for Anti-dengue IgM antibody. Ultrasound abdomen examination revealed mild hepatomegaly and moderate splenomegaly. Ultrasound chest showed massive pleural effusion.

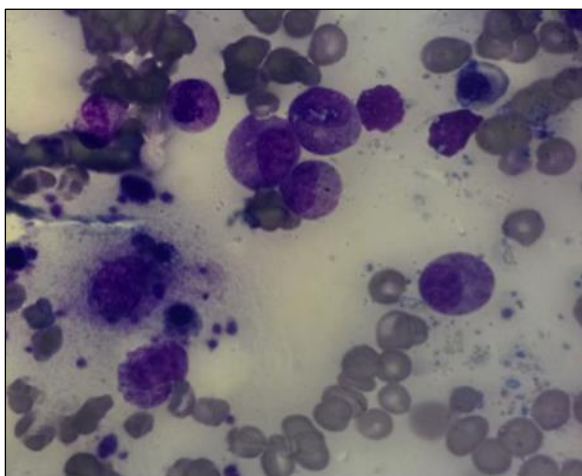


Figure 1: Phagocytosis of red blood cells by macrophages on bone marrow biopsy.

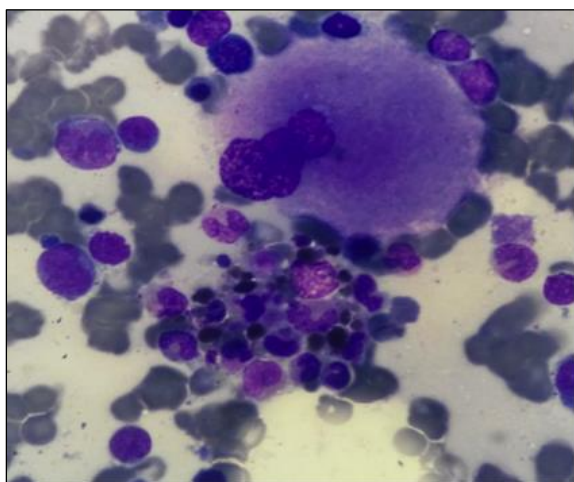


Figure 2: Phagocytosis of white blood cells by macrophages on Bone marrow biopsy.

Taking into account worsening clinical condition, persist fever, and a falling trend in total leucocyte and platelet counts, the possibility of Hemophagocytic lymphohistiocytosis (HLH) was considered. Further testing on day 9 of admission revealed low fibrinogen (150 mg/dL), and raised triglycerides (161 mg/dL), Lactic Dehydrogenase (4031 U/L) and ferritin (7211 ng/ml). Bone marrow biopsy was done on the 10th day of admission, which demonstrated phagocytosis of red and white blood cells by macrophages (Figures 1 and 2).

Hence the diagnosis of HLH was confirmed according to criteria given by Histocyte Society (Table 1)⁶. Along with general supportive care including multiple blood and platelet transfusions, and hemodialysis, corticosteroid therapy was started after diagnosis of HLH. In spite of all these measures, the condition of the patient did not improve. He died on day 28 of hospital admission.

Table 1: HLH diagnostic criteria, 2009.

Molecular diagnosis of hemophagocytic lymphohistiocytosis (HLH) or X-linked lymphoproliferative syndrome (XLP).	
Or at least 3 of 4:	Fever
	Splenomegaly
	Cytopenia (minimum 2 cell lines reduced)
	Hepatitis
And at least 1 of 4:	Hemophagocytosis
	Increased Ferritin
	Increased sIL2R α (age based)
Other results supportive of HLH diagnosis:	Absent or very decreased NK function
	Hypertriglyceridemia
	Hypofibrinogenemia
	Hyponatremia

DISCUSSION

HLH is typically characterized by fever, pancytopenia, splenomegaly, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and presence of hemophagocytes in bone marrow, spleen or lymph nodes.³ Pathophysiology of HLH includes excessive and uncontrolled immune response by macrophages and monocytes, leading to the overproduction of inflammatory cytokines like interferon- γ , tissue necrosis factor- α , interleukin-6, interleukin-10 and macrophage colony stimulating factor. These activated macrophages engulf red blood cells, white blood cells and platelets leading to pancytopenia. Decreased NK cell activity is also a feature of HLH.

Pathophysiology of HLH in dengue infection is not well established but association of HLH in dengue fever has been reported.^{4,5} Dengue Haemorrhagic fever and Dengue Shock Syndrome with multiorgan failure has been proposed as predisposing factor in HLH.⁷ It is difficult to diagnose whether dengue is associated with HLH or not

because haemophagocytic activity and increased ferritin levels may be present in dengue without HLH.⁸

Due to poor prognosis in most of the cases, HLH should be treated promptly with a combination of corticosteroids and chemotherapeutic agents like etoposide and cyclosporine.⁹

In this case, the patient had atypical presentation of dengue fever, without features of DHF or DSS. He presented with fever, acute gastroenteritis and signs of sepsis (raised procalcitonin). The overlap between reactive HLH and sepsis has been reported with common features like fever, hypotension, thrombocytopenia and multi-organ failure resulting from cytokine mediated multi-organ dysfunction.¹⁰ Patient did not survive due to the initial diagnostic dilemma and the rapid, fatal course of the disease. Because of rarity of HLH in dengue fever, this potentially fatal, yet treatable complication may be often overlooked. Authors hope that by adding another report of HLH in dengue fever to existing literature, clinicians will hold a higher clinical suspicion for this condition.

Authors hereby conclude that HLH is an atypical, life-threatening, yet potentially treatable presentation of dengue fever and should be considered early in patients presenting with dengue fever with pancytopenia and increased serum ferritin levels.

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