CASE REPORT

Recurrent Fever in Dengue? Think of This!

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Abstract

Introduction: Dengue is one of the commonest causes of fever in India. Also known as "break-bone fever" and "7-day fever," dengue most often causes fever lasting for a few days, severe body aches, and thrombocytopenia. Although rare, viral infections, including dengue, can trigger another autoimmune, life-threatening condition called hemophagocytic lymphohistiocytosis (HLH).

Clinical case: We describe one such case of dengue complicated by HLH, which was diagnosed and treated successfully.

Conclusion: Diagnosis of HLH in the critically ill requires a high degree of suspicion, as it mimics sepsis, severe dengue etc. One clue to suspect HLH-complicating dengue is a recurrent fever after initial defervescence and a new fever occurring beyond 7 days of onset.

Keywords: Dengue, Fever, Hemophagocytic lymphohistiocytosis, Severe dengue, Tropical fever.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is characterized by excessive immune activation leading to hyperinflammation.[1] The syndrome is frequently life-threatening. HLH occurs as a familial or sporadic disorder and is frequently started by a variety of events that interfere with immune homeostasis, including infection. Various viral infections, including dengue fever, have been described as a cause of secondary HLH.[2] Recognition of dengue-associated HLH requires a high degree of suspicion, and it may be confused with sepsis or severe dengue infection.[3] Reappearance of high-grade fever, persistent and prolonged fever, and hepatic injury are some of the clues which may warrant further investigation for HLH.

Case Description

A 17-year-old boy with no notable past medical history was presented with fever, myalgias, and body ache for 2 days. There was no history of cough, sore throat, loose motions, etc. On examination, he was febrile (102°F), lethargic, and clinically dehydrated but hemodynamically stable. The rest of the examination was normal. There was no organomegaly on the abdominal examination. Investigations were suggestive of thrombocytopenia (platelet count of 70000/mm^3), leukocyte count of 4600/mm^3 (*N* = 58%) and hemoglobin (Hb) of 13.9 gm/dL. Serum bilirubin was 0.8 mg/dL, alanine aminotransferase (ALT)—70 U/L and aspartate aminotransferase (AST) —91 U/L (Table 1). NS1 antigen was positive for dengue virus. There was no bleeding, petechiae, or any episode of hypotension. The patient was admitted and was given intravenous (IV) fluids and other supportive care. Over the next 2 days, his general condition improved, and his fever subsided completely.

However, on the 6th day of his illness, he started having episodes of high-grade fever (104.2°F) (Fig. 1). At this time, a search for any secondary infection was noncontributory—no infiltrates on chest X-ray, no growth in blood and urine cultures. Repeat platelet counts were 45000/mm^3, and leukocyte counts decreased to a value of 2000/mm^3. Abdominal examination was suggestive of mild splenomegaly. Secondary HLH was suspected. Further investigation showed increased triglycerides and decreased fibrinogen (Table 1).

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The serum ferritin was highly raised at 19045 µg/L. H-score was calculated (216 points) and showed a 96% probability of hemophagocytic syndrome. IV dexamethasone (8 mg—3 times a day) was started on day 6 of onset of illness. His fever subsided in the next 48 hours, and serum ferritin decreased over the next few days. On day 10 of illness, his platelet counts, and leukocyte counts normalized, and he was discharged after stopping dexamethasone.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal state of immune hyperactivation. Pathogenesis involves the defective activity of natural killer T-lymphocytes. This flawed immune response leads to enormous cytokine production and activation of immune cells, which culminates in the destruction of red blood cells, white blood cells, and/or platelets in the spleen and/or bone marrow. Its triggers could be genetic, infectious, or neoplastic. Though more common in children, it is seen and increasingly reported in all age-groups.[1]

Diagnosis of HLH in dengue infection remains challenging because of similar clinical features, including cytopenias. Diagnosis should be considered if five of the eight parameters are present in a patient, including fever, splenomegaly, bicytopenia, serum ferritin ≥500 µg/L, high serum triglyceride levels or low fibrinogen levels,

Table 1: Investigations

	Days since the onset of fever				
	Day 3	*Day 6*	*Day 7*	*Day 8*	*Day 10*
Hb (mg/dL)	13.9	13.6	13.5	13.8	13.5
Total leukocyte count/mm^3	4600	2000		3500	4500
Platelet count/mm^3	70000	45000		150000	292000
AST (U/L)	91	719		485	
ALT (U/L)	70	292		414	
Serum ferritin (µg/L)		19045	17350	10832	5404
Lactate dehydrogenase (U/L)		2297	2054		1344
D-dimer (ng/mL)		1105	1024		840
Fibrinogen (mg/dL)		222			
Triglycerides (mg/dL)		278			169

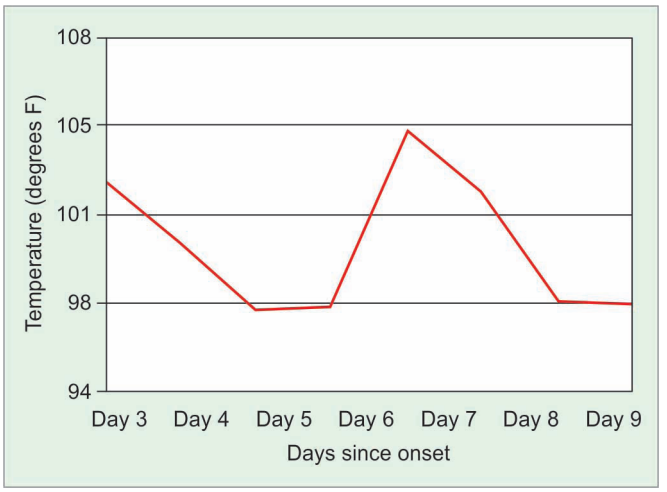

Fig. 1: Maximum daily temperature—IV dexamethasone was given on day 6

histological evidence of hemophagocytosis, high level of soluble CD25 and undetectable NK-cell activity. A serum ferritin level which is raised multiple times is highly specific for HLH.[4] Moreover; an H-score has been devised and validated to help in the diagnosis of HLH. A cut-off value of >250 suggests a 99% chance of HLH, whereas a score of <90 makes it extremely unlikely.[5,6]

In our case, we suspected HLH due to the reappearance of high-grade fever after it initially subsided. This was accompanied by an abrupt decrease in leukocyte and platelet counts. On further investigation, we found worsening liver functions and hypertriglyceridemia. An extremely high value of serum ferritin made the diagnosis of HLH highly likely.

In view of the high clinical suspicion of HLH, the patient was started on IV dexamethasone and responded well with the resolution of fever and improving leukocyte and platelet counts. His serum ferritin level decreased over the next few days. Steroids are used as first-line agents in the treatment of HLH. Use of etoposide, liposomal doxorubicin, ruxolitinib, emapalumab, etc. has been described.

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