ELEVATED SERUM FERRITIN, LACTATE DEHYDROGENASE AND CREATINE KINASE LEVELS IN CLASSIC DENGUE FEVER

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is an extremely rare scenario occurring in the presence of an infectious illness. It is most commonly associated with Epstein–Barr virus, but there aren’t many reports in association with dengue fever. There are fewer than 20 cases reported, most of which were reported in the paediatric and adolescent age group. Here, a case is presented of a 53-year-old man who developed HLH with underlying classic dengue infection. The trend in changing values of serum ferritin from baseline to 8-10 weeks after initiation of therapy can be useful as a predictive therapeutic response marker in HLH.

KEYWORDS

Haemophagocytic Lymphohistiocytosis, Dengue, Ferritin, Lactate Dehydrogenase, Creatine Kinase.


BACKGROUND

Dengue fever, caused by a positive-stranded encapsulated RNA virus belongs to the family Flaviviridae, is transmitted mainly by Aedes aegypti mosquitoes.[1] It is one of the diseases endemic to the coastal region of Karnataka. The complications associated with it range from mild-to-severe fatal consequences, which if overlooked, then providing the patient care becomes paramount. Haemophagocytic lymphohistiocytosis (HLH) is one amongst them. Virus-associated haemophagocytic syndrome/HLH is a disorder characterised by a benign histiocytic proliferation with marked haemophagocytosis in the presence of a systemic viral infection.[2] Its diagnosis in a varied set of presentations is challenging and puzzling to a physician. Here, we are discussing one such case.

CASE REPORT

A 53-year-old man presented with fever, abdominal pain and weakness since 3 days. He also had pain, numbness and tingling sensation in both lower limbs since 3 days. On examination, there was tenderness in the right and left hypogastric region. Bilateral basal crepitations were heard. General examination was otherwise normal. Biochemical investigations revealed raised Urea levels – 14.3 mg/dL; serum Creatinine – 5.3 mg/dL; Total bilirubin – 2.6 mg/dL; Direct bilirubin – 1.83 mg/dL; elevated transaminases (AST – 6861 U/L; ALT – 1982 U/L); Ammonia – 108 mg/dL; LDH – 8941 U/L; Calcium – 7.2 mg/dL; Phosphorus – 2.4 mg/dL; CK – 874.40 U/L; Ferritin – 37816 ng/mL; Fibrinogen – 135 mg/dL; Triglycerides – 286 mg/dL. Haematological investigations revealed thrombocytopenia 11000 cells/μL. Peripheral blood smear showed normocytic normochromic with thrombocytopenia. Bone marrow biopsy showed hypercellular smear with normal myeloid erythroid ratio; mildly increased erythropoiesis with normoblastic maturation and mildly increased megakaryocytes with normal morphology was seen, along with a few macrophages with engulfed erythrocytes. Microbiology revealed Dengue test reactive to NS1 Ag. Ultrasound abdomen showed hepatomegaly (15 cm) with moderate ascites, splenomegaly and bilateral pleural effusion. The patient was initially treated with antibiotics such as cephalosporins; there was clinical deterioration during empiric antibiotic and symptomatic therapy. Then, the patient was put on haemodialysis for 6 cycles due to acute renal failure. In the interim, the patient was transfused with 12 units of platelets and 10 units of fresh frozen plasma (FFP). With the diagnosis of haemophagocytic syndrome, the patient was put on methylprednisolone injections. The patient improved clinically and was discharged after 2 weeks with a prescription of prednisolone tablets and proton pump inhibitors. At the time of discharge, there was considerable improvement in ferritin levels (8804 ng/mL), liver function parameters and renal function tests.

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DISCUSSION
HLH is a very potentially disastrous condition, which may be either primary (genetic) or secondary (due to an underlying etiology). According to a systematic review of the HLH in the Indian subcontinent, about 6 cases were reported with dengue as the underlying viral infection.[9] Most of these were seen in association with dengue haemorrhagic fever. There are less than 20 cases reported of HLH associated with dengue worldwide, and most of them were seen in children and adolescents.[5,6] The manifestation of reactive infection-associated haemophagocytosis is rare and moreover in the background of classic dengue fever, rendering the case to stand apart.

Here, in this case the patient was diagnosed to be having a secondary HLH due to the Dengue infection. The syndrome is marked by an inflammatory cytokine storm due to the underlying viral infection with an overreaction of T-cell lymphocytes, which in turn activate & recruit monocytes and macrophages, eventually leading to haemophagocytosis in the bone marrow, spleen and lymph nodes.[7] According to the HLH-2004 guidelines, 5 of the 8 criteria were fulfilled to diagnose the case as having HLH, in addition to the supportive criteria of hyponatremia, hypoalbuminaemia, hyperbilirubinemia, elevated transaminases, and elevated lactate dehydrogenase levels (LDH). (Table 1). The hepatomegaly, elevated transaminases and bilirubin levels, may be due to infiltration of the liver with lymphocytes and macrophages. Hypoalbuminaemia may be due to loss of vascular endothelium integrity leading to plasma leakage.[9] Elevated LDH levels and creatine kinase (CK) levels may be due to early tissue injury in the acute phase of infection, which might be indicative of progression from dengue fever to a severe haemorrhagic form, which was abated in this patient due to prompt early intervention.[9] Most often, the presenting clinical picture might be more comprehensive, leading to the non-fulfilment of the diagnostic criteria, often leading to extremely challenging situations in the management.[4] In the absence of supportive bone marrow findings, a raised ferritin level of > 10,000 ng/mL is 93% specific for the diagnosis of HLH.[3,10] Furthermore, after the initiation of steroids, the patient improved which was evident by a 76% decrease in the ferritin levels (8804 ng/mL) from the initial value (Ferritin = 37816 ng/mL) at the time of discharge (i.e. ten days after initiation of the therapy). Rapid rate of fall of < 50% in ferritin values after 8 weeks of initiation of therapy for HLH is associated with increased mortality.[11] Hence, the percentage decrease in the ferritin levels from the initial value in response to the therapy may aid the clinician in ascertaining the responsiveness of the disease to the medical treatment. In addition, this case report highlights the fact that HLH should be considered in all patients with dengue, and not just limited to dengue haemorrhagic fever.

CONCLUSION
Haemophagocytic lymphohistiocytosis (HLH) can go underdiagnosed due to the high prevalence of tropical triggers in the subcontinent, especially amongst adults. Prompt recognition, correlation of the biochemical, haematological findings with the clinical picture and early intervention in the management would help in preventing mortality in this scenario. Serum LDH and CK can render as early prognostic markers for monitoring the illness from an acute phase to a severe haemorrhagic form of dengue. Serum ferritin estimation and the percentage decrease from the initial value may render as a useful predictive marker for the therapeutic response in HLH.

REFERENCES


