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Case report

Severe dengue due to secondary hemophagocytic lymphohistiocytosis: A case study

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ABSTRACT

Dengue, transmitted by the mosquito *Aedes aegypti* affects millions of people worldwide every year. Dengue induced hemophagocytic lymphohistiocytosis (HLH) is a serious condition and may prove fatal if not detected early and treated appropriately. Diagnosis of HLH is challenging and usually missed as clinical and laboratory findings are nonspecific. Moreover, the pathophysiology of the systemic inflammatory response syndrome and/or sepsis is remarkably similar to HLH. Secondary HLH following infection by the dengue virus is now being increasingly recognized as a cause of severe form of the disease. We report a case of dengue associated HLH in an otherwise healthy person who deteriorated during the course of hospitalization. A disproportionately high ferritin level and persistent bicytopenia prompted investigations for HLH. Diagnosis of dengue fever with virus-associated hemophagocytic syndrome was established according to the diagnostic criteria laid down by the Histiocyte Society. We discuss the diagnosis and management of this complex case and try to generate awareness about dengue induced HLH as one of the possible causes for severe manifestations of this infection

Introduction

Hemophagocytic lymphohistiocytosis (HLH), a potentially fatal condition that is often under recognised contributing to its high mortality and morbidity. Early recognition is crucial for any efforts at curative therapy. Although HLH is now being increasingly detected in clinical practice due to improved understanding on the part of physicians, pathologists and microbiologists; still much work remains to raise awareness, explore treatment options and improve outcome of this complex condition. We report a case of dengue associated HLH who had a successful outcome following timely diagnosis and appropriate intervention.

Case report

A 65 year old otherwise fit and well gentleman from eastern region of India presented in October 2015 with fever for three days and vomiting and pain abdomen for a day. Significant findings on examination were fever of 38.3 °C, epigastric and right hypochondriac tenderness and dullness over lung bases. Routine laboratory parameters revealed hemoglobin 10.9gm/dl, Leukopenia with presence of reactive Lymphocytes (WBC count 2230 mm^{-3}; reference value [RV]:4000–10000 mm^{-3}) and low platelet count (55000 mm^{-3}; RV: 150000–400000 mm^{-3}).There were significant derangements of the biochemical parameters as well. Liver enzymes were elevated, AST 239 U/L (RV: 10–42 U/L) and ALT 241 U/L (RV: 10–40 U/L). Serum amylase and lipase levels were high 305 U/L; (RV: 25–125 U/L) and 465U/L; (RV: 22–51 U/L) respectively. Serum ferritin level done at day 2 of admission was 75031 ng/ml (RV: 30–400 ng/ml) (Fig. 1).Serum procalcitonin level at admission was 2 ng/dl (RV: <0.5 ng/ml) which was indicative of bacterial sepsis. Serum triglyceride and plasma fibrinogen levels were within normal range. The platelet count dropped to 45,000 mm^{-3}on day three of admission with coffee ground vomiting. The patient subsequently received two units of single donor platelet. Ultrasound imaging showed mild splenomegaly (measured length13 cm), minimal free fluid in abdomen and edematous pancreas and bilateral pleural effusion. Chest X-ray showed pneumonitic changes in both lung fields.

Work up of locally common infectious causes were done including urine and blood cultures, Epstein Barr Virus (EBV) Viral

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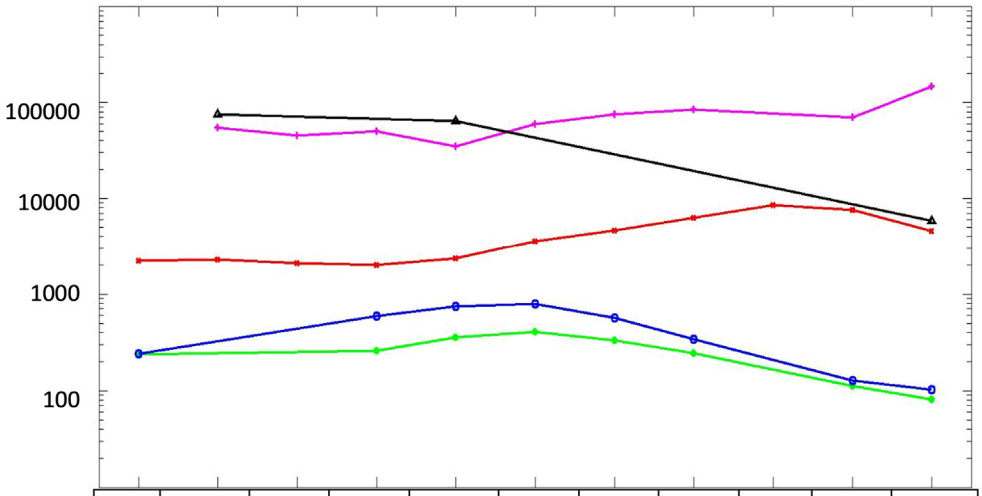

	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D13
WBC (Normal range 4000 – 10000 mm^{-3})	2230	2270	2100	2000	2340	3600	4640	6330	8570	7570	4600
ALT (Normal range 10 – 40 U/L)	239			259	356	405	334	245		112	81
AST (Normal range 10 – 42 U/L)	241			594	750	789	567	341		127	102
PC (Normal range 150000 – 400000 mm^{-3})		55000	45000	50000	35000	60000	75000	85000		70000	147000
Fe (Normal range 30 – 400 ng/ml)		75031			64337						5856

Fig. 1. Trend of laboratory results. D: Day of illness; WBC: Total white blood count (mm^{-3}); PC: Platelet count (mm^{-3}): AST: aspartate transaminase (IU/L); ALT: alanine transaminase (IU/L); Fe: ferritin (mg/L). All units are converted to Log_{10}scale in the figure.

Capsid Antigen IgM, Cytomegalovirus (CMV) IgM, Malaria smear and antigen detection, Dengue NS1 antigen detection, Leptospira IgM serology, Weil Felix screening test for rickettsial infections. The Dengue NS1 antigen test was positive (Panbio Dengue Early Elisa, Standard Diagnostics, Korea) while all other tests were negative including cultures. A diagnosis of dengue fever complicated by pancreatitis and hepatitis with associated chest infection was made. The patient was managed in high dependency unit.

Despite supportive therapy he remained unwell with spikes of temperature, worsening abdominal pain and progressive bi-basal crepitations. Laboratory investigations showed persistent leukopenia, thrombocytopenia and rising aminotransferases. A bone marrow aspiration and trephine biopsy was done for further evaluation on day 4 of admission triggered by high ferritin and bicytopenia. Bone marrow study showed normocellular reactive marrow with evidence of macrophage activation and hemophagocytosis (Fig. 2). A dengue serology on day 6 of fever was positive for IgM antibodies by capture ELISA (Index 5.71, RV: Index < 1.1; Panbio Dengue IgM Capture Elisa, Standard Diagnostics, Korea) but negative for IgG antibodies establishing the diagnosis of primary dengue infection with secondary HLH. Following the diagnosis of HLH, the patient was given intravenous immunoglobulin (400 mg/kg/day for 5 days) starting on day 5 of hospitalisation in view of associated pancreatitis and chest infection. The patient continued to be febrile (T max 38.3 °C) till day 8 of admission. He improved over the next few days, became afebrile and was discharged after 13 days in the hospital. At the time of discharge his blood counts

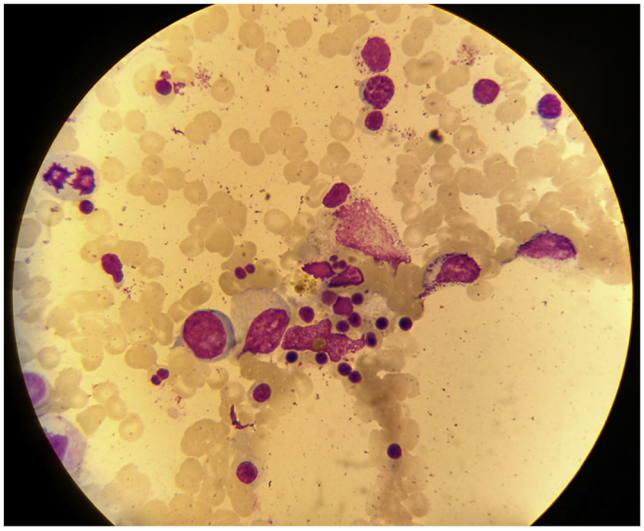

Fig. 2. Bone marrow aspirate showing macrophage with marked hemophagocytic activity.