Dengue-Associated Hemophagocytic Lymphohistiocytosis With Severe Multiorgan Complications—A Case Report

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening syndrome characterized by pathologic immune hyperactivation, extreme inflammation, and multiorgan involvement with variable cytopenias. We report a case of a 53-year-old male with no known comorbidities, who presented with unrelenting dengue fever, pancytopenia, high ferritin levels, and multiple organ dysfunction with progressive clinical deterioration despite treatment. Based on the clinico-laboratory findings, he was diagnosed as dengue-associated HLH on day 6 of admission. As per HLH treatment protocol, he was started on immunosuppressants and showed significant improvement. In dengue patients with severe disease, prolonged hospital stay, persistent cytopenia, and multiorgan dysfunction out of proportion to the plasma leakage phase should prompt a high index of suspicion for the possibility of infection-triggered HLH. Although prompt diagnosis and early initiation of therapy is the key to prevent irreversible end organ damage and mortality, the hindrance lies in its rarity in adults, variable clinical presentation, and nonspecific laboratory findings.

Keywords

Dengue, hemophagocytic lymphohistiocytosis, bone marrow aspiration

Introduction

Hemophagocytic lymphohistiocytosis (HLH) syndrome is a life-threatening hematologic disorder with multiorgan involvement arising due to an ineffective and hyperactive immunity with uncontrolled hyperinflammatory response. Primarily a pediatric syndrome, HLH can however affect adults of all ages.

Primary HLH is caused by an underlying genetic abnormality, whereas secondary HLH occurs due to heterogeneous triggers as infection, autoimmune conditions, malignancy, rheumatologic disorders, HIV infection, or immunosuppression.1

An unusual but severe complication of dengue infection, the presence of recurrent fever after defervescence, or persistent fever >7 days, any cytopenias or extremely high serum ferritin should raise a clinical suspicion of this disorder. It is being increasingly reported but remains under-recognized in dengue.

Cytopenias, elevated liver function tests, elevated ferritin levels, and hemophagocytosis on bone marrow analysis are commonly seen laboratory abnormalities in HLH. Specialized testing of immunologic parameters, HLA typing, and genetic testing are indicated for cases with a high clinical suspicion.2

Case Report

Our patient, a 53-year-old male, with no previously known comorbid conditions, presented with complaints of fever, severe weakness, high-colored urine, decreased appetite, and melena since 15 days. He was initially investigated elsewhere and treated with antibiotics and supportive care. His tests revealed positive dengue NS1, negative reverse transcription polymerase chain reaction (RT-PCR) for Covid-19, leucopenia (3,350 mm−3), thrombocytopenia (79,000 mm−3), elevated AST (622 IU/L), and ALT (412 IU/L) levels with ultrasound

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abdomen showing hepatosplenomegaly, gall bladder wall edema, and ascites.

Significant findings on admission were temperature of 101°F, heart rate of 110 beats per min, blood pressure of 136/90 mm Hg, and respiratory rate of 22 breaths per min with SpO₂ 94%. On examination, he had glossitis, pitting edema, icterus, mild hepatosplenomegaly, with normal respiratory system, cardiovascular system, and central nervous system findings.

Initial laboratory workup revealed hemoglobin (HGB) of 11.7 gm/dL, leukopenia (2,500 mm⁻³), and thrombocytopenia (64,000 mm⁻³) with conjugated hyperbilirubinemia (total serum bilirubin [TSB] 3.08 mg/dL) raised liver enzymes (AST 648 IU/L, ALT 498 IU/L), and severe hypoalbuminemia (2.3 g/dL). He had low vitamin D (17.46) and was also found to have HbA₁c of 6.3%. Electrocardiogram, 2 D Echo, thyroid profile, renal profile, and anti nuclear antibody (ANA) profile were within normal range. Urinalysis showed 2+ protein, 6 to 8 pus cells/hpf, and 8 to 10 rbc/hpf.

Workup of locally common infectious causes were done including dengue NS1 antigen, parasite V & F, hepatitis A & B serology, brucella and Leptospira serology, RT-PCR for Covid-19, and urine and blood cultures. The dengue NS1 antigen test was positive while all other tests were negative including cultures. A computed tomography (CT) abdomen showed gall bladder wall edema, mild splenomegaly, and mild ascites. CT chest showed mild bilateral pleural effusion.

On day 3 of admission, the patient developed severe headache. A noncontrast CT brain followed by magnetic resonance imaging brain was done with no significant abnormality. Cerebrospinal fluid analysis was within normal limits and negative for culture.

Despite supportive therapy, he continued having fever, headache, and significant loss of appetite. He also had episodic loose, dark stools, abdominal distension, breathlessness, anasarca, and depressive thoughts.

On day 6, he had hematochezia, worsening anasarca, breathlessness, and become extremely anxious and agitated, and hence was shifted to the intensive care unit. Metabolically, he had hyponatremia (125 mEq/L) and hypocalcemia (5.9 mg/dL) which were duly corrected. Blood tests revealed high levels of serum ferritin (>1,500 ng/mL), serum procalcitonin (3.37 ng/mL), D-dimer (4,210 ng/mL), LDH (>2,000 U/L), and serum triglyceride (430 mg/dL) with HGB of 8.8 gm/dL, leukopenia (3,700 mm⁻³), thrombocytopenia (98,000 mm⁻³), conjugated hyperbilirubinemia (TSB 6.17 mg/dL), raised liver enzymes (AST 1,040 IU/L, ALT 386 IU/L), low plasma fibrinogen levels (85 mg/dL) with normal Troponin I (28.5 ng/mL) and NT-proBNP (23.65 pg/mL). A bone marrow aspiration study showed normocellular reactive marrow with evidence of macrophage activation and hemophagocytosis with no features of malignancy (Figure 1). One unit blood transfusion was given in view of low HGB.

Figure 1. Bone Marrow Aspirate From the Patient Showing Phagocytosis by Benign Histiocytes (Geimsa stain, ×40).
A diagnosis of dengue fever complicated by HLH syndrome was made and the patient was started on dexamethasone and broad-spectrum antibiotics as specified by the HLH treatment protocol. The time from admission to diagnosis of HLH was 6 days.

On day 10, he had significant bleeding per rectum (PR), underwent sigmoidoscopy, which revealed grade 4 thrombosed, and actively bleeding hemorrhoids. He was advised stapler hemorrhoidectomy for which the patient was not willing.

The patient’s condition significantly improved over the next few days and he was discharged after 13 days in the hospital with near normal blood counts and biochemical parameters with a regular follow-up advice.

Discussion

HLH is characterized by systemic phagocytosis of blood cells and their precursors by benign histiocytes. Scott and Robb-Smith first described the disease in 1939 and Risdall associated HLH with viral infection.3

A study by George1 showed precipitating factor for secondary HLH to be viral infections (29%), malignancies (27%), other infections (20%), immune deficiency syndromes (6%), and rheumatologic disorders (7%).3 As per studies, the most common infectious trigger for acquired HLH is Epstein-Barr virus.2 Dengue-associated HLH was first reported in 1966 with over 45 cases reported till date.4

Clinical features can be extremely variable and overlap with other illnesses. Fever, hepatosplenomegaly, lymphadenopathy, neurologic involvement, and/or rash are common manifestations.1 Vomiting, diarrhea, irritability, headache, visual disturbances, and/or seizures are also frequently seen. Respiratory distress, coagulation, and renal dysfunction have all been recorded in HLH syndrome.1

According to the Histiocyte Society (2004), the diagnosis of HLH is established either by a molecular diagnosis consistent with HLH (Primary HLH) or by having 5 out of 8 of the following5: fever, splenomegaly, cytopenias (affecting 2 or more of 3 lineages in the peripheral blood), hypertriglyceridemia and/or hypofibrinogenemia, elevated ferritin, hemophagocytosis in bone marrow/spleen/lymph nodes, low or absent natural killer-cell activity, and elevated soluble CD25.5

Cytopenias, especially anemia and thrombocytopenia, are seen in >80% of patients on presentation.2 Raised ferritin levels >10,000 μg/L should be used as screening tool for early detection of HLH owing to a high sensitivity (90%) and specificity (96%).4 Hemophagocytosis seen on the bone marrow aspirate is neither necessary nor sufficient for the diagnosis of HLH.2

In a study by Tan et al.6 in 6 cases of dengue with hemophagocytosis, all had persistent fever, cytopenia, and elevated transaminases with markedly elevated ferritin levels. In a study by Kaito et al.7 in 34 patients of HLH, the risk factors associated with death were: age over 30 years, increased ferritin, anemia with thrombocytopenia, jaundice, and presence of disseminated intravascular coagulation. In a study by Shabbir et al.8 in 18 adults with HLH the median time from suspicion to diagnosis was 5 days (1-27 days) with overall mortality rate of 72%.8

In adults, the management includes treating the underlying triggering condition, immune-suppressive and immunomodulatory agents, chemotherapy, steroids, antibiotics, antiviral drugs, HLH-specific therapy, splenectomy, liver transplant, and stem-cell transplantation.3 Srishaikul et al had successfully treated 3 adult patients with dengue-related HLH with combination of intravenous immunoglobulin G and dexamethasone or methylprednisolone.4 Use of recombinant human thrombopoietin, TNF inhibitors, monoclonal antibodies, and plasmapheresis has been described in various studies.3

Conclusion

The rarity of this disease in adults, its potential fatality, the need for a very high-index of clinical suspicion, varied clinical manifestations, nonspecific laboratory findings, late detection, and the need for early initiation of specific treatment make HLH a difficult conundrum for the clinicians to decipher. Untreated, the disease is invariably fatal but survival has drastically improved with the implementation of the HLH-94 and 2004 protocol.

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