Case Report

Dengue associated hemophagocytic syndrome: a case report

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. Several conditions are responsible for triggering HLH in clinically stable patients who respond to treatment of the underlying condition alone. These conditions include infection, rheumatological diseases and lymphoid malignancies. We are discussing a case of HLH who presented at age of 22 years that was triggered by dengue virus infection. Patient presented with an acute febrile illness and was diagnosed with dengue hemorrhagic fever. Despite appropriate supportive therapy, he had clinical deterioration. Evaluation revealed features of HLH. He was successfully treated with glucocorticoids and had an uneventful recovery. This case adds to the limited adult cases of virus-associated hemophagocytic syndrome in the literature and emphasizes the need for prompt recognition and treatment of this rare complication.

***Key words**: dengue virus, expanded dengue syndrome, hemophagocytic lymphohistiocytosis.*

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and frequently fatal syndrome of pathological immune activation characterized by unregulated histiocyte proliferation and hypercytokinemia.[1] It may be primary or genetic and secondary or acquired.[2,3] The primary autosomal recessive form, also known as familial HLH (FHLH), is usually seen among children, though adult cases have been reported.[4] Secondary (sHLH) or acquired HLH was first established as a distinct clinico-pathological entity by Risdall in 1979[5], which is more common among adults and typically occurs after strong immunological triggers that may occur with a variety of viral, bacterial, tubercular, fungal and parasitic infections, collagen-vascular diseases and malignancies, particularly T-cell lymphomas.[6-10] Here, we report an adult case of secondary HLH complicating dengue fever.

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CASE REPORT

A 22-year-old male, without any known medical condition, presented with fever and body ache for two days. He also complained of headache with retro-orbital pain and abdominal discomfort. On examination, he was febrile with a pulse rate of 112/min, blood pressure of 100/60 mm Hg and respiratory rate of 28/min. He had a diffuse, blanching erythematous rash over the trunk.

Initial laboratory tests showed leucopaenia (2100/cmm), thrombocytopenia (47,000/cmm) and elevated C reactive protein (44 mg/L). His non-structural protein 1 (NS1) antigen came positive. Evidence of third space fluid loss, in the form of bilateral pleural effusions and ascites were found on 6th day of fever onset along with elevated levels of alanine aminotransferase (2471 IU/L) and aspartate transaminase (13189 IU/L) with serum bilirubin of 3.2 mg/dl.

As the patient had significant hepatic dysfunction; ischemic hepatitis, toxin-induced and viral hepatitis were

also considered. Despite conservative treatment, sustained high fever was observed and on 8th day of fever onset, patient became drowsy, lethargic, his Glasgow Coma Scale downed to 9/15 and he was shifted to the high-dependency unit. Broad spectrum antibiotic was added empirically along with other supportive managements. Two days later, he was shifted to the ward as his clinical condition improved.

However, while in the ward, the patient had persistent of high-grade fever and he developed features of systemic inflammatory response syndrome along with hepatosplenomegaly and worsening of ascites and pleural effusions. Ascitic fluid was exudative in nature. Although bone marrow examination did not show typical findings of hemophagocytosis, diagnostic criteria of HLH were met: fever, splenomegaly, cytopenia, hypertriglyceridemia (fasting triglyceride 308 mg/dL) and hyperferritinaemia (ferritin 15,107 ng/mL). Intravenous corticosteroids was given, as per the HLH-2004 protocol (dexamethasone 10 mg/m^2) on his 15th day of fever onset. There was a dramatic response to the same with resolution of fever on the next day and improvement of blood cell counts. The pleural effusions and ascites gradually improved. The patient was discharged from the hospital on day 20 after hospitalization without any sequelae.

DISCUSSION

HLH is a rare, life-threatening disorder characterized by tissue destruction due to abnormal immune activation. Afflicted patients present with fever and multiorgan dysfunction, which is often mistaken for sepsis.[6] The causes may be variable ranging from infections through autoimmune disorders to malignancy.[10] Secondary HPS may be triggered by viral infections like Epstein–Barr virus, dengue [6-7,9] but bacterial infections like tuberculosis[8] is not uncommon. This disorder is characterized by excessive macrophage activation and cytokine release due to a failure in natural killer (NK) cell function.[1,2]

Patients with HLH are acutely ill with fever, hepatosplenomegaly, effusions and lymphadenopathy. Laboratory findings include bicytopenia, coagulopathy, liver dysfunction, hyperferritinemia and elevated triglycerides and lactate dehydrogenase. Bone marrow infiltration by activated macrophages can be demonstrated and diagnosis is made based on the HLH-2004 protocol proposed by the Histiocyte Society—HLH can be established in the presence of (i) molecular diagnosis consistent with HLH or (ii) the presence of five out of eight criteria, namely, fever, splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in tissue, hyperferritinemia, increase in CD25/IL-2 receptor or reduced NK cell function. Glucocorticoids are used as the initial agent in the treatment of HLH. Other agents include etoposide, intrathecal methotrexate and intravenous immunoglobulin.[6,7] Early detection along with prompt treatment of the underlying condition and HLH can be lifesaving.[6]

Dengue-associated HLH has been more commonly noted in patients with dengue hemorrhagic fever, as in our patient. Dengue virus-infected T cells produce cytokines leading to uncontrolled histiocytic activity. It has been proposed that the increased production of cytokines, interferon-ã and tumor necrosis factor-á plays a role in the pathogenesis of HLH.[6] Till date, only three serotypes of dengue viruses have been attributed to cause HLH (DEN1, DEN3 and DEN4). Serotyping was not done in present case. As the febrile period in dengue lasts for 3–7 days, ongoing fever after 8 days with persistence of cytopenia and multiorgan dysfunction should alert clinicians towards a diagnosis of HLH. On review of other cases, dengue-associated HLH usually presented in the second week of illness.[7] There have been two previous reports of HLH occurring at the end of the second week following the onset of dengue fever.[6,7] In our patient, the diagnosis was established on day 15 of illness.

Conclusion

HLH is a rare but lethal complication of dengue hemorrhagic fever. Clinicians should suspect HLH as a possible complication in a patient with DHF having persistent fever, declining cell count (bicytopenia/ pancytopenia) and elevated ferritin. Early diagnosis and prompt treatment would help to reduce mortality.

Authors' contribution: AN, HFH, AKMHA managed the case. AN drafted manuscript. All authors read and approved the final manuscript for submission.

Conflicts of interest: Nothing to declare.

Consent: Informed written consent was taken from the patient regarding the publication of this case report and any accompanying images.

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