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# Hemophagocytic lymphohistiocytosis (HLH) is a rare complication of severe dengue infection – A Case Report

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**Abstract:** Hemophagocytic lymph histiocytosis (HLH) is a rare serious life-threatening condition due to reactive hyperactivity of cytotoxic cells, leading to cytokine storm. Subsequently leads to multiorgan dysfunction and ultimate failure. it could be primary (hereditary) or secondary (acquired) to various conditions including infections. It may occur due to dengue infection carries a grave prognosis even with appropriate treatment. Therefore, a high degree of clinical suspicion is crucial in diagnosing HLH. We report here a case of a patient infected with the dengue virus who developed HLH during hospitalization. A 30-year-old man was admitted to a tertiary care hospital in Rajshahi, Bangladesh with a 4-day history of fever, headache, and alteration of consciousness level. He was hemodynamically stable, and the serological investigation confirmed a dengue infection. On the fifth day of fever, he entered the critical phase of dengue infection, confirmed by ultrasound evidence of plasma leaking. However, he had ongoing high fever spikes during the crucial phase, and even after the critical phase was over, the fever spikes continued. Simultaneously, hepatosplenomegaly was noticed, and he showed persistent thrombocytopenia, neutropenia, and anemia despite the resolution of the critical phase. Further, the workup revealed a serum ferritin level of > 10500 ng/mL triglyceride level of 540 mg/dL. Secondary HLH was diagnosed based on criteria used in the HLH-2004 trial and successfully managed with intravenous dexamethasone 10 mg/body surface area/day for the first 2 weeks, followed by a tapering regimen over 8 weeks.

**Keywords:** Hemophagocytic lymphohistiocytosis (HLH), Dengue fever, Cytokine storm, Hyperferritinemia.

**Case Report**

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**Article at a glance:**

***Study Purpose:*** *To report a case of dengue fever associated with hemophagocytic lymphohistiocytosis (HLH).*
***Key findings:*** *A 30-year-old man was admitted to a tertiary care hospital in Rajshahi, Bangladesh with a 9-day history of high-grade continued fever, alterations of consciousness level, hepatosplenomegaly with cytopenias.*
***Newer findings:*** *Hemophagocytic lymphohistiocytosis can be occurred in a severe dengue fever.*
***Abbreviations:*** *Hemophagocytic lymphohistiocytosis, Dengue, Cytopenias, hepatosplenomegaly, Dexamethasone.*



## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a hyperimmune reaction characterized by an uncontrolled activation and proliferation of cytotoxic T lymphocytes and histiocytes that secrete large amounts of inflammatory cytokines leading to multiorgan dysfunction and failure.[1] Hemophagocytosis is a phenomenon where phagocytosis is done by histiocytes of leukocyte, platelets, erythrocytes, and their precursors in the bone marrow. The aetiology of HLH may be classified as genetic (primary) and acquired

(secondary).[2] Secondary HLH is usually acquired by viral infections, immunodeficiency states, autoimmune disorders, and cancers. Infections caused by EBV, human immune deficiency virus (HIV), dengue virus, cytomegalovirus (CMV), bacteria, fungi, protozoa, and now possibly severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) can be a cause of secondary HLH.[3]

HLH is associated with significant mortality and morbidity even with appropriate treatment, and the outcome is further poor if the diagnosis is delayed or left untreated.[4] Though Epstein-Barr virus (EBV) is the most common agent to cause HLH, Currently, there is increasing data that implicate that severe dengue virus infection also causes secondary HLH with poor outcomes.[5] The mortality may increase up to 43%. The overlap in clinical features makes diagnosing HLH in a dengue patient difficult, necessitating a bone marrow examination and other investigations. Therefore, a high clinical suspicion is paramount in diagnosing HLH associated with dengue. Here we present a case of HLH which occurred secondary to severe dengue fever, which was successfully treated and recovered.[6]

## CASE PRESENTATION

A 30-year-old man was admitted to a tertiary care hospital in Rajshahi, Bangladesh with a 4-day history of high-grade continued fever (highest recorded temperature 104° F) associated with nausea, and a few episodes of vomiting. He also had a severe frontal headache, retro-orbital pain, arthralgia, and myalgia for the same duration. The headache was not associated with photophobia or phonophobia. He developed an alteration of consciousness level 8 days of illness but didn't have seizures or neck rigidity. He had no abdominal cramps, right hypochondriacal pain, respiratory or urinary symptoms, any rash, or diarrhoea. He did not have any previous medical conditions. He was a nonsmoker and non-alcoholic. On admission, he was confused and mildly dehydrated. he was pale but not icteric. His pulse rate was 104 beats per minute with 110/80 mmHg blood pressure, Respiratory rate 20b/m, Temperature 103° F, Oxygen saturation was 98% on ambient air and capillary refilling time was less than 2 seconds. There was cervical lymphadenopathy that was non-tender, smooth, and not matted. Per-abdomen examination revealed splenomegaly 3cm from the left costal margin and Hepatomegaly 4 cm from the right costal margin. All other systemic examinations, including the cardiovascular, respiratory, abdominal, and neurological systems, were unremarkable.

Initial blood investigations (Table 1) revealed. In the full blood count, he had a white cell count of $4.9\times10^9$/ L, neutrophils $1.4\times10^9$/ L and lymphocytes $4.90\times10^9$/ L, and a red blood cell count of $5.18\times10^9$/μL. The hemoglobin level was 9.5g/dL, with a hematocrit of 43.3% and the platelet count was $60\times 10^3$/ μL, non-structural protein 1 (NS1) antigen for Dengue was positive. His C-reactive protein (CRP) level was 249 mg/L, and the alanine aminotransferase (ALT) level was 23.13 U/L. The investigation summary is given in Table.

After the initial workup, he was diagnosed with dengue fever, and conservative treatment was initiated with follow-up. He was administered oral paracetamol 1 g on an as-needed basis to control his fever. On day 6, he complained of chest tightness and an ultrasound found small free fluid in the chest. Then he was diagnosed with Dengue fever with warning signs and treated with crystalloid fluid. An investigation found leukopenia and thrombocytopenia with high hematocrit levels. In typical dengue hemorrhagic fever, the fever spikes, leucopenia, and thrombocytopenia improved when the critical phase was over, and all parameters of severe dengue were improved. However, in this patient even after the critical phase was over, he had continuous high-grade fever with persistent thrombocytopenia and a gradual drop in the hemoglobin level and developed alteration of consciousness level, especially in time place, and person. His subsequent red blood cell count was $3.91\times10^6$/μL, Hb was 9.5mg/dl, and the platelet count was $37\times10^3$/μL. He had also developed mild to moderate hepatosplenomegaly. The blood picture revealed thrombocytopenia with giant platelets and features suggestive of HLH. His serum ferritin level was >10500 ng/mL, triglycerides 540 mg/ dL. Based on these investigation findings, he was diagnosed with HLH. Then he was started with intravenous dexamethasone 10 mg per body surface area for the first 2 weeks, gradually tailed off over 8 weeks, and subsequently converted to oral dexamethasone,

where recovery was good. The fever settled within 24 hours after starting intravenous dexamethasone, and the white cell and platelet count were increased significantly. He was discharged after a 2-week hospital stay and completely recovered while reviewing in our hospital after 8 weeks.

**Table 1: Investigations summary**

| Investigation | Day 1 | Day 7 | Day 9 | Day 13 |
|---|---|---|---|---|
| White cell count | 5120/cumm | 8900/cumm | 1399/cumm | 17000/cumm |
| Red cell count (×10^9/μL) | 5.18 | 3.74 | 3.91 | 5.09 |
| Hemoglobin level (g/dl) | 14.7 | 10.5 | 9.5 | 14.2 |
| Haematocrit (%) | 43.4 | 30.1 | 30.9 | 43.9 |
| Platelet count | 116 | 60 | 37 | 160 |
| ALT (U/L) | 23.13 | 74 | 87 | 50 |
| Serum creatinine (mg/dl) | 0.9 | - | - | 0.6 |
| CRP (mg/L) | 249.00 | - | 77.8 | 21.0 |
| Urinalysis | | | | |
| Pus cell | Nil | Nil | - | - |
| Red cell | Nil | Nil | - | - |
| Protein | Nil | Nil | - | - |
| Blood culture | No growth | No growth | No growth | |
| Urine culture | No growth | No growth | - | - |
| Serum ferritin level (ng/ml) | - | - | 10500 | 7710.0 |
| Triglyceride (mg/dl) | - | - | 540 | 140 |
| ICT for Malaria | Negative | - | - | - |
| RBS | 4.8mmol/l | - | - | - |
| Electrolytes | Normal | - | - | - |
| Bone marrow study | - | - | Normal | - |

## DISCUSSION

Dengue fever is caused by the Dengue virus, which belongs to the family Flaviviridae, genus Flavivirus, and is mainly transmitted to humans by Aedes aegypti mosquitoes.[7] Four distinct serotypes are responsible for undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), and expanded dengue syndrome. HLH is a rare, potentially fatal hyperinflammatory and haemophagocytic syndrome with excessive activation of lymphocytes and macrophages. All forms of HLH are thought to be due to impairment in the function of cytotoxic T lymphocytes and natural killer (NK) cells, associated with a potentially fatal cytokine storm and hyperferritinemia. Dengue infection is a rare complication of secondary HLH which can be often difficult to diagnose due to the overlap of the clinical features.[8] As per HLH-2004 diagnostic criteria, HLH is diagnosed when at least five of the eight criteria listed are fulfilled. These criteria are fever, splenomegaly, cytopenia affecting at least two of three lineages in peripheral blood, ferritin ≥500 μg/L, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer (NK) cell activity, and high level of soluble interleukin-2 receptor alpha chain (CD25).[9]

In this case, having had typical clinical features of dengue fever and progressed to the critical phase of the infection. Even after the critical phase, the patient had a continuous high-grade fever, persistent thrombocytopenia, a gradual drop in hemoglobin levels, and hepatosplenomegaly. So, there was a high degree of suspicion of HLH and the diagnosis of HLH was made by having 5 criteria including fever, splenomegaly, cytopenias, elevated ferritin, and elevated triglyceride levels according to diagnostic criteria 2008.[10]

Hyperferritinemia is strongly associated with HLH, and a cutoff value of >10,000mcg/L is 90% sensitive and 96% specific for its diagnosis. It also correlates with disease activity. This emphasizes the need for closer monitoring in dengue virus-infected patients with hyperferritinemia.[11] HScore is another criterion

used for the diagnosis of HLH. A cutoff of 168 points reveals a sensitivity of 100 % and a specificity of 94.1%. Our patient had a HScore of 254. Bone marrow biopsy was also done which was normal, though it was unnecessary since the diagnosis could already be made with available information. However, we could do a trephine biopsy to confirm the diagnosis of HLH as well as exclude other possibilities like hematological malignancies.[12]

The management principles of HLH include suppression of severe hyperinflammation should be done to prevent life-threatening outcomes of HLH.[13] The treatment protocol includes induction, salvage, and continuation therapies. Suppression of hyperinflammation and the elimination of activated immune cells can be achieved with corticosteroids, intravenous immunoglobulins, cyclosporin A, anti-cytokine agents like etoposide, and monoclonal antibodies such as alemtuzumab and rituximab. Corticosteroids are the first choice to suppress hypercytokinemia.[14] The first-line option is dexamethasone, as it can cross the blood-brain barrier better than other steroids.[15] The 2004 treatment protocol developed at the second international meeting of the Histiocyte Society recommends an 8-week induction therapy with corticosteroids, etoposide, and cyclosporine A.[16,17] In our case, the patient had been treated with only intravenous dexamethasone therapy for 2 weeks followed by an 8-week tapering regimen with a good clinical outcome. However, this treatment differs from some of the others, where immunosuppressive agents were used.[18]

## CONCLUSION

HLH should be considered in dengue fever when persistent fever, hepatosplenomegaly, and cytopenias are present. Early diagnosis and prompt initiation of appropriate treatment with intravenous dexamethasone with immunosuppressive is necessary for good prognosis. Physicians should be aware of HLH, which can occur in dengue patients in dengue-endemic areas, especially in Bangladesh.

**Author contributions**

Md Abdul Brik collected the data, analyzed the data, and drafted this article. Rukshana Amin checked, analyzed, and interpreted the data. Md Mesbah-ul Alam assisted with the data acquisition and drafting. Md Asadul Islam assisted with data acquisition and drafting. Md. Mohimanul Hoque contributed to the conception and critical revision. Abu Shahin Mohammed Mahbubur Rahman led the concept, design, interpretation, critical revision, and final approval.

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