EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 13
Issue: 3
Year: 2026

A CASE OF DENGUE-PRESENTING AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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DOI: https://doi.org/10.5281/zenodo.18796792

How to cite this Article: *[1]Dr. J. Arun, [2]Dr. Marchwin Kingston, [3]Dr. Rathnakumar, [4]Dr. Arjunan, [5]Dr. Vinayak Moorthy. (2026). A Case Of Dengue-Presenting As Hemophagocytic Lymphohistiocytosis. European Journal of Biomedical and Pharmaceutical Sciences, 13(3), 270–273.

Article Received on 30/01/2026 **Article Revised on 19/02/2026** **Article Published on 01/03/2026**

ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) life-threatening systemic hyperinflammatory syndromes that can develop in most inflammatory contexts. We present a case of a 15-year-old boy persistent fever, generalized weakness, and altered mental status with elevated inflammatory markers & with the clinical history, examination & investigation findings, we present a compelling case of Dengue-associated Hemophagocytic Lymphohistiocytosis.

KEYWORDS: Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) life-threatening systemic hyperinflammatory syndromes that can develop in most inflammatory contexts.

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) represents a catastrophic failure of immune homeostasis, characterized by the uncontrolled activation of cytotoxic T lymphocytes and macrophages, resulting in a "cytokine storm" and immune-mediated destruction of host tissues, HLH is classified into "primary" (genetic/familial) and "secondary" (acquired) forms.In the adult population, secondary HLH is the predominant form, frequently triggered by malignancies (particularly lymphomas), autoimmune diseases (termed Macrophage Activation Syndrome or MAS), and infections. Among infectious triggers, viruses such as Epstein-Barr Virus (EBV) are classical etiologies due to their tropism for lymphocytes. However, in tropical and subtropical regions, arboviral infections like Dengue virus have emerged as significant, yet underrecognized, precipitants of this lethal syndrome. The prevalence of HLH in severe dengue is estimated to be significantly higher than in non-severe cases, yet the overlap in clinical features often leads to missed or delayed diagnoses.

A critical component of this analysis is the differentiation of HLH from the natural course of severe dengue (Dengue Hemorrhagic Fever/Dengue Shock Syndrome). Both conditions present with thrombocytopenia, leukopenia, and coagulopathy. However, the presence of extreme hyperferritinemia (>10,000 \mug/L), hypofibrinogenemia (in contrast to the capillary leak of dengue), and specific patterns of liver dysfunction serve as vital discriminatory tools in the clinician's arsenal.

CASE DETAILS

History

A 15-year-old boy presented with a chief complaint of insidious, persistent fever, generalized weakness, and altered mental status for the past 15 days. His past medical history was unremarkable. He had no known comorbidities & no significant family history.

Examination

The fever was initially high-grade (104°F) and associated with chills and rigors. On admission, the patient was awake, irritable and not oriented to time place and person and had irrelevant speech. No meningeal signs or rash were noted. The fever persisted at 103°F the next day and remained at 103°F on the third day. There was no identifiable focus of infection from the patient history and head to foot examination revealed no clues to the underlying etiology of fever/shock.

Investigations

AT ADMISSION– Initial laboratory findings revealed pancytopenia with hemoglobin of 8.8 g/dL, a platelet count of 25,000/µL, and white blood cells at 3.7 × 10^9/L.Liver function tests indicated elevated transaminases with SGOT of 744.8 U/L and SGPT of 142.3 U/L, hypoalbuminemia (albumin: 2.22 g/dL), and hyperbilirubinemia with total bilirubin at 0.92 mg/dL. Serum lactate dehydrogenase (LDH) was also markedly elevated at 1583 U/L.

Inflammatory markers, including C-reactive protein (CRP) at 60.9 mg/L, Ferritin -13000ng/dl, were significantly elevated, consistent with a hyperinflammatory state. Additional notable findings included – TRIGLYCERIDES: 540 MG/DL) ,HYPOFIBRINOGENEMIA (82 MG/DL), PT- 31.4, INR – 2.7, APTT - NO COAGULATION,PS – MICROCYTIC + NORMOCYTIC – DIMORPHIC ANEMIA,D DIMER – 20470, ESR -10.

Dengue IgM turned out to be Negative. Testing for other viral etiologies (HIV, Hepatitis B/C) and bacterial infections (Blood/Urine cultures, Leptospira IgM, Malaria antigen) was negative. Autoimmune screening (ANA, Rheumatoid Factor) was negative.

Imaging studies included an ultrasonogram of the abdomen, which confirmed hepatomegaly (16 cm), splenomegaly (14 cm), and minimal ascites. A chest radiograph was normal. A brain MRI, performed due to the altered sensorium, showed no evidence of encephalitis, hemorrhage, or space-occupying lesions, ruling out primary neurological dengue.

Bone marrow aspiration and biopsy

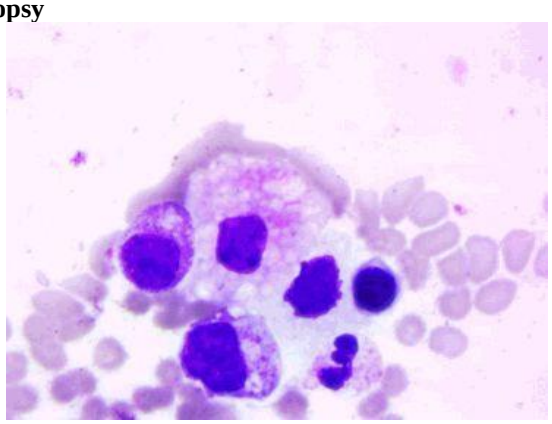

Figure 1 - Bone marrow aspirate showing foamy histiocyte.

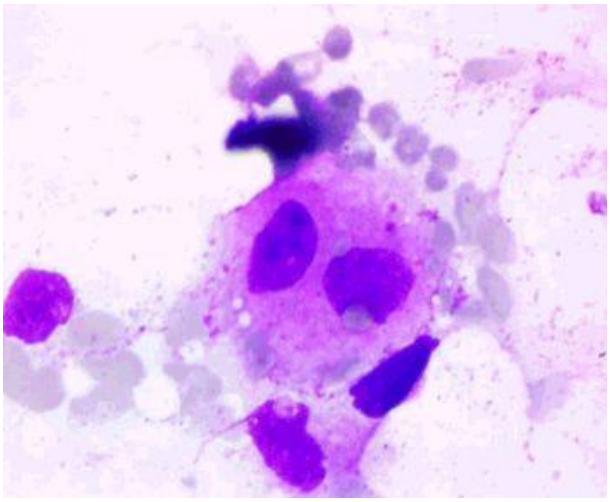

Figure 2: Bone marrow aspirate-phagocyitc histiocytosis.

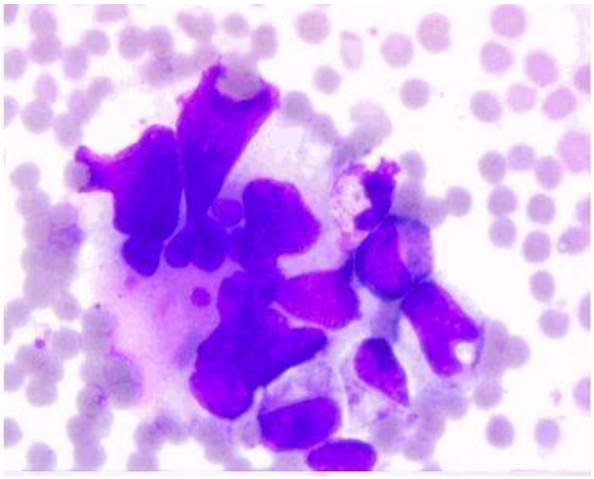

Figure 3: Showing histiocyte phagocyting an rbc.

The smear revealed a hypercellular marrow with prominent histiocytic hyperplasia(fig1,2 3). Crucially, numerous histiocytes were observed actively phagocytosing hematopoietic elements, including erythrocytes and platelets, confirming the phenomenon of hemophagocytosis. There was no evidence of blasts or granulomas.

DISCUSSION

The evaluation of this case follows a structured diagnostic paradigm designed to categorize systemic hyperinflammation and isolate the underlying pathology. The interplay between the viral trigger and the host immune response necessitates a deep dive into the diagnostic criteria, pathophysiology, and management protocols established in recent literature and standard texts.

Even though a definitive diagnostic criterion for HLH/MAS is unclear, in the presence of a combination of unusual, coexisting severe clinical and laboratory features that represent hyperinflammatory syndrome must prompt consideration of HLH, which includes features like Persistent fever, Elevated / rising ferritin or other inflammatory markers, Cytopenias (2 or more), Hepatic dysfunction, coagulopathy, splenomegaly,[3] Altered sensorium, Specialised markers of inflammation such as IL2R alpha, IL18, CXCL9 etc might further aid in diagnosis. Certain underlying infections, rheumatic diseases, malignancies, metabolic diseases and genetic inborn errors of immunity are frequently associated with HLH/MAS, Genetic testing in patents with probable HLH can dramatically affect diagnosis and management and hence must be considered early – the decision making of which must be based on the consideration of age, clinical and laboratory features. Further prognosis of the disease is based on the presence of the following CNS involvement, Prolonged active disease or MODS, Liver failure, Underlying malignancy. In case of managing a case of HLH, depending on the severity the disease immunomodulation must be decided keeping in mind the chances of obscuring the diagnosis of underlying malignancy or causing a flare up of an underlying infection. In this case the presence of persistent fever, CNS involvement occurring together with the presence of a hyperinflammatory state and other fitting criteria prompted a diagnosis of HLH and bone marrow aspiration study was done along with beginning of immunosuppression as CNS involvement was already evident at the time of presentation.[2]

Dengue virus is a potent and increasingly recognized trigger for HLH in endemic regions. The pathophysiology involves the phenomenon of **Antibody-Dependent Enhancement (ADE)**.

The clinical overlap between severe dengue and HLH is treacherous. Severe dengue (Dengue Hemorrhagic Fever) is characterized by plasma leakage (resulting in hemoconcentration) and thrombocytopenia. HLH, however, presents with **anemia** (due to hemophagocytosis and marrow suppression) and **hyperferritinemia** that is disproportionate to standard dengue infection.[6]

Early recognition and diagnosis of MAS-HLH are essential for efficacious management. A personalized and graded treatment approach is advised. Conventionally, corticosteroids are the first-line treatment. High-dose pulse methylprednisolone (1 g/d for 3-5 consecutive days) is frequent initial approach.[1]

- CSA (2-7 mg/kg per day) can be added in patients with an insufficient immediate response,
- as well as IL-1–blocking therapy with ANAKINRA at dose of 2 to 6 mg/kg up to 10 mg/kg per day subcutaneously in divided doses is suggested.[2]
- Experience with anti–IL-6 blockade with tocilizumab is also increasing.
- patients with severe active disease or CNS involvement, despite steroids, CSA, and/or anakinra,
- a reduced dose of etoposide - (50-100)mg/m2 once weekly) may be very effective.
- such treatment should be discussed with an expert but still not delayed.

Case Management

The patient's shock and dehydration were initially managed with fluid resuscitation and empirical antibiotics (ceftriaxone and doxycycline) for suspected tropical infections. Artesunate was also started due to the high persistent fever and suspicion of malaria but there was no significant response to artesunate. However, despite initial resuscitation, the patient had shock on day 2, prompting the initiation of noradrenaline and the patient was initiated on initial pulse of methyl prednisologe for 3 days followed by Dexamethasone 8mg IV bd. Subsequently after 3 doses of Dexamethasone steroid, patient recovered from shock.

By day 6 of admission, the patient became afebrile, and serial CBCs showed improvement, with hemoglobin rising to 10.1 g/dL and platelets to 108,000/µL by day 10.

The liver enzymes (SGOT, SGPT) and LDH (decreasing to 788 U/L) showed progressive normalization, with the patient's inflammatory markers gradually decreasing.

By day 14, the patient was clinically stable, with normalized hematologic parameters and complete resolution of symptoms.

CONCLUSION

In recent years, interest in adult HLH has increased markedly; as a result, HLH is more frequently diagnosed in adults. The dramatic therapeutic success in pediatric HLH has also positively affected the survival of adults with HLH. However, there are profound differences between adult and pediatric HLH; genetic HLH is rare in adults, pediatric diagnostic criteria are suboptimal, frequent (often occult) underlying malignancies or other conditions require a different diagnostic workup.

This case highlights the critical significance of recognizing Hemophagocytic Lymphohistiocytosis as a potential complication of arboviral infections like Dengue. While Dengue fever is a common diagnosis in endemic regions, the development of prolonged fever, worsening cytopenias (especially anemia), and organomegaly should trigger an immediate investigation for HLH. The identification of **massive hyperferritinemia** (>10,000 ng/mL) and **hypofibrinogenemia** serves as the most potent differentiator from the standard course of severe dengue.

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