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Dengue-Associated Hemophagocytic Lymphohistiocytosis: A Diagnostic and Therapeutic Challenge

Dr. Shaik Khadeer Ahamed[1]*, Sreeteja Panjala[2], Shravani Vanga[3], Chandraprakash Gollapelli[4], Dr. Rama Rao Tadikonda[5]

[1-5]Department of Pharmacy Practice, CMR College of Pharmacy, Kandlakoya, Hyderabad, Telangana, INDIA.

ABSTRACT: Dengue fever, a widespread arboviral infection, ranges in severity from mild febrile illness to life-threatening conditions such as dengue hemorrhagic fever and dengue shock syndrome. Rarely, dengue can precipitate hemophagocytic lymphohistiocytosis (HLH), a severe hyperinflammatory syndrome characterized by dysregulated macrophage and T-cell activation. We report a case of a 45-year-old female presenting with fever, hepatosplenomegaly, cytopenias, and hyperferritinemia, who was diagnosed with dengue-associated HLH. The diagnosis was established using clinical findings, elevated ferritin, cytopenias, splenomegaly, and hemophagocytosis in the bone marrow, fulfilling the HLH-2004 criteria. Early initiation of dexamethasone, along with supportive therapy, improved the patient's clinical status. This case underscores the importance of increased clinical vigilance for HLH in dengue patients with rapid clinical deterioration. Early diagnosis and prompt immunomodulatory therapy can significantly improve outcomes. Further research is needed to better understand the pathophysiology, diagnostic challenges, and optimal treatment strategies for dengue-associated HLH.

KEYWORDS: Dengue, Hemophagocytic lymphohistiocytosis, Hepatosplenomegaly, HLH-criteria, Hyperferritinemia, Immunomodulatory therapy.

INTRODUCTION

Dengue is an acute febrile illness caused by any of four mosquito-borne dengue viruses (DENV-1–4), that remains a significant global health concern. The disease spectrum ranges from mild febrile illness to severe manifestations, such as dengue hemorrhagic fever and dengue shock syndrome, leading to high morbidity and mortality in endemic regions. While complications like organ dysfunction and bleeding are well-documented, the association of dengue with hemophagocytic lymphohistiocytosis (HLH) is rare and underrecognized[1].Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome resulting from the dysregulated activation of macrophages and T-lymphocytes, leading to excessive cytokine release and multiorgan dysfunction [2]. HLH can be either familial (primary) or acquired (secondary).Acquired HLHmay be triggered by infections, malignancies, or autoimmune disorders, and is more common than primary HLH [3].In dengue-associated HLH, the infection acts as a precipitant, driving an uncontrolled immune response that exacerbates disease severity. Early diagnosis is crucial, yet challenging, due to overlapping features such as fever, cytopenias, and hepatosplenomegaly, which are common to both conditions. Thus, maintaining a high level of clinical vigilance is crucial for diagnosing HLH, particularly when the condition presents atypically. Treatment involves high-dose corticosteroids, and intravenous immunoglobulin (IVIG), with or without etoposide, to suppress the immune response. We report a case of severe dengue fever complicated by HLH.

CASE DESCRIPTION

A 45-year-old female patient presented with high-grade, intermittent fever associated with chills for 10 days. The patient had complaints of abdominal pain and distention, jaundice associated with dark-colored urine, bilateral lower limb edema, and SOB associated with orthopnea, lasting for 7 days.The cardiopulmonary examination was normal. Significant findings on examination were fever, mild hepatomegaly of 7-8 cm below the costal margin,and abdominal tenderness. Initial laboratory tests revealedanemia (hemoglobin 7.3 gm/dL)with low mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), thrombocytopenia (83,000/µL) with no atypical cells while WBC count(4820/µL)were within the normal range.Liver enzyme levels were also raised with aspartate transaminase (AST)820IU/L,alanine transaminase (ALT)158IU/L, andalkaline phosphatase (ALP) 256 IU/L.The INR (International normalized ratio)was 1.2 with a slightly prolonged prothrombin time (PT, 15.5sec)whereas activated partial

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thromboplastin time (aPTT, 35.4sec) remained normal. An iron study revealed a high ferritin level (1985 ng/mL) while the lipid profile was within normal limits. Serological tests, including ASO (Antistreptolysin O), RA (Rheumatoid Arthritis), widal, VDRL (Venereal Disease Research Laboratory), HIV, HAV, HCV,HBsAg,leptospira IgM, and ANA (Antinuclear Antibody) profiles, were all negative.Adirect Coombs test (DCT) was positive, while the indirect Coombs test (ICT) was negative andthe D-dimer level was elevated (3341 ng/mL).

The chest X-ray revealed no evidence of airspace opacity, effusion, or pneumothorax. Blood, urine, and stool cultures returned negative results. A CECT(Contrast-Enhanced Computed Tomography) abdomen demonstrated significant hepatomegaly, gross splenomegaly, and mild ascites. The initial diagnosis suggested a possible viral illness (dengue NS_1) associated with acute liver injury, and the patient was managed supportively with intravenous fluids, hepatoprotective agents, and antipyretics.

A hemolysis workup was ordered, including lactate dehydrogenase (LDH), reticulocyte count, indirect bilirubin, and platelet count. Additionally, a viral panel, a dengue test,and a blood smear were requested.

Lactate dehydrogenase levels were markedly elevated (LDH, 1056 IU/L), while retic count (2.03%) was normal. Both the dengue NS1 antigen test and (CRP) C-reactive protein tests returned positive results. The blood smear showed thrombocytopenia, anisopoikilocytosis, hypochromic, microcytic, target cells, and teardrops with adequate WBC. The hematology team was consulted and suspected HLH, prompting a bone marrow biopsy to be performed.

The cellular bone marrow aspirate from the manubrium sternum revealed normoblastic erythroid maturation, myeloid hyperplasia, and histiocytic hyperplasia with occasional hemophagocytosis.Given that the patient has liver dysfunction along with other signs of hyperinflammation, such as cytopenias, splenomegaly, and elevated ferritin, HLH was strongly considered. The treatment for HLH was initiated alongside supportive care.

DISCUSSION

HLH may be primary (familial) and secondary (acquired). Secondary HLH has been linked to various triggers, including viral, bacterial, fungal, and parasitic infections, as well as autoimmune disorders and malignancies, particularly T-cell lymphomas [4].Dengue-associated HLH is well-documented in children, though only a limited number of cases have been reported in adults. Dengue is the most prevalent arthropod-borne viral disease in humans, with clinical presentations ranging from asymptomatic infection to dengue hemorrhagic fever and dengue shock syndrome. HLH has been linked to DENV1, DENV3, and DENV4 serotypes [5], [6].

The exact mechanism of HLH remains unclear, but the prevailing theory suggests that excessive proliferation and activation of T-cells trigger macrophage activation with impaired intracellular killing [7]. Studies highlight the important roles of perforin and natural killer (NK) cells in HLH subtypes. Reduced NK cell activity leads to increased T-cell activation and expansion, resulting in excessive cytokine production (e.g., IFN-γ, TNF-α, GM-CSF), which drives persistent macrophage activation [8], [9]. Additionally, invariant natural killer T (iNKT) cells are known to be activated during acute dengue infection, potentially contributing to the inflammatory process [10].This cycle of inflammation, fueled by activated T-cells and macrophages, causes tissue damage, including in the bone marrow. HLH is a condition associated with significant challenges in both diagnosis and treatment. The diagnostic overlap between severe dengue and HLH necessitates a high index of suspicion for HLH when patients with dengue present with rapid clinical deterioration and laboratory abnormalities such as hyperferritinemia, hypertriglyceridemia, and cytopenias. Prompt use of the HLH-2004 criteria and evaluation of biomarkers like ferritin, triglycerides, and sCD25 can facilitate early diagnosis and initiation of treatment, improving clinical outcomes.

The HLH-2004 criteria are the most widely used and accepted for both pediatric and adult populations. The diagnosis of HLH was established in 1991 based on five key criteria: persistent fever, splenomegaly, bicytopenia, elevated triglycerides and/or low fibrinogen levels, and evidence of hemophagocytosis [11].In 2004, the Histiocyte Society updated the criteria for HLH diagnosis including three additional criteria: reduced or absent NK-cell activity, elevated ferritin levels, and increased soluble interleukin-2 receptor levels [12].The diagnosis of dengue-induced HLH is often missed because clinicians focus more on the underlying infection than on the excessive cytokine production. The pathophysiology of severe dengue (DHF, DSS) is not fully understood, but there is growing recognition that macrophage activation may contribute to the severity of some cases [13].

This case was about dengue virus-associated HLH presenting with typical features such as fever, splenomegaly, cytopenias, hemophagocytosis, and ferritinemia, meeting 5 of 8 HLH diagnostic criteria. The diagnosis of dengue-induced HLH is often

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overlooked because clinicians typically concentrate on the underlying infection instead of the excessive cytokine production associated with HLH. A review of the literature on dengue-associated HLH revealed that HLH is more commonly reported during the first episode of dengue infection, with only a few documented cases triggered by a second episode of dengue [14].

In this case, the patient initially presented with ongoing fever and signs of liver injury following a diagnosis of dengue fever. As the condition worsened, the patient required oxygen support and intensive care. By correlating the recent dengue history with laboratory findings, a diagnosis of dengue-associated HLH was made. The patient additionally experienced complications of ARDS (acute respiratory distress syndrome) and ALI (acute liver injury) [15].The patient was started on dexamethasone (4mg) for hyperinflammation. Additionally, piperacillin& tazobactam, UDCA (300mg), doxycycline (100mg), Nebulization with Duolin(Ipratropium and Levosalbutamol) and Budecort (Budesonide), and multivitamin supplements were planned. Early identification and diagnosis of dengue-associated HLH can allow physicians to initiate pulse dose steroid treatment promptly, which may improve clinical outcomes.In treating primary and secondary HLH, etoposide has proven to be a key treatment. Initial treatment involves the use of etoposide, dexamethasone, and cyclosporin A. Hematopoietic stem cell transplantation is also recommended as early as possible for a potential cure for those with genetic or familial HLH or persistent disease [12]. Treatment of HLH with dexamethasone is also considered very beneficial. Eight out of 10 patients with severe disease survived after the administration of dexamethasone in a study [16]. Intravenous immunoglobulin G can be used either alone or with dexamethasone or methylprednisolone.Studies have documented successful treatment in both children and adults using IVIG alone or in combination with steroids [17], [18].

CONCLUSION

This case highlights the need for further research into dengue-associated HLH, focusing on identifying predictive markers like ferritin levels, NK cell activity, and soluble IL-2 receptors to detect high-risk patients early. The overlap between severe dengue and HLH presents a diagnostic challenge, necessitating studies to better differentiate these conditions. Studies evaluating the timing and efficacy of immunomodulatory therapies, including steroids, IVIG, and etoposideare essential to improve treatment outcomes. Furthermore, longitudinal research is necessary to understand the long-term impacts of dengue-associated HLH, such as recovery patterns, relapse rates, and organ-specific complications. Addressing these gaps could significantly enhance diagnostic precision and therapeutic strategies in managing this rare but severe complication.

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Table I.

S.No.	*Variable*	*Presented Value*
1.	Haemoglobin (11.5 ~ 16.5 g/dL)	7.3
2.	Hematocrit (40 - 54%)	31
3.	White cell count (4 - 11x10^9/L)	4.8
4.	MCV (76 ~ 96 fL)	68.3
5.	Platelet (150 - 450 x10^9/L)	83
6.	INR (0.8 – 1.2)	1.21
7.	Creatinine (50 – 74 µmol/L)	0.46
8.	AST (5 – 34 IU/L)	820
9.	ALT (6 – 28 U/L)	158
10.	Total Bilirubin (2.1 – 15.5 µmol/L)	10.9
11.	Ferritin (24 – 336 µg/L)	1885
12.	Dengue NS1 Antigen	Positive
13.	Dengue IgG	Negative
14.	Dengue IgM	Negative
15.	HIV, HCV, HBsAg, HAV	Negative
16.	LDH (100 - 217 U/L)	1056
17.	D-Dimer (0 - 0.50 mg/L)	3341
18.	Total Cholesterol (~ 5.18 mmol/L)	4.4
19.	Triglyceride (< 1.70 mmol/L)	1.9

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