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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO DENGUE FEVER

Simon Kashfi[1], Joon Yup Kim[1], Naomi Shohet[2], Shams Shakil[1], Manile Dastagir[1]

[1] Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, USA
[2] SUNY Downstate Medical School, Brooklyn, USA

Corresponding author's e-mail: skashfi@northwell.edu

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome often misdiagnosed due to its rarity and overlapping symptoms with sepsis or organ dysfunction. This case report describes a 52-year-old male who developed dengue-induced HLH after traveling to Barbados, presenting with multi-organ failure and laboratory abnormalities, including hyperferritinaemia and elevated IL-2R. Diagnosed via bone marrow biopsy, he was treated with corticosteroids and the IL-1R antagonist anakinra, leading to recovery. Dengue-associated HLH in adults is rare but rising due to increased global dengue incidence. Early recognition and tailored treatment are critical for improved outcomes.

KEYWORDS

HLH, hemophagocytic lymphohistiocytosis, Dengue, anakinra

LEARNING POINTS

- Internists must maintain a high index of suspicion for hemophagocytic lymphohistiocytosis (HLH) in febrile patients with multi-organ dysfunction and hyperferritinaemia.
- This case addresses the diagnostic and therapeutic voids in adult HLH management, offering a practical framework for internists treating complex cases of infection-triggered hyperinflammatory syndromes.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by severe inflammation leading to multi-organ failure. Additionally, HLH can present with hypotension, hyponatremia or neurological, pulmonary, or renal complications[1]. Much to the detriment of patients, the diagnosis and early identification of HLH may be limited due to its rarity, complexity of diagnostic criteria, and clinical features resembling sepsis and multiple organ dysfunction syndrome. HLH can either be primary, more common in children, or secondary, due to illnesses such as malignancy, infection, or autoinflammatory/autoimmune disorders. If HLH occurs secondary to autoinflammatory or autoimmune disorders, it is known as macrophage activation syndrome. The predominant understanding of the diagnosis and treatment of HLH stems from paediatric literature, specifically HLH-2004 guidelines, which is problematic as these guidelines have not been validated for

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the adult population[2]. While there are many causes of HLH, pathogenesis generally involves an uncontrolled response of cytotoxic lymphocytes and macrophages ultimately causing cytokine-mediated tissue injury and organ dysfunction[3]. Infection with Dengue virus is a known cause of secondary HLH, and while it has been well-reported in children, cases in the adult population are rare. Dengue infection can range from asymptomatic to dengue haemorrhagic fever and dengue shock syndrome. Incidents of Dengue virus have risen over the years, causing an increase in dengue associated HLH[4]. We present the case of a 52-year-old male with no medical history to developed dengue induced HLH after a trip to Barbados.

CASE DESCRIPTION

A 52-year-old male with no medical history who presented to an outside hospital with 1 week of fever, chills, night sweats, rigors, orthostatic dizziness, postprandial nausea/vomiting and myalgias. He had presented 1 week after returning from a weeklong trip to Barbados. He initially went to an urgent care and was found to be influenza A positive and started on oseltamivir. He subsequently felt worse and then went to the emergency room, where he was found to be in multi-organ failure. He was admitted to the intensive care unit (ICU), started on continuous renal replacement therapy (CRRT), and was transferred to our institution for a higher level of care and liver transplant evaluation. Initial vital signs were temperature 39.5°C, heart rate 120 beats per minute, blood pressure 97/54, respiratory rate 30, oxygen saturation 92% on room air. His national early warning score was 14 points. Initial laboratory studies upon transfer to our hospital are shown in *Table 1*. Notably, labs from the outside hospital were significant for ferritin 34,010 µg/l, fibrinogen of 238 mg/dl,

Laboratory value	Result	Reference range
White blood cell count (K/ul)	26.95	3.8-10.5
Haemoglobin (g/dl)	7.6	13-17
Platelets (K/µl)	172	150-400
Blood urea nitrogen (mg/dl)	66	7-23
Creatinine (mg/dl)	6.01	0.5-1.3
Total bilirubin (mg/dl)	3.9	0.2-1.2
Alkaline phosphatase (U/l)	212	40-120
Aspartate aminotransferase (U/l)	1159	10-40
Alanine aminotransferase (U/l)	229	10-45
Lactate dehydrogenase (U/l)	8604	50-242
Lipase (U/l)	2000	7-60
Creatine kinase (U/l)	2009	30-200
Triglycerides (mg/dl)	162	≤149
INR	1.82	0.85-1.18
Arterial lactate (mmol/l)	6.4	0.5-2

Abbreviations: INR, international normalised ratio.

Table 1. Patient's hypercoagulable test results.

Laboratory value	Result
Blood culture	Negative
Lyme PCR	Negative
HIV 1-2 screen	Negative
Herpes Simplex Virus 1/2 PCR	Negative
Blood parasites – travel associated	Negative
Cytomegalovirus PCR	Negative
Epstein Bar virus DNA	Indicative of prior infection
Cerebrospinal fluid PCR panel	Negative
Cerebrospinal fluid culture	Negative
Urine Legionella	Negative
Babesia PCR	Negative
Hepatitis B	Negative
Hepatitis C	Negative
Dengue fever IgM	Positive 3.95 ISR (<1.65)
Dengue fever IgG	Negative 1.39 ISR (<1.65)
Chikungunya IgM and IgG	Negative
Leptospirosis antibody	Negative
Rocky Mountain spotted fever IgM and IgG	Negative
Strongyloides antibodies	Negative
Hanta Virus IgM and IgG	Negative
Q Fever antibody	Negative
Syphilis screen	Negative
Parvovirus IgM	Negative
Parvovirus IgG	Positive
Fungitell	Negative
HTLV1 + HTLV II antibodies	Negative

Abbreviation: HIV, human immunodeficiency virus; PCR, polymerase chain reaction; DNA, deoxyribonucleic acid; HTLV, human T-lymphotropic virus.

Table 2. Infectious disease investigation.

elevated IL-2R to 3069.6 U/ml, and thrombocytopenia (which had recovered by the time of transfer to our institution).

The patient was awake but not coherent, and he was started on a dexmedetomidine infusion for agitation. He was then intubated for acute hypoxemic respiratory failure in the setting acute uremic and hepatic encephalopathy. Haematology was consulted and bone marrow biopsy confirmed HLH *(Fig. 1)*. The patient was started on a steroid taper (8-week taper per the HLH-94 protocol), IL-1R antagonist anakinra, and atovaquone for pneumocystis pneumonia prophylaxis. *Table 2* shows the infectious disease investigation of this patient. *Table 3* indicates the autoimmune workup of this patient. *Table 4* describes the results of the various biopsies the patient had. The patient was transitioned from CRRT to intermittent haemodialysis and transitioned to the general medicine floors. Renal biopsy showed only mild fibrosis. He subsequently showed signs of renal recovery, with increased urine output, and was closely monitored off dialysis. Over time, he demonstrated continued improvement in renal function and his dialysis access was eventually removed. He was started on midodrine for orthostatic hypotension and was ultimately discharged to acute rehab. During this period his mental status also returned to normal, and he was able to do exercises in a seated position. At follow up 3 weeks after discharge, steroids were discontinued, and the patient was maintained on anakinra 100 mg subcutaneously daily.

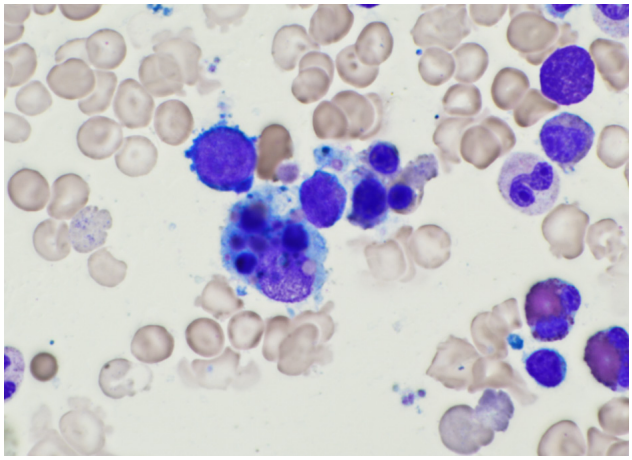


Figure 1. Bone marrow aspirate smear showing hemophagocytosis of erythroid cells.

Laboratory value	Result
Anti-Nuclear Antibody	Negative
Double stranded DNA antibody	<12 (<29 IU/ml)
Anti-ribonuclear protein antibody	Negative
Anti-smith antibody	Negative
c-ANCA antibody	Negative
p-ANCA antibody	Negative
Rheumatoid factor	Negative
Smooth muscle antibody	Negative
Mitochondrial antibody	Negative
Microsomal antibody assay liver and kidney	Negative

Abbreviations: DNA, deoxyribonucleic acid; p- ANCA, perinuclear antineutrophil cytoplasmic antibodies; c-ANCA, cytoplasmic antineutrophil nuclear antibodies.

Table 3. Autoimmune workup.

Biopsy	Result
Liver	Large droplet macro vesicular steatosis, focal zone 3 to zone 2 parenchymal dropout and mild canalicular cholestasis.
Kidney	Acute tubular injury with pigmented casts. Mild interstitial oedema/early fibrosis.
Bone marrow	Cellular marrow (50-60%) with erythroid predominant, maturing trilineage haematopoiesis, dyserythropoiesis and increased histiocytes showing occasional haemophagocytosis.
Bone marrow aspirate (flow cytometry)	No significant increase in myeloblasts, normal myeloid granularity with subset showing loss of CD10, and normal monocytic antigen maturation pattern.

Table 4. Biopsy results.

DISCUSSION

Dengue virus is a Flavivirus transmitted by the Aedes aegypti mosquito, a species presents in most areas of South America, the Caribbean, Central America, and southern regions of the United States. Symptoms of dengue fever typically arise between 4-7 days after a bite by an infected mosquito. Typically, dengue fever in its primary infection leads to a simple fever. Secondary infections separated by >18 months lead to more severe disease with increased mortality. The guideline for dengue fever classification established in 2009 by the World Health Organization (WHO) classifies dengue fever into three categories: dengue without warning signs, dengue with warning signs, and severe dengue[5]. Furthermore, dengue fever presents in three distinct phases: febrile phase, critical phase, and recovery phase. Febrile phase presents with high grade fever >38°C accompanied by clinical symptoms consistent with dengue with or without warning signs. Haemorrhagic manifestations may begin presenting at this stage. The critical phase typically begins on days 3-7 around the time of defervescence. The patient may develop a systemic vascular leak syndrome characterized by plasma leakage leading to bleeding, hypovolemic shock and subsequent organ failure. This phase typically lasts for 24 to 48 hours. The recovery phase presents with reversal of plasma leakage and resolution of haemorrhage[5].

There have been many reports of HLH triggered by dengue fever. The overall mortality rate of HLH in critically ill

Biopsy	Scoring Criteria
Underlying immunocompromised state	No: 0
	Yes: 18
Temperature (°C)	<38.4: 0
	38.4-39.4: 33
	> 39.4: 49
Organomegaly	No: 0
	Hepatomegaly or splenomegaly: 23
	Hepatomegaly and splenomegaly: 38
Number of cytopenia	1 lineage: 0
	2 lineages: 24
	3 lineages: 34
Ferritin (ng/ml)	<2,000: 0
	2,000–6,000: 35
	>6,000: 50
Triglyceride level (mmol/l)	< 1.5: 0
	1.5–4: 44
Fibrinogen (g/l)	> 2.5: 0
	≤ 2.5: 30
Serum glutamic oxaloacetic transaminase (IU/l)	<30: 0
	≥ 30: 19
Haemophagocytosis seen on bone marrow biopsy	No: 0
	Yes: 35

Table 5. HScore adapted from Khare et al. 2021[8].

patients can be up to 57% and given that symptoms of HLH can overlap with severe manifestations of dengue fever, early recognition and treatment of HLH is imperative. In adults, the diagnostic criteria for HLH are a heterozygous mutation in a HLH-associated gene (STX11, SH2D1A, PRF1, UNC13D, and ITK), or at least five of the 8 clinical and laboratory features: fever ≥38.5°C, splenomegaly, peripheral blood cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, haemophagocytosis in bone marrow, spleen, lymph node or liver biopsy, low natural killer cell activity, ferritin >500 ng/ml, and elevation of CD25 (IL-2R Alpha) by >2 standard deviations about age-adjusted laboratory reference range[6]. The HScore was developed by Fardet et al. as a predictor of HLH[7]. The clinical and laboratory criteria and the number of points assigned are listed in *Table 5*[8]. The Fardet group's study found that with this scoring system, an HScore of <90 suggested a diagnostic probability of HLH <1%, while an HScore >250 was >99% diagnostic probability. Our patient's HScore, being 235, was highly suggestive of HLH.

As in our case report, treatment of HLH often involves systemic corticosteroids, IVIG, immunomodulating agents, or chemotherapy[9]. Any patients with high suspicion of HLH and signs of organ dysfunction must immediately start HLH-specific treatment even if confirmatory testing such as biopsy is pending. Some clinical and laboratory data that signal the need for initiation of HLH-specific therapy include rapidly increasing ferritin, D-dimer, alanine aminotransferase (ALT)/aspartate aminotransferase (AST), worsening anaemia and thrombocytopenia, and elevating creatinine[10].

The HLH-94 treatment protocol was developed and 54% of patients treated with the HLH-94 regimen achieved survival at the 5-year mark. The HLH-94 protocol involves an 8-week induction therapy with etoposide and dexamethasone. If there is central nervous system (CNS) involvement, hydrocortisone and methotrexate are administered intrathecally. In those with impaired hepatic function, alemtuzumab is used instead of etoposide. For patients who do not show response in two to three weeks, salvage therapy is considered[10]. Some patients require allogeneic hematopoietic cell transplant if they show lack of response to initial HLH therapy, have CNS involvement refractory to intrathecal therapy, have recurrent HLH in the setting of homozygous HLH gene mutations, or if their HLH is triggered by an underlying hematologic malignancy[6].

Many other protocols for the treatment of HLH exist, but so far studies have yet to show whether other protocols produce outcomes superior to the HLH-94 protocol. For instance, the HLH-2004 study added cyclosporine to etoposide and dexamethasone but found that the addition of cyclosporine did not improve outcomes[11]. The treatment regimen used in our patient involved the interleukin 1 receptor antagonist, anakinra. Anakinra has shown promise as an alternative to chemotherapy agents such as etoposide and has been favoured in patients with underlying rheumatologic diseases and in patients with secondary HLH with multiorgan dysfunction[12]. In a study of 21 patients with secondary HLH being treated with anakinra, anakinra, when used with or without steroids, produced rapid resolution of inflammatory changes associated with HLH. Fever resolved in 1 day, and there were significant decreases in CRP, ferritin, and AST levels by the 1 week mark[12].

The patient's clinical course often determines management. For example, supportive care may be appropriate in patients with clinical stability[4]. Similarly, Chang et al described 2 cases that were both managed with short courses of dexamethasone[9]. A recent paper includes a review of dengue associated HLH with treatments modalities and patient outcomes[13]. Interestingly, anakinra was not used in any of these cases, possibly due to concern for secondary infection. Baverez et al describes cases of HLH in two university hospitals (cases were of various aetiologies, none of which included dengue virus) that involved anakinra. Four of those patients were treated with a combination of

anakinra and corticosteroids, while anakinra was used as a second line treatment after corticosteroid therapy failure in seven patients[12]. Anakinra was used in our case due to the hepatotoxic nature of etoposide and our patient's liver failure.

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