CASE REPORT

Secondary Hemophagocytic Lymphohistiocytosis with Severe Dengue: A Rare but Dreadful Complication

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a devastating and rare multisystemic disorder characterized by an autoimmune phenomenon leading to reactive hyperactivity of cytotoxic T cells and histiocytes mediated by cytokine storm. HLH could be primary (hereditary) or secondary (acquired). Unremittent fever, organomegaly, lymphadenopathy, and neurologic dysfunction are among the common manifestations of HLH, along with abnormal lab parameters like hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and transaminitis.

We report a case of a 16-year-old adolescent girl presenting to the emergency department with a history of high-grade fever, with partial response to antipyretics, body aches, and severe headache for 4 days. The physical examination revealed significant hepatomegaly. enzyme-linked immunosorbent assay was positive for dengue nonstructural protein 1 (NS1) antigen (Ag) assay. The patient was managed as per the World Health Organization (WHO) protocol and started improving from dengue; however, during the second week of the illness, the patient continued to have persistent fever. A repeat lab workup revealed bicytopenia with elevated ferritin levels (17891 ng/mL). Diagnosing dengue-associated HLH is challenging unless the treating team is aware of this association, as early recognition and timely institution of immunosuppressive and specific therapy for the underlying infection is associated with improved outcomes. Physicians should collaborate with pathologists and microbiologists for early diagnosis.

Keywords: Case report, Cytokine storm, Dengue fever, Dengue fever with warning signs, Hemophagocytic lymphohistiocytosis.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening fatal disease characterized by dysregulated systemic hyperinflammation due to the proliferation of activated lymphocytes and histocytes, which secrete a large number of inflammatory cytokines.[1] HLH is of two types—primary (hereditary) due to mutations in genes that are responsible for the production of cytotoxic T-cells and natural killer (NK) cells such as syntaxin 11, syntaxin binding protein 2, perforin 1, Unc-13 homolog D, interleukin 2 (IL2)—inducible T-cell kinase; secondary (acquired) developed during infections, malignancies or rheumatological disorders.[2–4]

Secondary to viral infections, HLH is most common in tropical countries and manifests when infectious agents either evade or interfere with immune recognition and cytokine balance. Deoxyribonucleic acid viruses like Epstein–Barr virus have been the most documented agents leading to HLH, but as per recent reports, infections caused by ribonucleic acid viruses like dengue are also associated with secondary HLH.[3] HLH due to dengue is an uncommon entity and can be confused with dengue shock, leading to high mortality in patients if not anticipated and managed in time.[5] Dengue fever (DF) is one of the common arthropod-born viral illnesses; out of four serotypes of dengue virus (DENV), DENV1, DENV3, and DENV4 are known to cause HLH.[6]

We report here a case of secondary HLH as a complication of severe dengue infection with an associated unusual manifestation of prolonged conjugated hyperbilirubinemia.

Case Description

A previously healthy, 16-year-old adolescent female presented with complaints of high-grade fever for 3 days, vomiting, pain in the abdomen for 2 days, and fast breathing for 1 day. Fever was associated with chills, rigors, body aches, and headache with partial response to antipyretics and developed multiple episodes of vomiting, with diffuse, dull, and aching abdominal pain and fast breathing on the day the index patient reported to the emergency.

Examination in the emergency room revealed a temperature of 102.2°F, respiratory rate: 54/minute, peripheral oxygen saturation: 85% on room air, pulse rate: 110/minute, blood pressure: 94/78 mm Hg (5th–50th centile), and with CRT of <2 seconds, was irritable, anxious, and icteric with pitting edema around ankles. Systemic examination revealed evidence of respiratory distress and hepatosplenomegaly.

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After stabilization in the ER, the patient was shifted to the pediatric intensive care unit and managed with IV fluids, antibiotics, and antipyretics (Table 1).

Based on clinical presentation and lab parameters, the patient was managed as a case of severe dengue disease (SDD) with serositis and conjugated hyperbilirubinemia as per World Health Organization (WHO) guidelines. On day 3 of admission, the respiratory distress improved, but the patient continued to have a persistent high-grade fever, and repeat lab workup revealed neutropenia (0.62×10^9/L) and thrombocytopenia (30×10^3/L), and based on bicytopenia, HLH biomarkers were ordered, which revealed hyperferritinemia (17891 ng/mL), hypertriglyceridemia (481 mg/dL) with elevated CRP (248 mg/dL) and normal D-dimer levels. The patient was diagnosed with HLH secondary to SDD, and intravenous (IV) methylprednisolone as pulse therapy 500 mg once a day for 3 days was added; supportive management and antibiotics were omitted. After 24 hours of steroids, the patient's clinical and hematological parameters started improving, with serum ferritin and triglyceride levels showing a declining trend. After 3 days of IV pulse therapy, the patient became afebrile and was switched to oral prednisolone (2 mg/kg/day).

During the hospital stay, the total and direct bilirubin showed an upward trend (Table 1) from the day of admission and were 8.9 and 6.5 mg/dL, respectively, at discharge and could not ascertain etiology for this unusual, abnormal lab parameter despite normal investigative work up for cholestasis.

The patient was discharged on oral prednisolone with tapering doses over the next 2 weeks. On follow-up, serum bilirubin and transaminases showed a declining trend and normalized after 4 weeks of discharge, and the patient is well after 4 months of follow-up.

Discussion

Dengue fever (DF), an endemic disease caused by DENV, family Flaviviridae, is transmitted mainly by *Aedes aegypti*. The WHO estimates there to be 390 million dengue infections annually, with 96 million manifesting clinically.[7] According to National Vector Borne Disease Control, Government of India 110,000 cases with 86 deaths were reported in 2022. The DF usually presents with fever, myalgia, arthralgia, eye pain, and headache. The clinical manifestations of dengue can range from asymptomatic disease to dengue with warning signs and severe dengue.[8,9] SDD is characterized by plasma leakage leading to hypovolemic shock, severe bleeding, organ failure, and encephalopathy.[9] DF is usually a self-limiting illness with complete recovery in the majority, but few patients with severe dengue can develop secondary HLH.[8,9]

Hemophagocytic lymphohistiocytosis (HLH) is secondary to any infection and should be suspected when a patient, after a usual course of the disease, manifests with either recurrent or persistent fever, bicytopenia, and organomegaly. The septic workup in these patients is noncontributory, and in DF, the reappearance of fever or unremitting fever after 1 week of illness with associated clinical and laboratory abnormalities should alert the treating physician toward the possibility of HLH.[10]

Hemophagocytic lymphohistiocytosis (HLH) in DF remains a diagnostic challenge and can be misdiagnosed as sepsis because of overlapping clinical presentation. The diagnosis of HLH should meet five out of eight clinical and laboratory criteria as per the HLH 2004 protocol.[11]

- Fever.
- Splenomegaly.
- Cytopenia in ≥2 cell lineages.
- Hypertriglyceridemia (>265 mg/dL) or hypofibrinogenemia (<150 mg/dL).
- Hyperferritinemia (>500 ng/mL).
- Soluble CD25 >2400 U/mL (or elevated compared with laboratory-defined normal ranges).
- Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver.
- Low or absent NK cell cytotoxicity.

In the index case, the patient had persistent fever during the second week of illness with hepatosplenomegaly, bicytopenia,

Table 1: The table depicts the lab parameters of the patient during the stay

	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 6*	*Day 9*
Hemoglobin	9.2	9.3	10.2	10.2	10.4	10.8
Platelet count	52000	37000	30000	82000	112000	145000
Absolute neutrophil count	1824	1100	620	3192	4138	6385
Serum glutamic oxaloacetic transaminase (U/L)	2108	885	690	640	482	201
Serum glutamic pyruvic transaminase (U/L)	719	327	266	221	192	111
Total billirubin (mg/dL)	3.10	5.81	5.6	7.4	8.9	8.9
Direct billirubin (mg/dL)	1.81	3.40	4.3	5.5	6.5	6.5
Serum ferritin (ng/mL)	–	–	17891	28368	5368	825
Serum triglycerides (mg/dL)	–	–	481	180	161	110

Day 1 investigations:
- Urine routine: normal.
- Dengue nonstructural protein 1 (NS1) antigen (Ag) and immunoglobulin M (IgM): positive.
- Malaria rapid: negative.
- Chest X-ray: bilateral pleural effusion.
- Ultrasonography (USG) abdomen: hepatosplenomegaly with normal echotexture, acalculous cholecystitis with free fluid.

Day 2 investigations:
- Scrub typhus IgM: negative
- IgM for hepatitis A and E: nonreactive.
- Day 3: blood culture—no growth.
- Day 6: second blood culture—no growth.

hyperferritinemia, hypertriglyceridemia, and conjugated hyperbilirubinemia. Based on these, a diagnosis of secondary HLH to dengue disease was made, and the patient responded to steroid therapy.[11,12] It is also important to remember that the sensitivity and specificity of hemophagocytes for HLH are documented as 83 and 60%, respectively; however, in the absence of hemophagocytes on histopathological examination with suggestive clinical features of HLH, hemophagocytes may not always be present at the initial marrow examination, and serial examinations may reveal its presence, the appropriate treatment for HLH should not be delayed.[11,12] The newer clinical testing options, such as IL-18 levels C-X-C motif chemokine ligand 9 (indicating interferon-gamma pathway activity), are being used frequently.[11] The management of HLH is the immediate suppression of cytokine storms to prevent life-threatening outcomes of HLH and is achieved using corticosteroids, intravenous immunoglobulin (IVIg), and anti-cytokine agents like etoposide.[12] Corticosteroids are the first choice, and dexamethasone is recommended in case of central ervous system involvement due to HLH.[11,12] In recent times, anakinra, a newer IL-1 inhibitor, has also shown better outcomes in secondary HLH, refractory to corticosteroids and immunoglobulins.[13]

The primary HLH 2004 protocol recommends an 8-week induction therapy with corticosteroids, etoposide, and cyclosporine for primary HLH.[14] Hematopoietic stem cell transplantation is recommended for patients with familial HLH and with severe persistent or reactivated HLH.[11] The patient with secondary HLH must also be subjected to genetic studies to prevent severe disease if recurrence occurs. In patients with milder forms of HLH, corticosteroids with or without immunoglobulins may be sufficient to control hyperinflammation.[14,15] The index patient had a marked clinical improvement after initiation of methylprednisolone, and the unusual association of cholestasis with DF is a very uncommon entity; hence, this case is being reported.

Conclusion

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life-threatening association of DF and SDD, and the presentation is nonspecific and overlaps with septicemia; therefore, a high index of suspicion is important to diagnose secondary HLH. Therefore, it is recommended that clinicians should be aware of this uncommon but serious complication of secondary HLH following dengue, and disproportionately raised ferritin levels should alert the physician to work up these patients for the possibility of HLH and timely institution of steroids or IVIg therapy, in addition to the specific management of the triggering infection, are crucial for a successful outcome.

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