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Case Report

Secondary Hemophagocytic Lymphohistiocytosis in an Adult Female with Dengue Fever

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Introduction

Secondary Hemophagocytic Lymphohistiocytosis (HLH) due to dengue fever is a rare presentation in adults. We aim to report a case of dengue fever that presented as unrelenting fever in the background of HLH which responded to steroids.

Case Summary

A 30-year-old lactating female with no known comorbid conditions came to our emergency department with an undocumented high-grade fever for five days. The fever pattern was intermittent with chills, no diurnal variation, partially relieved by antipyretics, and associated with episodes of vomiting. With a fever, she had significant myalgias and mild gum bleeding. On presentation, she was dehydrated, tachypneic, and tachycardic with positive dengue NS1.

Pertinent laboratory findings were, hemoglobin of 12.2 mg/dl, hematocrit of 35.9% and platelets of 33 x109/L, hemoparasite, and immunochromatographic test for malaria were negative. Her examination was most notable for dry mucous membranes, mild epigastrium tenderness, and a macular erythematous branch able rash involving the lower extremities. She was treated symptomatically with good intravenous hydration, antipyretics, and antiemetics.

Due to continuous high-grade fever that was not touching the baseline and gastrointestinal symptoms, a diagnosis of concomitant enteric fever was made and blood cultures were sent on the eighth day of illness, novel COVID-PCR was also reported negative. She was started on intravenous meropenem, serum Liver Function Tests (LFTs), and an ultrasound of the abdomen were ordered, her LFTs showed raised SGPT and GGT. The ultrasound whole abdomen had significant findings of hepatomegaly of 16.5 cm, gall bladder wall edema; ascites, and minimal right-sided pleural effusion.

On the 4th day of admission, her daily fever spikes of 101F escalated to 104F despite intravenous antibiotics, every 8 hourly antipyretics, and sponging. Her blood cultures were ongoing negative and a procalcitonin of 0.37 ng/ml made bacteremia less likely. Due to continuous high-grade fever and ongoing negative blood cultures, blood tests to support the diagnosis of HLH were ordered. Her workup revealed a serum ferritin > 33511mg/dL, triglycerides of 157mg/dL, fibrinogen of 130 mg/dl, SGPT of 957U/L, Hb of 14.0mg/dl, total leukocyte count of 12.3 x 109/L and platelets of 23 x109/L. Her calculated HScore for HLH was 215, suggesting a 93 to 96% probability of hemophagocytic syndrome. Due to the high probability of HLH, she was started on intravenous dexamethasone of 4 mg twice per day on the 5th day of her admission and the 10th day of illness. On the following day, her fever spaced out and reduced in intensity. On the third day of intravenous dexamethasone, she became completely afebrile. Serum fibrinogen and ferritin were monitored on alternate days that were in a declining trend. Intravenous meropenem was continued till her blood cultures came reported negative.

Discussion

Since its discovery in 1939 by Scott and Robb-Smith, HLH has remained difficult to diagnose [1]. The challenge to diagnosing comes from the rarity of this disease and the limited literature in the adult population. Malinowska, Machaczka et al. found the incidence of HLH to be 1 per 280,000 among Swedish adults per year; mostly associated with malignancy [2]. Similarly, Ishii Ohga, et al. found the prevalence of HLH among Japanese adult and pediatric populations to be 1 per 800,000 [3].

HLH is defined as the hyperactivation of inflammatory cells, which causes a spectrum of presentations. It can be genetic (primary) or acquired (secondary). The primary HLH is associated with genetic factors affecting perforin-mediated cytotoxicity and dysregulated lymphocyte interactions [4]. The secondary HLH has no familial history but is closely associated with infections, malignancies, and autoimmune disorders [5]. As per the 2004 HLH guideline, the diagnosis requires either a molecular diagnosis of various genetic variants of HLH or five out of the following eight criteria: **Table 1** [6].

Primary HLH is nearly 100% fatal without adequate treatment. However, in some studies, treatment with dexamethasone and the cytotoxic drug etoposide has increased survival to 60% [7,8].

Some other treatment modalities include IVIG for macrophage activating syndrome, plasma exchange for patients with serum ferritin ≥ 10,000 µg/L and LDH ≥ 1000 IU/L, splenectomy for relapsed HLH of unknown cause, and recombinant human

Table 1: Revised Diagnostic Guidelines for HLH-2004.

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
(A) Initial diagnostic criteria (*to be evaluated in all patients with HLH*)
1-Fever
2-Splenomegaly
3-Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
4-Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L)
5-Platelets $<100 \times 10^9$/L
6-Neutrophils $<1.0 \times 10^9$/L
7-Hypertriglyceridemia and/or hypofibrinogenemia:
8-Fasting triglycerides ≥3.0 mmol/L (i.e., ≥265 mg/dl)
9-Fibrinogen ≤1.5 g/L
10-Hemophagocytosis in bone marrow or spleen or lymph nodes
11-No evidence of malignancy
(B) New diagnostic criteria
1-Low or absent NK-cell activity (according to local laboratory reference)
2-Ferritin ≥500 µg/L
3-Soluble CD25 (i.e., soluble IL-2 receptor) ≥2,400 U/ml

thrombopoietin (rhTPO) have also been recommended [9]. Despite the rarity of this disease, its unestablished association with many common diseases should always be considered. Severe dengue is closely associated with secondary HLH and a recent meta-analysis reveals the highest number of dengue-associated hemophagocytic lymphohistiocytosis in Southeast Asia (62 cases), followed by the Western Pacific region and the Americas [10].

A five-year retrospective study conducted in Malaysia determined the association of secondary HLH in severe dengue and found that 21 cases out of 180 developed secondary HLH, out of these 9 expired. Elevated ferritin, AST, and ALT with low platelet counts and high LDH were directly related to fatality [11].

As per the World Health Organization, Pakistan has reported a total of 25,932 confirmed dengue cases from January 2022 till September 2022 with 74% alone in the month of September, this surge is attributable to the recent flood crises in the region. Due to the growing number of dengue cases, one must be attentive to the association of severe dengue with HLH. Persistent high-grade fever, cytopenias, visceromegaly, and high ferritin in dengue fever should prompt a physician to consider a diagnosis of HLH and manage it timely.

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