Case study

Case report: Primary hemophagocytic syndrome triggered by dengue infection

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Abstract

HLH is a progressive syndrome of unchecked immune activation and tissue damage. If left untreated, patients with HLH survive for only a few months, due to progressive multi-organ failure. Prompt initiation of treatment for HLH is essential for the survival of affected patients. Several conditions are responsible for triggering HLH in clinically stable patients who respond to treatment of the underlying condition alone. These conditions include infection, rheumatological diseases and lymphoid malignancies. We report a rare case of primary HLH in a 32-year-old female who presented with fever, abdominal pain, pancytopenia and splenomegaly with the triggering factor being Dengue infection.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. It most frequently affects infants from birth to 18 months of age, but the disease is also observed in children and adults of all ages. HLH can occur as a familial or sporadic disorder, and it can be triggered by variety of events that disrupt immune homeostasis. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases. We are discussing a rare case of inherited HLH who presented at age of 39 years that was triggered by dengue infection.

Case

A-39-years old female presented to emergency department (ED) with a 10-day history of flu-like symptoms, fever, abdominal pain and vomiting. There was no known family history of autoimmune conditions, malignancy or consanguinity. She is a mother of three children and one of her child was diagnosed with Charcot-Marie-Tooth disease which is an inherited disorder. She denied alcohol consumption, smoking, illicit drug use and confirmed receipt of childhood vaccinations. Two days after admission, there were features of severe sepsis, with the following observations: temperature 39.4 °C, heart rate 144 bpm, blood pressure 91/45 mmHg with worsened respiratory parameters. She appeared alert but dehydrated with no palpable lymphadenopathy. However, she had tender epigastrium with palpable spleen of 4 cms below left costal margin. There was no focal neurological deficit. She was continued on supportive management including broad spectrum antibiotics and non-invasive respiratory support.

Complete blood count revealed Hb 8.9 gm/dl, MCV 79fl, WBC 1.7 × 10^9/L, ANC 4.2 × 10^9/L and platelet count of 26 × 10^9/L. Her C-reactive protein was elevated (42 mg/L) with normal liver and renal function tests, and a mildly elevated venous lactate (2.4 mmol/L). Chest radiograph showed bilateral pleural effusion and electrocardiogram was unremarkable. Echocardiogram demonstrated a preserved left ventricular ejection fraction with no valvular vegetation or pericardial effusion. Multiple blood cultures, urinary pneumococcal and legionella antigens, nasopharyngeal swab for COVID 19, malaria rapid immune-chromatographic tests, EBV, HSV, Hepatitis B, C, HIV serology and autoimmune profile were done, returning negative results. Acute Dengue virus infection was confirmed (through Dengue IgM serology) and subsequent bone marrow biopsy analysis demonstrated increased hemophagocytic activity (Fig. 1) with positive immunohistochemical stains CD68 and CD31 (Fig. 2).

Based on the laboratory results, her genetic work-up for primary HLH was sent and she was started on dexamethasone with dose of 10 mg/m^2 as HLH-directed therapy. In the next 3 weeks, we observed resolution of HLH markers along with reduced requirements for multi-organ support after initiation of dexamethasone treatment. Eventually she was dis...
charged on tapering doses of steroids. She remained on weekly follow-up for 3 weeks and was stable. However, in the fourth week of follow-up she again presented to ER with history of fever and diarrhea. Investigations revealed Hb 9.3 gm/dl, MCV 85fl, WBC 1.2 × 10⁹/L, ANC 61 × 10⁹/L, and platelet counts 101 × 10⁹/L. Increased ferritin of 53,670 ng/ml, prothrombin time >170 s, activated partial thromboplastin time >170 s, fibrinogen <30 mg/dl and D-Dimer > 30 mg/L. Repeat pan cultures were negative but dengue IgM serology was still positive. Her genetic testing results were received during this time and it showed homozygous mutation at STXBP2 gene (variant c.1247-1G > C). This mutation is associated with autosomal recessive familial HLH.

During her second admission, she was managed with transfusion support, broad spectrum antibiotics and HLH-94 protocol. Her condition improved in 2-weeks and she was discharged from in-patient to continue the protocol in day care-based set-up at our hospital. She was counseled regarding allogeneic stem cell transplant and a search for sibling matched donor is in process. Summary of laboratory parameters is given in Table 1.

### Discussion

Hemophagocytic lymphohistiocytosis is a rare hyper-inflammatory disorder related to macrophage activation and usually presents as prolonged fever and sepsis-like syndrome [1]. Two types of HLH are seen that include primary (familial) form which is a fatal autosomal recessive disorder, whereas the secondary or reactive form is associated with viral, bacterial, fungal, or parasitic infections as well as with connective tissue disorders and malignancy [2]. The importance of the association between HLH and infection lies in the fact that both forms of HLH may be preceded by infection. Genetic defects of HLH can present at any age and infections also can be a triggering mechanism in such patients [3]. Criteria for the diagnosis of HLH proposed by the Histiocyte Society updated in 2004 [4] include clinical, laboratory, and histopathologic features. Fever and splenomegaly are the most common clinical signs, but hepatomegaly, lymphadenopathy, jaundice, and rash are also seen. Five different forms of familial HLH have been described based on defects in different genetic material and genes, including mutations present on chromosome arm 9q which include (FHL1), PRF1 (FHL2), UNC13D (MUNC13-4) (FHL3), STX11 (FHL4), and STXBP2 (MUNC18-2) (FHL5) [5].

In this case of a 39-year-old female who presented with fever and splenomegaly associated with cytopenias and raised biochemical markers, our initial working diagnosis was secondary HLH due to presence of Dengue infection and presenting age. However, genetic mutation for primary HLH was positive i.e. STXBP2 which has been associated with FHL5 [6]. The distinction is important as allogeneic bone marrow transplantation is the therapy of choice in patients with familial HLH as compared to sporadic HLH that has a better prognosis [7]. Histopathologically, hemophagocytosis is seen in bone marrow,
spleen, and lymph nodes and occasionally the central nervous system and skin. Activated macrophages may engulf erythrocytes, leukocytes, and platelets, their precursors, and cellular fragments [3].

On review of largest cohort of patients with FHL5 reported so far with 37 patients from a widespread ethnic origin, deficient NK-cell degranulation seems to be a uniform finding in all patients with FHL5. Compared with other FHL types, median age of diagnosis in the FHL5 cohort seems to be similar to that found in patients with FHL2 (3 months) and is slightly less than in patients with FHL3 (4 months). In patients with FHL4 the age of onset varies widely with a median of 14 months. The most frequent symptom seen in this cohort was severe diarrhea that often affected the patients before they developed classical HLH symptoms. Most of these patients needed parenteral feeding. Diarrhea persisted during HLH treatment; this study also described an increased bleeding tendency in some of the patients with FHL5 [8]. In our patient, STXBP2 mutation was positive categorizing her as FHL5. She had a rare presentation with respect to symptoms and presenting age triggered by infection. Early recognition and treatment with chemotherapeutic agents or bone marrow transplant may reduce mortality [3] as initiated this case where she responded well on prompt HLH directed therapy and has been planned for allogeneic stem cell transplant.

Conclusion

We present the rare case of primary HLH at age of 39 years, triggered by dengue infection with underlying STXBP2 homozygous splice-site mutation. Our patient responded well to HLH-94 protocol and has been planned for allogeneic stem cell transplant.

References

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