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Case Report

Hemophagocytic lymphohistiocytosis wildfire kindled by a tropical spark: a case report on HLH secondary to typhoid fever

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening disorder of immune regulation that can rapidly progress to end-organ damage and death. HLH is characterised by uncontrolled activation of cytotoxic T lymphocytes, natural killer cells, and macrophages that can lead to a cytokine storm. Primary HLH is a rare genetic disorder seen predominantly in the pediatric population, resulting from inherited defects in genes regulating immune function. Secondary HLH, on the other hand, can affect individuals of any age and is triggered by various conditions such as infections, autoimmune diseases, or malignancies. The problems in achieving successful outcomes are the variable clinical presentation and the lack of specificity of the clinical and laboratory findings. Clinical manifestations of HLH include persistent fever, splenomegaly, cytopenias, hyperferritinemia, and organ dysfunction. Prompt recognition and treatment, which may involve immunosuppressive therapy, chemotherapy, or hematopoietic stem cell transplantation, are crucial for improving outcomes. Here we present a case of Hemophagocytic lymphohistiocytosis triggered by Typhoid fever.

Keywords: Hemophagocytic Lymphohistiocytosis, Typhoid fever, T lymphocytes

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathologic immune activation which is characterised by clinical signs and symptoms of extreme inflammation.[1] It was first recognized as a familial immune dysregulatory disorder which affects the pediatric population, called "familial hemophagocytic reticulosis" in 1952. Later, HLH was described as both a familial disorder and as an acquired one, in association with infections, malignancies, or rheumatologic disorders.[2] The pathology of HLH includes an uncontrolled activation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages resulting in hypercytokinemia and multiple organ dysfunction.[1-3] Phagocytosis of blood cells and their precursors is a classical sign of hemophagocytic syndromes. Monocytes and macrophages are the predominant cells implicated in Hemophagocytosis.[4] HLH is an intriguing diagnosis and a multifaceted syndrome which often presents as a diagnostic dilemma to doctors across many specialities. Physicians should be aware of this, because early recognition may help in preventing irreversible organ damage and related mortality.[5] Various laboratory investigations can be employed to aid in diagnosing HLH and the same can also serve as biomarkers for monitoring disease activity.[6] Primary or familial HLH is mainly seen in the paediatric age group and is due to certain genetic defects in the immune system.

Secondary HLH is due to various triggers like infection, autoimmune conditions, and malignancy and can occur in any age group. In secondary HLH triggered by various factors, persistent fever, cytopenias, rising liver enzymes, and unresponsiveness to appropriate antimicrobials are the pointers that should raise an early suspicion.

However, since typical features of HLH like splenomegaly, cytopenias, and deranged liver function tests are present in tropical infections and sepsis as well, therefore the diagnosis of HLH secondary to infections is often delayed and even missed. As the characteristics of HLH may be mistakenly linked to infections themselves, it is imperative to maintain a high index of suspicion for HLH in cases of severe or deteriorating patients with infections or sepsis. (Particularly tropical infections like dengue, malaria, typhoid, and tuberculosis).[7] Here we present a case of secondary hemophagocytic lymphohistiocytosis (HLH) triggered by typhoid fever.

CASE REPORT

An 18-year-old female patient presented with complaints of generalised tiredness, fever with chills, vomiting, myalgia and loose stools for 6 days. Fever was high grade, intermittent in nature which was relieved with antipyretics, and was associated with multiple episodes of vomiting that was non-bilious and non-projectile in nature. She had initially consulted a local hospital and her symptoms were managed conservatively. Her condition worsened in the following 2 days, with recurrent episodes of fever, chills, myalgia, also had postural instability and increased side to side sway on walking, severe fatigue-confining her to bed. She was then brought to our institution.

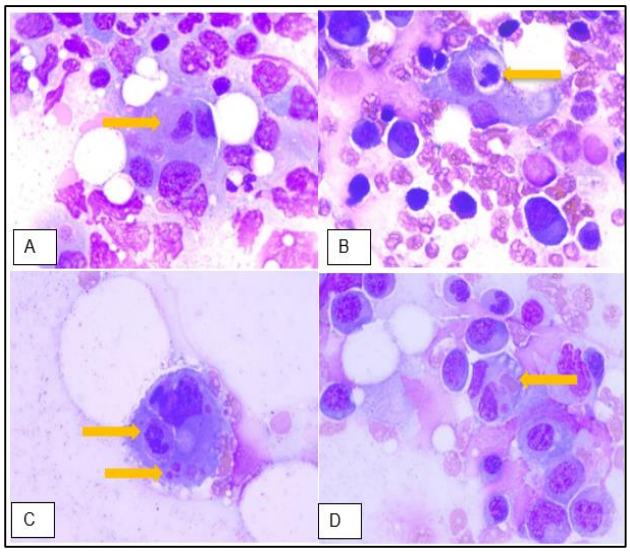

Figure 1: Cellular marrow with trilineage hematopoiesis, increased reticuloendothelial activity with evidence of hemophagocytosis (yellow arrow) - Bone marrow macrophages displaying phagocytosed myeloid precursors, neutrophils and platelets (A-C), red blood cell phagocytosis (D).

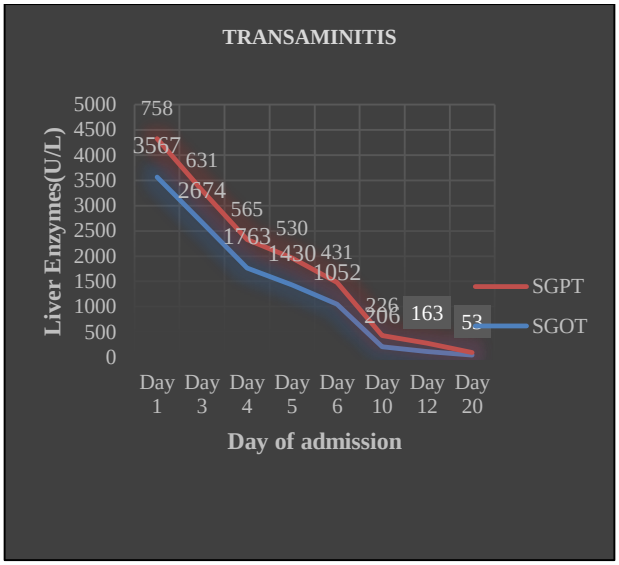

Figure 2: Trends in liver enzymes vs day of hospital stay.

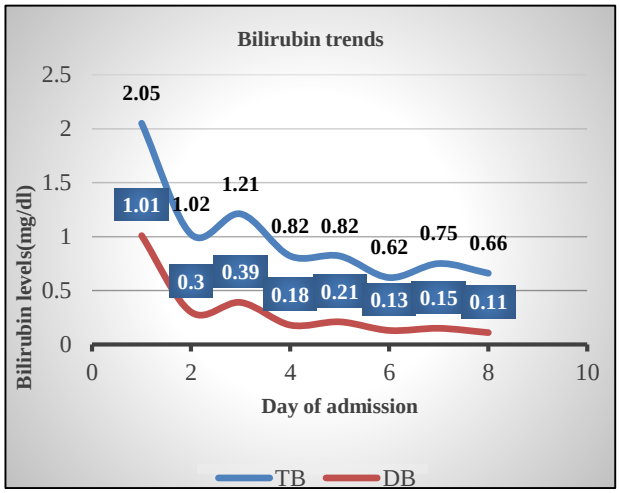

Figure 3: Decreasing hyperbilirubinemia over the course of treatment.

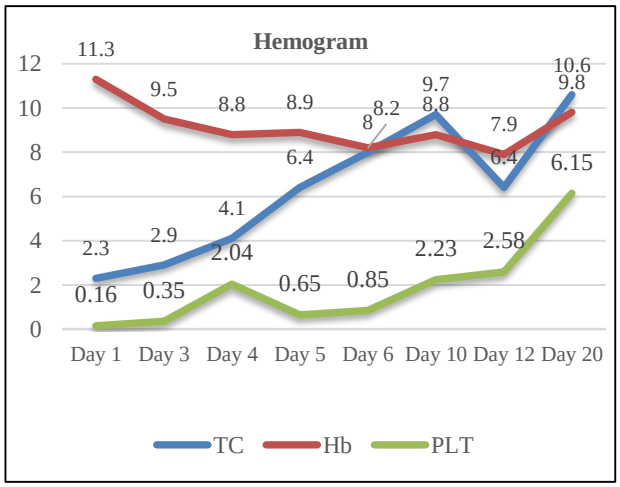

Figure 4: Trends in hemogram over the course of treatment.

Her blood workup showed Leucopenia (TLC: 2300, P/L/M: 85/8/4) Severe thrombocytopenia (Platelets:16000/cumm), deranged Liver function test with Hyperbilirubinemia (T/D/I:2.05/1.01/1.04) severe transaminitis (AST/ALT:3567/758) and hypoalbuminemia (2.66). Peripheral smear showed predominantly normocytic normochromic RBCs along with normocytic hypochromic RBCs with a few ovalocytes, microcytic hypochromic RBCs and occasional burr cells seen. There were no nRBC/RBC inclusions/hemoparasites seen with no increase in RBC fragmentation/schistocytes seen, WBC, leucopenia with mild neutropenia.

Absolute neutrophil count=1955/cumm, lymphopenia with absolute lymphocyte count=<500/cumm, Neutrophils show mild shift to left, no abnormal cells seen, Toxic changes noted, Platelets, marked thrombocytopenia, microscopic platelet count ranges from 30,000 to 45,000/cumm, Seen scattered singly, Few large platelets and occasional giant platelets seen. Her D-Dimer levels showed a marked elevation D-Dimer: >10000.

She was evaluated for renal loss of albumin which revealed positive results with (ACR: 147.42) and non-selective proteinuria (Urine protein: 4.81). A thorough infection work up was done and she tested negative for Malaria, Leptospira, Dengue, Brucella and Scrub typhus. Widal test showed positivity for Salmonella O and H antigen at (1:1280) and (1:2560) titres respectively. Progressive leukopenia (2470 -> 2300) and thrombocytopenia along with other aforementioned features elicited a strong clinical suspicion for the diagnosis of HLH following which a screening for HLH was done yielding positive results-hyperferritinemia (13678.9), hypertriglyceridemia (180) and low levels of fibrinogen (168). A bone marrow aspiration and biopsy were done which is shown in figures.

Bone marrow culture showed no evidence of microbial growth. An extensive genetic study including HLH Panel and Whole Exome sequencing were carried out to evaluate for primary HLH but revealed no clinically significant mutations. Given the severe transaminitis, investigation for autoimmune hepatitis was pursued, encompassing assessment for anti-smooth muscle antibodies and anti-liver kidney microsomal antibodies, both of which returned negative results.

Considering severe albuminuria and proteinuria, a comprehensive renal profile was performed, incorporating urine culture, complement levels, and lipid profile revealing C3 hypocomplementemia. In view of her neurological signs, a detailed neurological workup including CSF study and neuroimaging was done which were non-contributory. Nerve conduction studies of bilateral upper limbs and lower limbs were reported normal.

The CSF study revealed no significant abnormalities. In view of the critical nature of her illness and positive Widal results, she was treated with broad spectrum antibiotics (Inj. Meropenem and T. Azithromycin). She was commenced on intravenous immunoglobulin (IVIg) therapy following which she underwent continuous monitoring through daily CBC and LFT. Sequential evaluations of LFT indicated a discernible downward trend and CBC revealed a demonstrable improvement. There was a notable clinical amelioration in her condition in response to IVIg.

She developed a right IJV thrombosis secondary to catheter in situ and was initiated on parenteral anticoagulation which was later switched to oral anticoagulants (Apixaban).

Table 1: Showing the diagnostic criteria for HLH as per American histiocyte society.

S. no.	Criteria
1.	Molecular diagnosis consistent with HLH
	OR
2.	Should fulfil 5 of the 8 criteria listed below
	Fever ≥38.3°C
	Splenomegaly
	Cytopenia (affecting at least two of the three lineages in the peripheral blood
	Hypertriglyceridemia (≥265 mg/dl) and / or Hypofibrinogenemia (≤150 mg/dl)
	Hemophagocytosis in bone marrow or spleen or lymph nodes or liver
	Low or absent Natural Killer cells activity
	Ferritin ≥500 ng/ml
	Soluble CD 25 (soluble Interleukin 2 Receptor α) ≥2400 U/ml

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life-threatening disease characterised by excessive immune system activation. The diagnosis of HLH is challenging, and early diagnosis and prompt treatment are important for better outcomes.[8] It can be primary i.e., genetic or secondary to triggers like infections, malignancies, and autoimmune conditions.[7] Genetic hemophagocytic syndrome is divided into two subgroups depending on whether it is associated with immune deficiencies or genetic mutations. The familial

form of hemophagocytic lymphohistiocytosis was first described in 1952 and is estimated to occur in one out of 30 000–50 000 births. Familial hemophagocytic lymphohistiocytosis will manifest in the first year of life in 70–80% of cases.[9] Secondary HLH are often triggered by infections, systemic malignancies and autoimmune diseases. Unexplained cytopenias, elevated liver enzymes, and unresponsiveness to appropriate antibiotic therapy are the pointers that should raise an early suspicion.

However, since typical features of HLH like cytopenias, splenomegaly, and deranged liver function tests are usually present in tropical infections and sepsis as well, the diagnosis of HLH secondary to infections is often delayed and even missed. It is thus essential to keep a high index of suspicion for HLH in cases of complicated or deteriorating patients with infections or sepsis, because features of HLH can be falsely attributed to the infections themselves (particularly tropical infections like dengue, malaria, enteric fever, and tuberculosis). A late or missed diagnosis of HLH possess a high mortality risk.[7]

The American Histiocytic Society made a diagnostic criterion for HLH in 1994 which was modified in 2004. It is as depicted in Table 1.

The main aim of HLH therapy is to suppress the exaggerated immune response through the use of immunosuppressive agents. The 2004 treatment protocol which was formulated at the second international meeting of the Histiocyte Society recommends an 8-week induction therapy with corticosteroids, etoposide, and cyclosporine A as the backbone of HLH treatment. Intrathecal methotrexate therapy is only suggested in cases if there are progressive neurological symptoms after 2 weeks of therapy or if the abnormality in cerebrospinal fluid has not improved. 5-10 As these drugs can often produce various levels of end-organ dysfunction, it is important to monitor for drug toxicity in order to differentiate the treatment-related events from HLH progression.[11] Other treatments such as, intravenous immunoglobulin, and anti-thymocyte globulin are also used.[8]

Enteric fever is a common disease in tropical countries which is caused by salmonella typhi and paratyphi. Most of the time the patient presents with a history of continuous fever with gradual worsening of the laboratory parameters.[12]

Since, the association between typhoid fever and HLH are rare, this case emphasises the significance of taking uncommon aetiologies into account when diagnosing HLH. Particularly in endemic areas, the clinicians should be aware of this association to ensure early diagnosis and timely management.[8] Our patient demonstrated significant clinical response as early as day 2 of IVIG. Her cytopenias improved drastically and normalised on day 4 post admission.

CONCLUSION

This case emphasises the need for recognizing typhoid fever as a potential trigger for secondary hemophagocytic lymphohistiocytosis (HLH), a rare but life-threatening hyperinflammatory condition. Early suspicion and diagnosis of HLH in the context of prolonged fever, cytopenias, and organ dysfunction are crucial to prevent fatal outcomes. Identifying the underlying infection and prompt initiation of appropriate antimicrobial therapy, along with immunosuppressive treatment for HLH, can significantly improve patient outcomes. This case underscores the need for heightened clinical vigilance in patients with severe or atypical presentations of typhoid fever to facilitate timely identification and management of secondary HLH.

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