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RESEARCH ARTICLE

Typhoid Fever Complicating as Secondary Hemophagocytic Lymphohistiocytosis

G. Sree Theja*, B. Palani Kumar, M. Ilamaran and S. Pon Senthil Kumar

Department of General Medicine, Madurai Medical College, Madurai - 625020, Tamil Nadu, India; sreetheja.g@gmail.com

Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is an aggressive hematological disorder caused by an uncontrolled activation of Cytotoxic T-Cells (CTL), Natural Killer (NK) cells, and macrophages, leading to hyperinflammation and cytokine storm. It can be classified into either primary or secondary. Triggers like infections, malignancies, and autoimmune conditions can lead to secondary HLH. Viral infections (Epstein–Barr Virus (EBV), Cytomegalovirus (CMV), and parvovirus) are commonly known to cause HLH. Tropical infections like Typhoid are common in India but have infrequently been reported to cause HLH. HLH is a rare complication of typhoid fever. We report a case of an adolescent boy who presented with typhoid fever complicated by secondary HLH.

Keywords: Hemophagocytic Lymphohistiocytosis (HLH), *Salmonella typhi*, Typhoid Fever

1. Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a potentially fatal caused by uncontrolled immune activation. Fever, cytopenias, splenomegaly, hepatitis, hyperferritinemia, hypertriglyceridemia and hemophagocytosis are the key features of this syndrome. It can be primary or secondary. Primary (or familial) HLH is due to genetic defects in the immune system, mainly seen in the paediatric age group. Secondary HLH is due to triggers like infection, autoimmunity, and malignancy and can occur in any age group[1].

The diagnosis of HLH secondary to infections is often delayed, and even missed, as the typical features of HLH, like leukopenia, thrombocytopenia, splenomegaly, and deranged liver function tests, are also present in tropical infections and sepsis[2].

Typhoid fever, also called enteric fever, is a common tropical infection in India transmitted via contaminated food and water. Enteric fever is caused by *Salmonella* serotypes – *S. Typhi* and *S. Paratyphi* A, B, C. Complications of typhoid include gastrointestinal bleeding, disseminated intravascular coagulation, hepatitis, and nephritis and neurological complications like encephalopathy, GBS, meningitis and delirium. Hemophagocytic lymphohistiocytosis is a rare but serious complication of typhoid fever, and so far, only a few cases have been reported[3]. In this article, we present a case of secondary HLH due to typhoid fever in an adolescent male.

2. Aims and Objectives

To present the case report of a rare complication of typhoid fever presenting as Hemophagocytic Lymphohistiocytosis (HLH)

3. Review of Literature

Hemophagocytic Lymphohistiocytosis (HLH) is characterised by an uncontrolled hyper-inflammatory state and can be triggered by infections, autoimmune diseases, malignancies (called secondary HLH), or genetic defects in the immune system (called primary

*Author for correspondence

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or familial HLH)[4]. Clinical (fever, hepatosplenomegaly) and laboratory manifestations (cytopenias, hemophagocytosis, hepatitis, hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia) of HLH are due to the pathophysiology involving both high cytokine levels (interleukin 2, interleukin 6, interferon-gamma, and tumour necrosis factor-alpha and activated histiocytes (macrophages) infiltrating the tissues[5].

Enteric fever includes typhoid fever (caused by *Salmonella typhi*) and paratyphoid fever (caused by *S. paratyphi A, B, and C*). In any patient with prolonged fever, abdominal symptoms (pain, diarrhoea, or constipation), a coated tongue, and hepatosplenomegaly, particularly in endemic areas, typhoid fever should be suspected. Early physical findings include rash (rose spots), hepatosplenomegaly, epistaxis, relative bradycardia and high fever[6]. It can present with a spectrum of non-specific symptoms like malaise, arthralgia, anorexia, headache, and rash to severe or complicated disease with continuing fever, anaemia, weight loss, gastrointestinal bleeding, encephalopathy, disseminated intravascular coagulation, hepatitis, nephritis and neurological complications like GBS, meningitis and delirium[7].

In the case presented, clinical features of fever, abdominal symptoms, relative bradycardia, and hepatosplenomegaly raised the suspicion of enteric fever. Findings on CT imaging of the abdomen guided the diagnosis, Typhidot positive further supported this diagnosis, and a blood culture growing *Salmonella typhi* confirmed the diagnosis.

However, unlike the usual insidious deterioration of patients with untreated enteric fever, despite broad-spectrum antibiotics, our patient started deteriorating rapidly. He was having high-spiking fevers, worsening cytopenias, hepatitis, and ARDS. Thus, HLH was suspected. Further investigations revealed hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia, and bone marrow aspirates showed hemophagocytes. A high H-score satisfied the Modified 2009 HLH criteria, favouring the diagnosis of HLH (Table 2).

4. Materials and Methods

4.1 Case presentation

A 16 year old boy presented with complaints of fever for 21 days, loose stools for 15 days, abdominal pain for 1week and vomiting for 5 days. Fever was high-grade, associated with chills, aggravated during night and temporarily relieved with paracetomol tablet. He had watery green coloured loose stools 4-5 episodes per day without blood or mucus. Abdominal pain was dull aching, around umbilical region without any aggravating or relieving factors. He had malaise, decreased appetite with nausea and vomiting for 5 days. He had been consuming food at his hostel mess for last 2 months. He had not noticed any rash, swelling or recent weight loss. He denied any travel history or similar illness in his friends and family. He had no history of tuberculosis in the past and also in the family. He got treated with I.V antibiotics in a nearby hospital, as the patient's condition worsened further, he was referred to our hospital for further management.

On examination, he was drowsy, irritable, and partly obeying commands. He was febrile (100.8°F), normotensive (100/60 mm Hg), had a pulse rate of 86 bpm (relative bradycardia), regular, a respiratory rate of 22 breaths per minute, and normal O_2 saturation. There was no pallor, icterus, clubbing, lymphadenopathy, or oedema. There was no rash on the skin or oral mucosal lesion. The abdomen was moving with respiration equally in all quadrants; the spleen was palpable, which is soft and non-tender (Hackett's grade 1 splenomegaly). Liver was palpable two-finger breaths below the subcostal margin in the midclavicular line. Neck rigidity was absent. The rest of the systemic examination was unremarkable. Our main differential diagnoses included enteric fever, acute gastroenteritis, abdominal tuberculosis, pancreatitis, acute appendicitis, dengue fever, and malaria.

On presentation, the patient was empirically started on ceftriaxone 1gm Intravenously (IV) twice daily (BD). An ultrasonogram of the abdomen was suggestive of hepatosplenomegaly with a thickened ileocecal junction and mesenteric adenitis without any features of appendicitis. Peripheral smear for the malarial parasite, RDT malarial antigen was negative, and dengue NS1 antigen/IgM were negative, ruling out dengue fever and malaria. Pancreatitis was ruled out with normal Serum amylase and lipase (repeated at at 48-hour interval). The chest X-ray did not show any significant abnormalities. The patient continued to have fever spikes with a haemogram suggestive of deteriorating cytopenias even after 72 hours.

Table 1. A Timeline of laboratory investigations and clinical trends relevant to the case on different days after admission

Patient parameter	Reference range	Day1	Day 3	Day5	Day6	Day 7	Day 12
Hb(gm/dl)	12 – 14.5	10.8	9.3	8.7	7.8	7.5	9.8
TLC(/cumm)	4,000- 11,000	3,500	3,100	2,200	2,000	3,000	6,200
Platlets(/cumm)	1,50000-4,50000	83,000	76,000	47,000	65,000	80,000	1,50,000
Total bilirubin(mg/dl)	< 1.0	0.5	1.2	1.5	1.3	1.2	1.1
AST (U/L)	10 - 45	51	49	400	270	250	20
ALT (U/L)	10 - 45	53	58	195	175	148	30
Serum creatinine (mg/dl)	0.5 -1.2	0.6	0.8	1.0	1.1	1.0	1.0
Fever spikes		present	present	present	present	present	absent
Oxygen requirement		No	no	yes	yes	yes	no

Therefore, on day three of admission, antibiotics were escalated to intravenous meropenem 1 gm three times daily (TDS). Blood, urine and stool cultures were awaited. Due to persistent fever, worsening cytopenias, and elevated liver enzymes, we suspected HLH and investigated with serum ferritin, fasting triglycerides, serum fibrinogen, as well as a bone marrow aspiration and biopsy to rule out other causes of pancytopenia with persistent fever, like leukaemia (Table 2). Serum IgM srub typhus, leptospira and Viral markers (hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibodies, HIV antibodies, hepatitis A virus (HAV) IgM, and hepatitis E virus (HEV) IgM) were negative. ECHO showed normal study. CSF analysis was normal. CSF ADA – 1U/L. qCRP- 62.6, ESR -30mm/hr. Normal stool examination.

On day five of admission, the patient started complaining of breathing difficulty with Arterial Blood Gas (ABG) suggestive of hypoxemia, for which he was started on O_2 therapy with a nasal mask (6 L/min) and shifted to the intensive medical care unit.

CT of the thorax and abdomen done urgently revealed patches of ground glass opacities in bilateral lung fields with a few non-necrotic mediastinal nodes, hepatosplenomegaly, thickened ileocecal junction with multiple enlarged non-necrotic and a few necrotic mesenteric lymph nodes in the right iliac fossa, peripancreatic region, mild ascites, and bilateral pleural effusion. Hemophagocytosis was demonstrated on bone marrow aspirate, he was also started on dexamethasone (16 mg IV OD for HLH) on day five itself. Typhidot was positive. Stool culture grew commensals. Sputum and urine were negative for organisms. Sputum AFB and CBNAAT were negative. Blood culture was reported to have isolated *Salmonella typhi*, sensitive to gentamycin, amikacin, and meropenem. So, Meropenem was continued, but still the patient didn't improve so inj. Dexamethasone 8mg iv OD was added. Patient drastically improved clinically with normalising lab parameters, and Meropenem continued for 14 days with tapering of steroids.

Therefore, we arrived at the diagnosis of HLH (Table 2) with acute respiratory distress syndrome (multiorgan dysfunction) secondary to typhoid fever.

5. Results and Observation

Patients were diagnosed with Typhoid fever complicated by secondary HLH. Then he was treated with inj. Meropenem 1gm iv TDS, but still the patient didn't improve, so inj. Dexamethasone 8mg iv OD was added. Patient drastically improved clinically with normalising lab parameters. Treatment was continued with Meropenem iv antibiotics for 14 days, and steroids were tapered off, and patient was discharged.

6. Discussion

Hemophagocytic Lymphohistiocytosis (HLH) is a potentially fatal hyper-inflammatory state that is caused by a highly activated but ineffective immune system. It can be primary or secondary to triggers like infections, malignancies, and autoimmune conditions. When it comes to secondary HLH triggered by infections, persistent fever, cytopenias, rising liver enzymes, with multiorgan dysfunction and unresponsiveness

Table 2. Patient's parameters compared to modified 2009 HLH criteria

Modified 2009 HLH criteria	Patient parameters
At least three of the following	
Fever	**yes**
Splenomegaly	**yes**
Cytopenias in atleast 2 cell lines	
Hemoglobin < 9 gm%	**Yes (8.7g/%)**
Platelet < 100000/cumm	**47,000**
Absolute neutrophil count < 1000/cumm	**Yes (880/cumm)**
Hepatitis	**yes**
At least one of the following	
Ferritin elevation (> 500ng/ml)	**yes (> 1000ng/ml)**
Elevated soluble CD25	Not available
Hemophagocytosis	**yes**
Low/absent NK cell activity	Not available
Other supportive features (not required)	
Hypertriglyceridemia (fasting > 265 mg/dl)	**Yes (446mg/dl)**
Hypofibrinogenemia (< 1500mg / dl)	**Yes (260mg/dl)**
Hyponatremia	**Yes (124meq/dl)**

to appropriate antimicrobials should raise an early suspicion. The diagnosis of HLH secondary to infections is often delayed, and even missed as the typical features of HLH, like leukopenia, thrombocytopenia, splenomegaly, and deranged liver function tests, are also present in tropical infections and sepsis[2]. Therefore, a high index of suspicion for HLH is required in cases of complicated or deteriorating patients with infections or sepsis, as features of HLH might be falsely attributed to infections themselves (particularly tropical infections like dengue, malaria, enteric fever, and tuberculosis). A late or missed diagnosis of HLH results in poor outcomes[8].

The HLH 2004 criteria (and the more recent Modified HLH 2009 criteria) can be used to arrive at a diagnosis and start early treatment. In addition to these, the H-score with higher sensitivity (90%) is a validated criteria score to estimate the probability of HLH. It consists of graded clinical and laboratory parameters(Table 2)[9].

The treatment of HLH secondary to infections in adults should be individualised and tailored depending on the clinical condition of the patient. As the protocols which have immunosuppressive regimens consisting of multiple elements like corticosteroids, cyclosporine, etoposide, etc. were developed for primary HLH in the paediatric age group[9]. Resolution of HLH secondary to infections with appropriate treatment of the infectious trigger alone (without any immunosuppression) has frequently been seen. The role of corticosteroids in treating secondary HLH is controversial. However, Corticosteroids (dexamethasone) with or without etoposide may be used if clinical conditions and organ function deteriorate despite infection-directed treatment. Secondary infections and secondary malignancy are associated with use of Etoposide[10,11]. Thus, treatment of HLH secondary to infections like infection-directed treatment or immunosuppression is individualised and added based on clinical judgement and organ function[12].

7. Summary and Conclusion

Hemophagocytic Lymphohistiocytosis (HLH) is a rare and serious complication of typhoid fever. A high index of suspicion is required in patients with tropical infections like enteric fever, tuberculosis, malaria, dengue, etc., that worsen despite appropriate treatment, as late diagnosis is associated with multi-organ dysfunction and greater mortality. Early diagnosis and treatment prevent catastrophic outcomes and death. The decision to add immunosuppression in treating infection-related HLH has to be tailored according to clinical conditions and organ dysfunction.

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