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Secondary Hemophagocytic Lymphohistiocytosis In Typhoid Fever: Case Report

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ABSTRACT

Background: In poor countries, typhoid fever is a major cause of fever. The illness can vary in severity from an uncomplicated febrile illness to sepsis and complications like hemophagocytic lymphohistiocytosis (HLH), which affects multiple organs. A delay in diagnosis is frequently the biggest obstacle to a good outcome due to the rarity of this syndrome. ***Case:*** A 38-year-old male was admitted with complaints of persistent intermittent fever for three weeks. Other complaints were maculopapular rashes, epistaxis, black-colored stools, abdominal pain, nausea, vomiting, fatigue, and decreased appetite. He was transferred to our hospital due to progressive clinical deterioration. On physical examination, he was pale, with a temperature was 39.5C, a dry tongue with petechial spots at the root of the tongue, and some maculopapular rash of the entire body. There was splenomegaly. Laboratory investigations showed pancytopenia. IgM salmonella typhi was positive. A liver function test revealed transaminitis. Additional laboratory tests showed hypertriglyceridemia, hyperferritinemia and hyponatremia. USG's abdomen showed splenomegaly. Patient possibility of secondary HLH was considered and investigated accordingly. He was given packed red blood cells, platelets transfusion, and a high dose of methylprednisolone orally. He showed dramatic improvement, complete blood count (CBC) normalized on day 7 with complete recovery on follow-up. ***Conclusion:*** We report a hemophagocytic lymphohistiocytosis in typhoid fever with persistent intermittent fever. Based on our case, early diagnosis and prompt treatment are critical to a successful patient's recovery.

Keywords: typhoid fever; hemophagocytic lymphohistiocytosis; pancytopenia; hyperferritinemia

INTRODUCTION

In developing countries, typhoid fever continues to be a major source of fever due to the Salmonella typhi bacteria.[1,2] The severity of the condition can vary from a simple febrile sickness to sepsis and complications like hemophagocytic lymphohistiocytosis (HLH), which affects multiple organs.[1,3] HLH is an extremely rare, underdiagnosed, life-threatening condition that often causes multiorgan failure and mortality as a result of immune dysregulation.[4]

HLH could be linked to genetic (familial) disorders or secondary causes. Familial HLH is rare. In adults, secondary causes of HLH include infection, autoimmune disease, and cancer.[5,6] The disease presentation is caused by the immune system's inability to regulate the vast release of inflammatory cytokines (cytokine storm) into circulation. The most common impediment to a good result is a delay in identification, which is challenging due to the scarcity of this condition.[3,6] Identifying can be difficult because of similarities in signs and symptoms with other illnesses. Therefore, early detection and prompt treatment initiation are vital for minimizing the disease's significant mortality rate.[4,5]

CASE

A 38-year-old male was admitted with complaints of persistent intermittent fever three weeks ago. He also had maculopapular rashes all over the body, epistaxis, black-colored stools, abdominal pain, nausea, vomiting, fatigue, and decreased appetite. He was transferred to our hospital due to progressive clinical deterioration, including persistent fever. The patient was diagnosed with typhoid fever and had a history of intravenous antibiotics prior to his arrival at our hospital. He denied consuming raw or outside-prepared food in addition to animal contact. No other family members or close acquaintances experienced similar symptoms. There were no reports of comorbidities such as diabetes, obesity, additional infections, or alcoholism. He was celibate from alcohol and did not smoke; he denied any history of intravenous drug abuse, blood transfusions, sexual promiscuity, or hepatitis infection.

On physical examination showed, his vital sign showed blood pressure 120/70 mmHg, heart rate 105/min, respiratory rate 22/min, SPO 97% on room air, and a temperature was 39.5C. A general physical examination showed a dry tongue with petechial spots at the root of the tongue. There was splenomegaly without lymphadenopathy, hepatomegaly, or abdominal tenderness. He had some maculopapular rash on the entire body. Examination of other systems was normal.

Initial laboratory investigations in our hospital (day 21) completed blood count (CBC) showed WBC 30.61 103/uL, HGB 9.8 g/dl, MCV 85.4 fL, MCH 29.6 pg, platelet count 20 103/uL.

The widal test was 1/320, and IgM salmonella typhi was positive, while HIV was non-reactive, and other infectious markers anti-HAV, HBsAg, anti-HCV, anti HEV, and serologist dengue were negative. During treatment, WBC continued to decrease without clinical improvement. Then on the 28th day of fever, the laboratory results showed pancytopenia, WBC 1.59 10^3/uL, HGB 7.7 g/dL, and PLT 13 10^3/uL. Liver function test revealed transaminitis SGOT 113 IU/L, SGPT 108 IU/L, bilirubin total 2.29 mg/dL, bilirubin indirect 0.94 mg/dl, bilirubin direct 1.35 mg/dl. Additional laboratory tests showed hypertriglyceridemia (842 mg/dL) and hyperferritinemia (>1000 ng/mL). Serum sodium and potassium showed 130 mmol/l and 4.6 mmol/l. Profil renal function and albumin were normal.

Abdominal USG showed splenomegaly. Peripheral blood film did not show any significant findings. Chest X-ray was normal.

At first, he was treated as typhoid fever with symptomatic treatment and antibiotics intravenous such as ceftriaxone, ciprofloxacin, and ampicillin-sulbactam. In addition, he was also given meropenem. However, there was no discernible improvement in the patient's clinical condition; consequently, the likelihood of secondary HLH was considered and evaluated. He was given packed red blood cells, platelets transfusion, and high-dose of methylprednisolone oral 16 mg 3 times a day. His complete blood count (CBC) returned to normal on day seven, and he made a full recovery by the time the follow-up appointment came around.

TABLE 1: laboratory investigations.

Parameter	Day 7	Day 10	Day 14	Day 21	Day 24	Day 28	Day 32	Day 35
WBC (10^3/uL)	9.74	42.7	41.0	30.6	8.90	1.59	3.09	5.6
HGB (g/dL)	10.4	10.6	10.2	9.8	8.90	7.7	9.9	9.8
PLT (10^3/uL)	50	17	20	20	20	13	24	145
SGOT (IU/L)	79					113		
SGPT (IU/L)	84					108		
Bil total (mg/dL)						2.29		
Bil indirect (mg/dL)						0.94		
Bil direct (mg/dL)						1.35		
Ferritin (ng/mL)						>1000		
Trigliserida(mg/dL)						842		
Serum sodium (mmol/l)						130		
Serum potassium (mmol/l)						4.6		
Ureum (mg/dl)						60		
Serum creatinine (mg/dl)						1.19		
Albumin (g/dL)						3.92		

DISCUSSION

Salmonella typhi-caused typhoid fever can result in severe complications in up to 10% of patients, including gastrointestinal bleeding, intestinal perforation, hepatitis, pancreatitis, typhoid encephalopathy, DIC, HUS, endocarditis, pneumonia, and infrequently hemophagocytic lymphohistiocytosis.[1,6] HLH is a highly uncommon, underdiagnosed, potentially fatal condition frequently resulting in multiorgan failure and death due to immune dysregulation. It may be primary HLH, which is supposed to be an inherited disorder affecting infants and children. Secondary HLH is associated with infections, autoimmune diseases, or cancer and is typically diagnosed in adolescents and adults. Infections are potential triggers for primary and secondary HLH cases.[5,7] Viruses are the most common cause, but many other bacterial, fungal, and tropical infections have been associated; the prevalence of These include viral infections (29%), other infections (20%), malignancies (27%), rheumatologic disorders (7%), and immune deficiency syndromes (6%).[3] Typhoid fever is an endemic tropical disease. HLH is infrequently reported as a complication of typhoid. In complicated typhoid fever, the possibility of secondary HLH must be considered.[1] In the presented case, a patient was an adult male aged about thirty. He was diagnosed with typhoid fever, caused by a widal test of 1/320 and positive IgM salmonella typhi.

The exact pathogenesis of secondary HLH has yet to be understood entirely. The pathophysiology of infection-associated HLH following infection with nonviral organisms may indeed entail high levels of activating cytokines produced by the host's lymphocytes and monocytes.[8,9] The relative prevalence of association between infectious organisms (e.g., Salmonella Typhi, Mycobacterium tuberculosis, and Leishmania sp.) that induce a TH1 immune response and reactive hemophagocytic syndromes may imply that the syndromes are caused by an improperly regulated or inappropriate TH1 response to intracellular pathogens. It is responsible for the production of proinflammatory cytokines, INF-, which activate macrophages and mediate the production of IL-6, TNF- , plasminogen activator, and ferritin.[6,8]

The pathogenesis of HLH is related to all of the manifestation and test results. HLH is a generalized disease, most often presenting as fever (90-100%), maculopapular or petechial rash (10-60%), as was in our case. The cause of fever is inflammatory activity.[8] Cytopenia, splenomegaly, hypertriglyceridemia, and bone marrow suggestive of hemophagocytosis may directly result from infiltration by lymphocytes and macrophages and direct haemophagocytosis. Elevated ferritin has been demonstrated to be 96% specific and 90% sensitive for HLH.

Despite this, a prolonged non-responsive clinical profile and decrease in platelet count without any other plausible reason led us to explore further. [3,8,9]

HLH is usually diagnosed using both molecular and clinical criteria by Histiocyte Society's HLH-2004.[3,4] Nowadays, alternative modified measures 2009 have been proposed. It might be more clinically optimal to detect HLH in the adult population earlier.[5,10]

Our reported cases are defined as HLH based on both of these two criteria. In our patient, fever, cytopenia and splenomegaly were the initial indicators. In addition, elevated ferritin, hypertriglyceridemia, transaminitis and hyponatremia suggested the diagnosis later on. The delay in diagnosis was likely due to the disease's extreme rarity.

TABLE 2: Criteria of diagnosis.

HLH 2004 Criteria	Modified 2009 HLH Criteria
At least five of the following • Fever >38.5 • Splenomegaly • Cytopenia in at least two lines with HGB <90 g/L, neutrophil count < 100 x 10^9 • /L and PLT < 1 x 10^9/L • Hyperferritinemia >500µg/L • Hypofibrinogenemia <1,5 g/L or hypertriglyceridemia >3 mmol/L • High soluble CD25 >2400 U/ml • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Low or absent NK cell activity	At least three of the following • Fever • Splenomegaly • Cytopenia • Hepatitis At least one of the following • Ferritin elevation • Elevated soluble CD25 • Hemophagocytosis in bone marrow, spleen, or lymph nodes Other supportive feature • Hypertriglyceridemia, hypofibrinogenemia, hyponatremia

Identifying, providing supportive care, and treating the underlying cause of HLH may be the most crucial intervention for these patients. However, severely ailing or deteriorating patients may require steroid or immunomodulatory therapy. Most patients treated for the underlying cause will recover between 60-70%, sufficient to neutralize the immune activation trigger and suppress the inflammatory cytokine onslaught.[5,11] Based on the guidelines from the Histiocytic society HLH 2004, a combination of cyclosporine, corticosteroids, etoposide, and intrathecal methotrexate can be used as a specific immunomodulatory therapy for HLH. IvIg is an option to treat secondary HLH since it is as efficacious as the HLH 2004 guidlines with less adverse effects. The use of corticosteroids is the most common form of treatment for HLH.[4,5,8]

Treatment of the underlying condition, as well as quick steroid treatment, are life-saving in this condition. In our instance, a combination of sequential antibiotics was most likely used to treat the underlying infection. In this instance, steroid therapy was deemed the most suitable treatment option.[4,5,8] We adopted the strategy of using a steroid to reduce inflammation and hypercytokinemia. The patient responded to corticosteroids, and pancytopenia improved, fever resolved, transaminitis enhanced, and ferritin dropped. Both the diagnostic assessment and the therapeutic management of these patients are ultimately hampered due to the need for more clarity surrounding the underlying mechanisms present in the vast majority of patients with secondary HLH.[3,12] In this case, continuous monitoring, logical diagnostic planning, and prompt intervention were instrumental in preventing a poor result.

CONCLUSION

Typhoid fever manifests as a serious febrile illness accompanied by cytopenias, which may indicate secondary HLH. It is an uncommon and unique case. We report a patient with secondary HLH in typhoid fever, whose pathophysiology is still unknown. This complication is frequently missed and consequently has a poor prognosis.

Recognizing the disease is necessary for immediate identification and therapy with the appropriate antibiotics to avert serious complications and death risk. As a first-line intervention, treating the etiology of HLH would be an efficient way to restrict the disease's progression. Therefore, early diagnosis and treatment of HLH are crucial for preventing mortality.

Competing interests
No competing interests were disclosed.

Conflict of interest
The authors declare no conflict of interest, financial or otherwise.

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Ethical approval
The patient has given permission and informed consent to publish this case report.

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