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Case report

Enteric fever complicated by hemophagocytic lymphohistiocytosis: an unusual case report

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Abstract

We report the case of a 15-year-old girl with enteric fever, a common infectious disease in developing countries, who presented with multiple unusual complications including pancreatitis, myocarditis and thrombocytopenia in the first week and who developed secondary hemophagocytic lymphohistiocytosis, a clinical masquerade, secondary to *Salmonella typhi* infection. The patient recovered completely with appropriate antibiotics, intravenous steroids and supportive treatment, with complete resolution of the symptoms.

Keywords

Enteric fever, pancreatitis, myocarditis, hemophagocytic lymphohistiocytosis.

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Introduction

Enteric fever, caused by *Salmonella typhi*, a Gram-negative bacterium, is known to have a diverse clinical manifestation with 10-15% of patients

developing complications. Common complications reported are neuropsychiatric manifestations (2-40%), gastrointestinal bleeding (10%), and intestinal perforation (1-3%) [1]. Uncommon complications reported in various studies are myocarditis, acute pancreatitis, splenic abscess, osteomyelitis, cutaneous vasculitis, and many more. There are very few case reports of hemophagocytic lymphohistiocytosis (HLH) secondary to enteric fever in children. HLH occurs due to an overwhelming immune response; although rare, it is a life-threatening condition. HLH is primary when caused by an underlying genetic mutation or secondary when cases are incited by infection, malignancies, and autoimmune diseases [2-7]. We report the unraveling of twists and turns in the course of a disease, in a young adolescent girl with typhoid fever, who developed multiple uncommon complications including pancreatitis, myocarditis, and HLH, a clinical masquerader. Judicious use of corticosteroids and rational antibiotics resulted in accomplishing a favourable outcome.

Case report

A 15-year-old girl was brought to the hospital with complaints of fever of 5 days duration, associated with chills and rigors, diffuse painful abdomen, vomiting which was nonprojectile and nonbilious, and loose stools. The loose stools were watery, not blood-stained. The girl was residing in a hostel in a rural area where there had been an outbreak of enteric fever for a few days. At admission, the child was febrile (102°F) with a heart rate of 118/min, respiratory rate of 26/min, and blood pressure of 130/80 mmHg. On physical examination, she was conscious and oriented but irritable, her throat was congested and she had conjunctival suffusion. There was no icterus, pallor, significant lymphadenopathy, or edema. Abdominal examination revealed tender hepatomegaly 3 cm below the right costal margin, soft with rounded borders with a liver span of 12 cm, and splenomegaly 1 cm below the left costal margin, non-tender, soft in consistency. There was no evidence of free fluid. Examination of other systems was unremarkable. A provisional diagnosis of enteric fever was considered. Initial investigations revealed Hb of 13.9 gm%, total count (TC) of 8,090 cells per mm^3 with neutrophilic predominance and eosinopenia, and platelet count of 82,000 per mm^3. The Widal tube agglutination test was positive with TO and TH titers of 1 in 320; dengue NS1 and IgM were negative. Chest X-ray was normal with no evidence of pleural effusion. Although thrombocytopenia was present, in view of the positive Widal test and dengue serology being negative, enteric fever was the diagnosis. Ceftriaxone was started for enteric fever with pending blood culture along with paracetamol, intravenous fluids, and other supportive treatment.

On day 2 after admission, the child developed severe abdominal pain, greatest in the right hypochondrium and epigastric region, with an increase in the frequency of loose stools and melena. Repeat investigations revealed Hb of 13.3 gm%, WBC count of 5,680 cells per mm^3, the platelet count had dropped to 28,000 cells per mm^3, and both PT and ApTT were significantly prolonged. One unit of FFP and 2 units of platelets were transfused.

On day 3 after admission, high fever spikes continued with worsening of abdominal pain but no further melena. Investigations showed Hb of 11.3 gm%, WBC count of 2,450, platelets 12,000 per mm^3, and PCV of 32.1%. Amylase (275 U/L) and lipase (610 U/L) were elevated more than thrice the normal levels, suggestive of acute pancreatitis. Liver function tests (LFT) and renal function tests (RFT) were within normal limits. USG abdomen showed a bulky and hyperechoic proximal body of the pancreas and bilateral minimal pleural effusion. Blood culture showed *Salmonella typhi* growth sensitive to ceftriaxone. Diagnosis of complicated enteric fever with pancreatitis was made. Intravenous meropenem was added in view of persistent fever spikes associated with pancreatitis. Gastroenterologist and pediatric surgery opinions were sought.

On day 5 after admission, the child had persistent fever with persistent tachycardia of 150 per min with S3 gallop and muffling of heart sounds, with hepatomegaly increased to 5 cm below the right costal margin and tachypnoea. Echocardiography showed global hypokinesia of the left ventricle with ejection fraction of 35% with trace pericardial effusion. CKMB was normal but troponin T was elevated. Myocarditis was considered and the patient was started on digoxin, enalapril and furosemide, with spironolactone, following the cardiologist's guidance. The provisional diagnosis of complicated enteric fever with pancreatitis and myocarditis was considered. Investigations on day 5 revealed Hb of 10.6 gm%, TC of 1,650, and platelets 18,000

per mm^3, with PT INR of 1.46. Secondary HLH was suspected in view of the persistent fever lasting more than 7 days, splenomegaly, and bicytopenia. Relevant investigations were performed which revealed ESR of 85 mm/h, CRP of 60 mg/L, hyperferritinemia with ferritin level more than 5,905 ng/mL and hypertriglyceridemia of 493 mg/dL. ANA was negative. Bone marrow biopsy to look for hemophagocytes was deferred as the patient was clinically unstable. A diagnosis of complicated enteric fever with pancreatitis, myocarditis, and secondary HLH was made. A rheumatologist's opinion was sought and the patient was started on parenteral dexamethasone at 10 mg/m^2/day divided into 3 doses as per the HLH-2004 protocol. Repeat echocardiography on day 7 showed akinetic apical segments and hyperkinetic basal segments and an ejection fraction of 45%. Cardiac MRI was suggestive of myocarditis; the cardiologist advised continuing digoxin, enalapril, and parenteral dexamethasone.

Subsequently, the child improved clinically and symptomatically with an increase in TCs, platelet counts, and a decrease in ESR, CRP, and ferritin levels with normal PT and ApTT. Amylase and lipase levels decreased to normal. On day 5 of dexamethasone therapy and day 11 after admission, intravenous dexamethasone was changed to oral prednisolone (1 mg/kg/day). Repeat echocardiography on day 12 after admission showed normal biventricular function with an ejection fraction of 60%.

Parenteral ceftriaxone was given for 14 days and parenteral meropenem was given for 10 days. With the resolution of the fever, abdominal pain, hepatosplenomegaly, and cytopenia, and decrease in triglyceride levels and ferritin to the normal range, the patient was discharged on oral prednisolone with plan to taper steroids on follow-up. On follow-up examination, the child did not have any new signs or symptoms; prednisolone was tapered, and stopped after 8 weeks.

Discussion

Enteric fever is caused by Gram-negative bacteria, either *Salmonella typhi* or *Salmonella paratyphi*. *Salmonella typhi*, which belongs to the genus *Salmonella*, subspecies *enterica* and serotype *typhi*, is still a cause of serious illness requiring hospitalisation, with significant morbidity among children in developing countries, even in the 21st century [8, 9].

The most common age group susceptible to enteric fever and its complications is 5 to 10 years [1]. In a meta-analysis done by Britto et al., the prevalence of enteric fever was shown to be maximal between the ages of 5 and 9 years, followed by 10 to 14 years and then under 5-year-old children [10]. Almost one-third of cases of enteric fever requiring hospital admission may develop complications. The spectrum of clinical presentation of acute enteric fever is diverse, with complications occurring in 10-15% of patients [1]. The common complications documented are neuropsychiatric manifestations (2-40%), gastrointestinal bleeding (10%) and intestinal perforation (1-3%) [1]. Less common complications reported in the literature are myocarditis, acute pancreatitis, splenic abscess, osteomyelitis and cutaneous vasculitis [10].

In a study by Malik, complications reported, in the order of frequency, were anicteric hepatitis, bone marrow suppression, paralytic ileus, myocarditis, psychosis, cholecystitis, osteomyelitis, peritonitis, pneumonia, haemolysis, and syndrome of inappropriate release of antidiuretic hormone (SIADH) [8].

In a study published by Alshok and Alamidi, abdominal complaints (12.3%) were the most common complications of enteric fever [11]. In another study, by Esmailpour et al., 4.6% of cases had cardiac complications such as pericarditis, myocarditis and pulmonary emboli [12]. Disseminated intravascular coagulation (DIC) was more common in infants, with increased risk of mortality, in a study done by Bhutta [13]. Ascites [10, 14, 15], enteric hepatitis [10, 16, 17] and central nervous system complications [10, 18] have been reported in various studies.

In this case, the child presented with thrombocytopenia at the time of admission, on the fifth day of fever. Although thrombocytopenia is not very commonly reported in typhoid fever, literature search reveals an incidence of around 26% in children and it also has been considered to be an indicator of severity in typhoid fever, heralding the development of further complications [19]. Among infections, in terms of incidence enteric fever ranks fifth after malaria, dengue fever, acute human immunodeficiency virus (HIV) infection and infectious mononucleosis (EBV). The pathophysiology, clinical course and management of thrombocytopenia in enteric fever needed to be evaluated further. Hematological manifestations of enteric fever, including thrombocytopenia, are explained by several hypotheses, including destruction of the reticulo-endothelial system, autoimmune mediated bone marrow sup-

pression, or *Salmonella* endotoxin-mediated thrombocytopenia [19].

There are very few case reports of secondary HLH in children occurring in the course of enteric fever caused by *Salmonella typhi* [2-7]. Infections are potential provoking agents for primary and secondary HLH. Although viral infections are the most common inciting agents, bacterial infections and even fungal and parasitic infections have also been implicated [2]. In children with enteric fever, persistent fever with abdominal pain, splenomegaly, hepatitis with elevated aspartate transaminase, neurological manifestations, progressive anemia and thrombocytopenia, severe enough to require blood and platelet transfusion, should raise the suspicion of HLH. However, the diagnosis of HLH secondary to typhoid fever, when based only on clinical criteria, is challenging because fever, splenomegaly, hepatitis and cytopenia may be primary manifestations of *Salmonella typhi* infection [7].

The definitive diagnosis of HLH is based on the HLH-2004 diagnostic criteria, which include clinical, laboratory, and histochemical findings [20, 21]. A diagnosis of HLH is established if one or both of the following criteria are fulfilled:

1. a molecular diagnosis consistent with HLH;
2. 5 out of the following 8 signs and symptoms:
   a. fever;
   b. splenomegaly;
   c. cytopenia (affecting ≥ 2 cell lineages; haemoglobin ≤ 9 g/dL or ≤ 10 g/dL for infants < 4 weeks of age, platelets < 100×10^9/L, neutrophils < 1.0×10^9/L);
   d. hypertriglyceridemia (≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 150 mg/dL);
   e. hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy;
   f. low or absent natural killer (NK) cell cytotoxicity;
   g. hyperferritinemia (≥ 500 ng/mL);
   h. elevated soluble CD25 (i.e., soluble IL2 receptor ≥ 2,400 U/mL).

The criteria may appear simple but because all the clinical manifestations may not be present initially and may evolve later in the course of disease, and early treatment can be lifesaving, it may not be mandatory to fulfil the diagnostic criteria before initiating treatment, especially in cases like the one described herein where clinical findings of HLH may overlap with those of the primary disease.

In this child, HLH was suspected in view of persistent fever of more than 7 days' duration, splenomegaly, and bicytopenia. Relevant investigations were performed which revealed ESR of 85 mm/h, CRP of 60 mg/L, hyperferritinemia with ferritin level more than 5,905 ng/mL and hypertriglyceridemia. Fever, splenomegaly, bicytopenia, elevated ferritin, and elevated triglycerides were the 5 out of 8 criteria that confirmed the diagnosis of HLH in our case. Fibrinogen levels could not be measured. Bone marrow biopsy to demonstrate hemophagocytosis was not carried out because the child was hemodynamically unstable.

In most of the secondary HLH cases due to enteric fever, improvement occurs after 5 or 6 days of appropriate antimicrobial treatment. Prompt clinical response to antibiotics without requiring HLH specific medications such as immunomodulators or chemotherapeutic agents has been reported. In secondary HLH, because the primary infection itself can result in hyperferritinemia, it is recommended to consider a higher cut-off value for ferritin, that is, 2,000 ng/mL rather than the 500 ng/mL mentioned in the HLH-2004 protocol [22]. In our patient, ferritin was very high, being more than 5,000 ng/mL.

Many cases do not fulfil 5 of the 8 recommended criteria for HLH diagnosis [21]. According to proposed modified criteria in 2009, "presence of at least 3 out of 4 clinical parameters (fever, splenomegaly, bicytopenia and hepatitis) and at least any 1 out of 4 laboratory criteria (hemophagocytosis, hyperferritinemia, increased soluble IL2 [CD25] receptor, and absent or very decreased NK function), along with hypertriglyceridemia, hypofibrinogenemia, and hyponatremia supports the diagnosis" [3, 22].

Means of assessing possible genetic anomalies related to the familial form of HLH (*PRF1*, *UNC13D*, *STX11*, *STXBP2*, *SH2DIA* and *XIAP* in X-linked lymphoproliferative disorders) and the immunological profile (immunoglobulin levels, CD25, NK cell function/degranulation test, flow cytometry for perforin expression, granzyme B proteins, CXCL9, etc.) were not available on site and these investigations also could not be done because of financial constraints.

Initial management for secondary HLH associated with infections is to treat the inciting cause, which will remove the stimulus and control immune activation and the cytokine storm due to inflammatory mediators [3, 22], as seen in most

of the reported paediatric cases of HLH secondary to infection with *Salmonella typhi*. However, in critically ill children or those with progressively worsening disease, immunosuppressant or immunomodulator therapy for HLH may be warranted.

In our case, parenteral dexamethasone was used as soon as the diagnosis of HLH was suspected and later changed to oral prednisolone. Specific immunomodulatory therapy for HLH, as recommended by the Histiocyte Society (HLH-2004) protocol, involves high-dose chemotherapeutic and immunosuppressant agents and may be considered on case-to-case basis. IVIG may also be beneficial in secondary HLH because it has shown promising results with very few side effects in the treatment of primary HLH and is included in the HLH-2004 protocol [23]. In most case reports, treatment of the inciting infection in secondary HLH is the most effective measure. In children who are critically ill with rapid deterioration and in those who do not improve despite the initial treatment of enteric fever with appropriate antibiotics, steroids and supportive treatment, IVIG with or without steroids, to reduce the overwhelming immune response, may be considered as per the HLH-2004 protocol.

Typhoid fever is posing challenges with the emergence of antibiotic resistance and its association with multiple atypical and perplexing complications, which pose a diagnostic dilemma, and may even be fatal if not treated early and appropriately.

This case is reported to emphasize the importance of considering HLH, especially in a child who continues to have high grade fever, progressive hepatosplenomegaly, and decreasing cell counts in association with other common infections. Clinical features of secondary HLH and those of a primary infection overlap, posing a diagnostic challenge. Strong suspicion, prompt diagnosis and timely appropriate management can be lifesaving. This case also demonstrated enteric fever presenting with multiple complications in the first week of illness and thrombocytopenia at the time of presentation itself. This should alert pediatricians to monitor children with enteric fever for complications and treat them appropriately to decrease morbidity and mortality.

Declaration of interest

The Authors declare that there is no conflict of interest.

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