

CASE OF THE MONTH

A Catastrophic Presentation of Enteric Fever with Secondary Hemophagocytic Lymphohistiocytosis

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Abstract

A 19 year old boy presented to the emergency room with fever of one week duration along with bleeding manifestations, few gastrointestinal symptoms, tachycardia, tachypnea and subtle encephalitic features. He was worked up for the usual causes of short duration fever, which proved inconclusive. In view of clinical worsening and cytopenias, a careful investigation process helped us in ruling out common etiologies for such a fever, alongwith unearthing the possibility of an underlying secondary hemophagocytic lymphohistiocytosis which led to severe thrombocytopenia and persistent high grade pyrexia. Widal test was positive in high titres, and patient was continued with antibiotics. Prompt treatment led to the uneventful recovery of the patient without any sequelae. Bleeding manifestations subsided, patient had rapid clinical improvement and was discharged after completing the course of antibiotics.

Introduction

Enteric fever is a common disease in tropical countries caused by salmonella typhi and paratyphi. Most of the time the presentation is with a history of continuous fever with gradual worsening of the laboratory parameters. Complications worsen the course of disease in the second or third week of onset of illness. Here we have a patient who developed multiple complications soon after the onset of fever, which is quite unlikely in enteric fever.

Case Report

A 19-year old male presented to the emergency room with history of high grade continuous fever for 5 days with non-projectile vomiting and greenish coloured loose stools for 3 days. One day before the presentation to hospital, he developed hemorrhagic manifestations in the form of bleeding from the gums and malena. He developed confused behaviour with slurring of speech and had mild headache; without any episode of seizures. He developed few erythematous rashes over the trunk along with arthralgia of elbow, wrist and knees. He didn't have any

hematuria or jaundice during the course of the illness. There was no history of any oral ulcers or joint swelling.

On examination he was confused, pulse rate was 130/minute, oxygen saturation was 97% on room air, BP 100/80 mm Hg, respiratory rate was 28/minute and temperature was 102 degree F and there were signs of dehydration with a well collapsible inferior vena cava. He had mild hepatosplenomegaly. No murmurs were detected on auscultation of the chest and his lung fields were clear. There was no neck stiffness. Initial lab investigations showed a haemoglobin level of 12.3 g%, total WBC count of 3300/mm³ and a low platelet count of 10000/mm³. ECG was normal, and screening echo was normal. A screening ultrasound abdomen showed evidence of retroperitoneal bleed with mild hepatosplenomegaly. Non contrast CT brain was normal. In view of the bleeding manifestations, 4 units of random donor platelets were transfused immediately. Considering the differentials for an acute onset fever with thrombocytopenia with some encephalitic features, the possibilities of dengue, malaria, leptospirosis and scrub typhus were considered as the differential diagnosis, and he was

started empirically on Inj Ceftriaxone 2g iv bd and Inj Doxycycline 100 mg iv bd along with supportive measures including hydration and antipyretics. Optimal test was negative. In view of the presentation with fever, splenomegaly and cytopenia with rapid clinical deterioration, a workup for secondary hemophagocytic lymphohistiocytosis was considered. Serum triglycerides turned out high. Serum ferritin levels were >2000 ng/mL.

The fever persisted for the next day along with malena, however there was an improvement in sensorium and dehydration. Platelet counts on the day after transfusion was 20000/mm³ (Table 1). Peripheral smear examination showed thrombocytopenia. One unit of single donor apheresis platelets was done, following which the bleeding signs halted, however loose stools persisted. There was an elevation of liver enzymes which subsided during the course of hospital stay. Blood culture was sterile, and the reports for dengue, scrub typhus, leptospirosis and malaria turned out to be negative. The urine output and renal functions were found to be normal. Chest X-ray was normal. A CT scan of the abdomen was done in view of persisting abdominal symptoms, showed ileocecal thickening and multiple lymph nodes without central necrosis (Figure 1) and the biopsy of node showed reactive changes. Widal test results were showing O titre of >1:320. The antibiotics were continued and on the 7th day of admission, patient got afebrile.

A presentation of acute onset high grade fever less than 1 week, with bleeding manifestations, and

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Table 1: Laboratory profile

	12-1-18	13-1-18	15-1-18	20-1-18
T.L.C	3900/mm ³	6000/mm ³	8000/mm ³	4800/mm ³
Hb	13.1g%	12.0g%	13.4g%	10.3g%
Platelet count	10000/mm ³	20000/mm ³	60000/mm ³	90000/mm ³
Esr	35 mm/hr		26 mm/hr	
Blood Urea	29 mg%	31 mg%	40 mg%	12 mg%
Creatinine	0.7 mg%	0.7 mg%	0.5 mg%	0.6mg%
Sodium	129 meq/L	129 mEq/L	136 mEq/L	134 mEq/L
Potassium	3.09 mEq/L	3 mEq/L	2.8 mEq/L	3.6 mEq/L
Bilirubin total	1.3 mg/l	1.4 mg/l	0.7 mg/l	0.4 mg/l
SGOT (AST)	745 U/L	704 U/L	451 U/L	93 U/L
SGPT (ALT)	193U/L	122 U/L	92 U/L	62 U/L
ALK PHOS (ALP)	271 U/L	336 U/L		468 U/L
LDH	3017 U/L	1514 U/L		502 U/L
Triglycerides		566 mg%	287 mg%	121 mg%
D dimer	>0.5			
Fibrinogen	300 mg/dl	175 mg/dl		245 mg/dl
INR	0.9	1		1
Widal test			>1:320	

TLC-Total Leucocyte count, Hb-Hemoglobin, ESR- Erythrocyte sedimentation rate, SGOT- Serum Glutamate oxaloacetate transaminase, AST- Aspartate transaminase, SGPT-Serum glutamic pyruvic transaminase, ALT- Alanine transaminase, ALP- alkaline phosphatase, LDH- Lactate dehydrogenase, INR- International Normalised ratio, U/L- Units per liter, mg/dl- milligram per deciliter

tachycardia is quite unlikely in a case of enteric fever. The rapidity with which the cytopenias developed is in favour of the possibility of secondary hemophagocytic lymphohistiocytosis, which was emphasized with the high triglyceride and ferritin levels and the cytopenias, thereby making up five criteria out of eight for diagnosing (fever, cytopenias, splenomegaly, hypertriglyceridemia, hyperferritinemia) hemophagocytic lymphohistiocytosis. The presence of gastrointestinal symptoms, leucopenia, and subtle CNS symptoms were in favour of enteric fever. A differential diagnosis of tuberculosis was considered following the CT scan report, however that possibility was negated after the repeat imaging which showed clearing of the lymphadenopathy. As the positive findings in the tests was the mesenteric lymphadenopathy without necrosis as well as the positivity found in the Widal test, the final diagnosis was complicated Enteric fever with secondary hemophagocytic lymphohistiocytosis. The patient has been following with us in a healthy state.

Due to the rarity of such a menacing presentation of enteric fever within one week of onset of fever, this case is being reported.

Discussion

Enteric fever is a nonspecific febrile illness caused by typhoidal

salmonella (*Salmonella Typhi* and *Salmonella paratyphi A, B, and C*) and is characterised by inflammation of peyer's patches, intestinal ulceration and mesenteric adenitis. The diagnosis should be considered in any patient with otherwise unexplained prolonged fever. Other clinical features include headache, chills, cough, myalgia, arthralgia, anorexia, abdominal pain, diarrhea, constipation, coated tongue, hepatosplenomegaly and rarely a rash.¹ The disease has an estimated 1% mortality worldwide.²

Usually the fever is insidious and increases over the first week of illness. In contradiction to this, our case had high grade fever from the first day of illness. A similar presentation has been mentioned in a case report by Margaret et al where the patient required multiple drugs for defervescence.³ Relative bradycardia is a classic sign of enteric fever⁴ whereas our case had persistent tachycardia. Among the laboratory findings, either leucocytosis or leukopenia is present along with normal or slightly low haematocrit and platelet counts,⁵ but in the aforementioned case the initial presentation itself was bleeding manifestations due to severe thrombocytopenia.

The sinister presentation in our case made us workup the case in lines of secondary hemophagocytic lymphohistiocytosis in enteric fever. Similar presentation has been mentioned by Sood et al in a study in

India in 1997⁶ and a 2015 case report by Non et al where the patient had rhabdomyolysis, sepsis and secondary HLH in a setting of enteric fever.⁷ Our patient had severe thrombocytopenia which required platelet transfusion, elevated D-Dimer levels, high LDH (lactate dehydrogenase), high AST and ALT levels, increased triglycerides which all pointed out to the possibility of HLH.⁸

Hemophagocytic syndromes (HPSs) are rare, life-threatening conditions characterized by overstimulation of the immune system leading to systemic inflammation, hypercytokinemia and multi-organ failure.⁹ They are broadly divided into primary hemophagocytic lymphohistiocytosis (HLH) and secondary hemophagocytic syndromes. Primary HLH is caused by genetic mutations impairing the cytotoxic function of natural killer (NK) and cytotoxic T cells and typically present in infancy and childhood. Regarding secondary HLH, it has been speculated that hypercytokinemia may impair the normal functions of CTLs, NK cells, or both, and individual genetic polymorphisms on leukocyte common antigen might increase susceptibility for secondary HLH.¹⁰ As per the diagnostic criteria proposed by Henter et al in 2004,¹¹ widely renowned as HLH 2004 guidelines, our patient satisfied hypertriglyceridemia, fever, splenomegaly and bicytopenia in the form of anemia and thrombocytopenia. However due to technical issues, the other parameters in the criteria could not be completed in our case. Due to the rapid progression of thrombocytopenia and high grade fever of rapid onset, along with hypertriglyceridemia and high LDH and liver enzymes, the case satisfies the criteria for secondary HLH.

The suggested line of management of secondary HLH is to first treat the underlying condition which led to HLH. Steroids or immunosuppressants like etoposide are indicated in certain cases, which are non-responsive to the treatment of underlying disorder. In this case, the patient responded well to the treatment of the primary pathology, i.e. enteric fever and hence specific treatment in lines of secondary HLH was not required.

The individual atypical laboratory parameter discrepancies that were seen in this case have been reported in certain other studies also. Pohan et al, in a

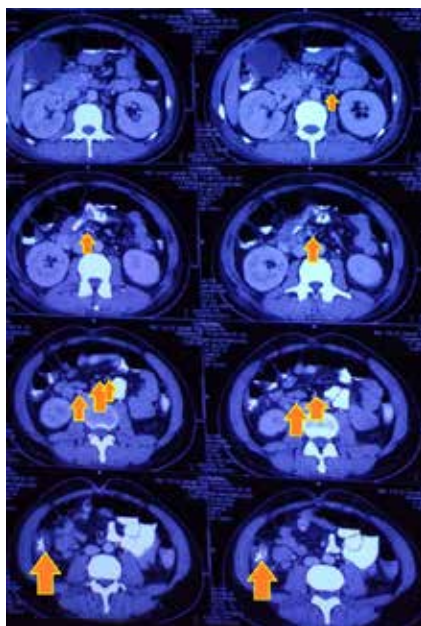


Fig. 1: CT Abdomen showing multiple mesenteric lymph nodes without necrosis, along with ileocecal thickening

study involving 119 patients of typhoid fever, reported thrombocytopenia (platelets between 10,000 to 50,000/cumm) in 2.6% patients¹² A case of typhoid fever in a 4-year-old Asian male returned traveler, admitted with prolonged fever and found to have severe thrombocytopenia (platelets $16 \times 10^9/L$) was reported by Muhammed al Reesi et al.¹³ Elevated serum aspartate transaminase and alanine transaminase is common in enteric fever. In a study conducted in an outpatient clinic in Germany, 3.8% of returned travelers had thrombocytopenia of which Typhoid/paratyphoid fever was responsible for 14% of the cases, ranking fifth after malaria, acute human immunodeficiency virus (HIV) infection, dengue fever, and Epstein-Barr virus (EBV) infectious mononucleosis.¹⁴

Untreated disease increases over the second week of illness and may progress to complications, like gastrointestinal haemorrhage, perforation, jaundice, encephalopathy, myocarditis,

endocarditis, anemia, disseminated intravascular coagulation. In our case, some of these complications like retroperitoneal bleed, liver function abnormalities, anemia, subtle encephalopathic symptoms occurred within the first week itself, which makes the case an atypical one; which could be explained by the occurrence of secondary HLH after the disease onset. Prospective studies have proved that lowering the trigger of platelet transfusion to $10 \times 10^9/L$ in stable patients with cancer or blood disorders is safe. In our case, there were definite bleeding manifestations in the form of malena, which prompted early platelet transfusions. There are no studies or guidelines addressing the management of thrombocytopenia or secondary HLH in typhoid fever which infact made us at crossroads while managing the case. Some case reports have described platelet normalization shortly after starting antibiotic therapy without a need for platelet transfusion. In one report, the platelet count fell from $154 \times 10^9/L$ to $14 \times 10^9/L$ despite antibiotic therapy,¹⁵ and this was associated with multi-organ failure; plasma exchange was given to correct the thrombocytopenia and other abnormalities.

In the depicted case report, the management involved a multi pronged approach including antibiotics, platelet transfusions, and iv fluids. A workup in lines of secondary HLH gave explanation to most of the atypical events that occurred during the course of illness of our patient, which subsided with adequate treatment. This emphasises the need for having tailored regimens for investigating and treating each patient, considering the overall clinical scenario rather than following the strict protocol for fever management.

Conclusion

Enteric fever is a common clinical scenario in tropical countries. However its clinical manifestations keeps varying and a possibility of secondary HLH

should be considered in the presence of a menacing presentation in enteric fever. Careful investigations in case of atypical manifestations of a common disease will answer most of the paradoxes in clinical medicine.

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