CASE REPORT

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Aquired Haemophagocytic Lymphohistiocytosis in Enteric Fever

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Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a somewhat rare, yet aggressive and life-threatening, syndrome of excessive immune activation and tissue destruction. Here we discuss a case of haemophagocytic lymphohistiocytosis secondary to Salmonella typhi infection in a 22-year-old female.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a distinct clinical entity characterised by fever, pancytopenia, splenomegaly, and haemophagocytosis in bone marrow, liver, or lymph nodes[1]. HLH is a somewhat rare, yet aggressive and life-threatening, syndrome of excessive immune activation and tissue destruction, which can be genetic or aquired. It involves a final common pathway of hypercytokinaemia, which can result in end-organ damage and death. It generally affects the young mostly from birth till 18 months of age; however, it is also seen in children and adults at all ages[2,3].

We shall discuss here a case of HLH secondary to *Salmonella typhi* infection.

Case report

A 22-year-old female, resident of Delhi, presented with complaints of high-grade fever associated with chills and rigors for 7 days followed by loose stools and vomiting for 4 - 5 days. Patient also complained about mild abdominal pain which was diffuse and non-colicky in nature. She gave history of bleeding per vaginum 3 - 4 days ago which resolved spontaneously. Fever was not associated with burning micturition, yellowish discolouration of eyes, cough, expectoration, sore throat, or rhinorrhoea. Patient gave history of dengue fever 5 years ago. General and systemic exam was largely unremarkable. Her initial reports were as follows:- Hb - 10.7 g/dl, TLC 3,400/cumm, platelets 70,000/cumm total. Bilirubin 0.9 mg/dl, SGOT 974 U/L, SGPT 412 U/L, ALP 195 U/L, blood urea 10 mg/dl, serum creatinine 0.7 mg/dl, Typhidot IgM was positive, dengue IgG was also positive but IgM was negative (Table I). For these complaints the patient had visited the emergency room multiple times and was given oral antimalarials and oral cefixime in view of positive Tyhi dot IgM report.

Table I: Laboratory parameters during treatment.

	Day 7	Day 12	Day 15	Day 25
Hb (g/dl)	10.7	9.8	7.9	10.6
TLC/cumm	3,400	2,900	3,800	8,800
Platelet/cumm	70,000	61,000	45,000	4,22,000
T Bil mg/dl	0.9	0.6	0.4	0.82
SGOT U/L	974	790	192	55
SGPT U/L	412	358	173	166
ALP U/L	195	249	139	95
Blood urea mg/dl	10	19	16	26
Sr. creat mg/dl	0.7	0.4	0.5	0.4
Sr. Na meq/l	131	137	138	142
Sr. K meq/l	3.7	3.6	2.8	4.5
Typhi Dot IgM	Positive			
Dengue IgM	Negative		Negative	
Sr. Ferritin ng/dl			974	125.32
Sr. Fibrinogen mg/dl			126	189.7

Despite the above treatment, patient had persistent high grade fever and diarrhoea considering which she was admitted to hospital and started on intravenous ceftriaxone and azithromycin on day 2 of admission, with other symptomatic treatment. Subsequently, patient's blood culture report revealed *Salmonella typhi* sensitive to ceftriaxone and azithromycin.

Despite continuing the above treatment, patient had unremitting high grade fever (104° F), had continuous

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diarrhoea, developed non-productive cough, worsening leucopenia (2,900/cumm) and falling haemoglobin even on day 11 of illness. During this time she also developed hypokalaemia with serum potassium of 2.8 meq/l which was corrected by intravenous KCl. In view of persistent fever, diarrhoea, pancytopenia, hypokalaemia and transaminitis, despite 7 days of appropriate antibiotics, secondary HLH was considered and further necessary investigations were ordered. Patient was given injection methylprednisolone 125 mg/d for 2 days pending the investigations as secondary HLH was the more likely diagnosis, clinically. Further reports were suggestive of fibrinogen degradation product > 20 ug/ml, D-dimer of 7,094.1 ng/ml, ferritin of 974.32 ng/dl, LDH of 783 u/l, triglycerides of 167 mg/dl and dengue IgM negative. Blood peripheral smear showed no evidence of fragmented RBCs or schistocytes ruling-out thrombotic thrombocytopenic purpura. Chest X-ray was normal. Bone marrow aspiration was done.

Methylprednisolone pulse was followed by injection dexamethasone 15 mg/day for 5 days. Patient became afebrile, diarrhoea and cough improved along with improvements in pancytopenia and transaminitis after 2 days of steroid therapy. Patient was then shifted to oral cefixime to complete 10 days of therapy for enteric fever.

Subsequently, the bone marrow aspiration report suggested presence of haemophagocytes (Figs. 1 and 2) thus confirming the diagnosis of HLH.

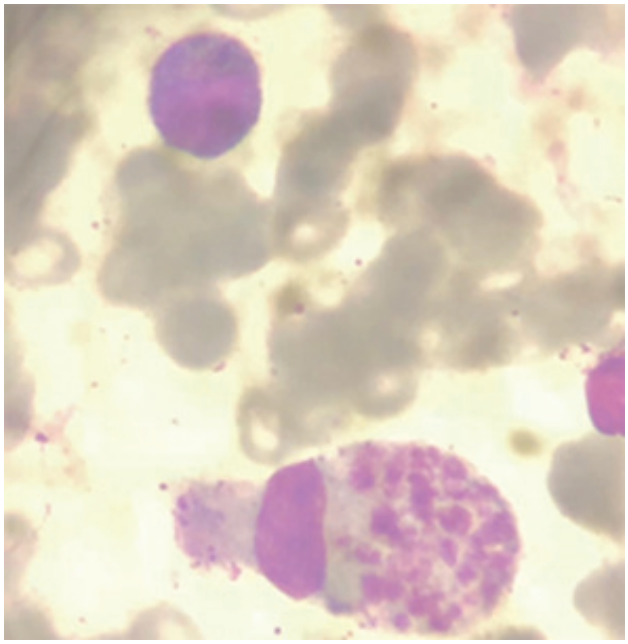

Fig. 1: *Macrophage engulfed platelets.*

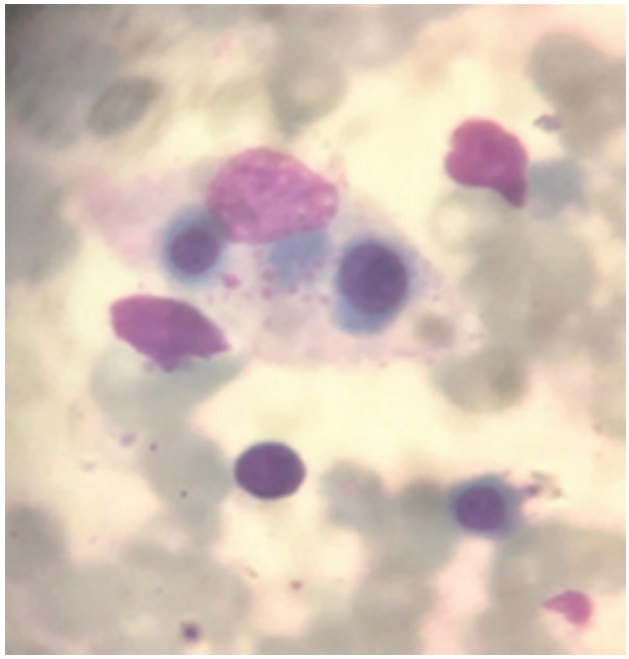

Fig. 2: *Macrophage engulfed RBCs and Nucleated RBCs.*

Discussion

Typhoid fever by *S. typhi* can result in severe disease with complications in 10 - 15% of patients, including gastrointestinal bleeding, intestinal perforation, hepatitis, pancreatitis, typhoid encephalopathy, disseminated intravascular coagulation, haemolytic uraemic syndrome, endocarditis, pneumonia, and rarely, secondary HLH[4,5].

All of the clinical and laboratory findings are readily linked to the pathophysiology of HLH. Fever is the result of inflammatory activity. Splenomegaly, cytopenia and hypertriglyceridaemia may be the direct result of infiltration by lymphocytes and macrophages as well as direct haemophagocytosis. Elevated ferritin > 10, 000 µg/l has been demonstrated to be 90% sensitive and 96% specific for HLH[6]. The pathophysiology of infection-associated HLH following infection with non-viral pathogens may also be related to production of high levels of activating cytokines by host lymphocytes and monocytes. The relative frequency of association between infecting organisms (e.g., *Mycobacterium tuberculosis*, *Salmonella typhi*, and *Leishmania sp.*) that trigger a TH1 immune response and reactive haemophagocytic syndromes might suggest that the syndromes result from a poorly regulated or inappropriate TH1 response to intracellular pathogens[7].

HLH is diagnosed using clinical and molecular criteria. A molecular diagnosis consistent with HLH or five of eight clinical findings are required – fever; splenomegaly; cytopenia; hypertriglyceridaemia and/or hypofibrinogenaemia; demonstration of

haemophagocytosis in bone marrow, spleen, or lymph nodes; decreased natural killer cell function; elevated ferritin level; and an elevated soluble CD25 or IL-2Rα chain ≥ 2,400 IU/ml[8]. This criteria is more appropriate for use in paediatric population.

A study done by Tamamyan *et al,* suggested new diagnostic criteria consisting of 18 variables rather than 8 as previously suggested. These criteria are more suitable in adult population with a suspicion of HLH. These 18 variables include BM/lymph node/spleen haemophagocytosis per pathology evaluation, fever, splenomegaly (clinically palpable spleen), hepatomegaly (clinically palpable liver), anaemia (haemoglobin< 9.0 g/l), thrombocytopenia (platelets < 100 × 109/l), neutropenia (absolute neutrophil count (ANC) < 1.0×10^9/l), monocytosis (absolute monocyte count (AMC) > 1.0 × 109/l), renal failure (≥ 50% of increase of creatinine over baseline), elevation of hepatic enzymes (≥ 2.5 × upper limit of normal), hypofibrinogenaemia (fibrinogen ≥ 150 mg/dl), hyperferritinaemia (ferritin ≥ 500 microgram/l), coagulopathy (PT ≥ 1.5 × upper limit of normal and/or PTT ≥ 1.5 × upper limit of normal and/or D-dimer ≥ 10.0 mcg/ml), hypoalbuminaemia (< 3.5g/dl), elevated LDH (≥ 2.5 × upper limit of normal), hypertriglyceridaemia (≥ 265 mg/dl), elevated b2-microglobulin (≥ 2 mg/l), and elevated soluble IL-2 receptor (i.e., CD25) ≥ 2,400 U/ml. Sensitivity analysis suggested that patients meeting 5 of 18 above mentioned criteria are considered to have a high likelihood of aquired HLH[9]. According to Weitzman[10] as liver is the most commonly affected organ, in the absence of transaminitis the diagnosis of HLH is unlikely. Non-productive cough and respiratory distress unresponsive to antibiotics is also reported to be a warning symptom of HLH in an appropriate clinical scenario[11].

According to Schram[12], if diagnosis of HLH is highly suggested by clinical parameters, treatment with steroids should be started immediately, pending the investigations.

In our case persistence of fever for more than 7 days despite being on appropriate antibiotics, pancytopenia, raised serum ferritin and decreased fibrinogen level suggested a possibility of HLH. In addition to the above findings some additional features which suggest a diagnosis of HLH, according to the extended criteria, in our patients were elevated hepatic enzymes, raised D-dimer, elevated LDH but splenomegaly was absent and triglycerides were nearly normal. Based on these features patient was treated with high dose steroids pending investigations and a bone marrow was planned. Patient responded to steroids and there was improvement in pancytopenia, resolution of fever, transaminitis improved and ferritin decreased.

We would like to conclude that persistence of fever for more than 7 days in spite of use of sensitive antibiotics in a setting of enteric fever should raise a suspicion of aquired HLH and treatment for same should not be delayed pending investigations.

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