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BMH Med. J. 2023;10(1):9-13. **Case Report**

An Uncommon Presentation of Typhoid Fever - HLH

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Abstract

Typhoid fever has an estimated worldwide prevalence of 12-33 million cases with high incidence in India, especially urban centres. Hemophagocytic lymphohistiocytosis is a rare complication of typhoid fever, which may be fatal, if untreated. We describe the case of a young male, with a history of travel from Mumbai, who presented to our tertiary care centre with high grade fever, body pain, slurring of speech and loose stools. Investigations showed bicytopenia, hyperferritinemia, hypertriglyceridemia and bone marrow biopsy revealed erythrophagocytic histiocytes and granulomas. Blood culture grew Salmonella typhi. After ruling out other possibilities, including underlying immunodeficiency conditions, the diagnosis of HLH was made as per the HLH 2004 diagnostic criteria. The patient responded to culture sensitive antibiotics, steroids and supportive care. We discuss this case to create awareness about an uncommon complication of a common disease such as typhoid fever.

Keywords: typhoid fever, Hemophagocytic lymphohistiocytosis, HLH

Introduction

Enteric fever is an acute febrile illness caused by Salmonella enterica serovar typhi (S. typhi) or serotype Paratyphi A,B, or C which spreads by feco oral route. In India, an annual estimate of 4.5 million cases with a case fatality rate of 0.2%, with high incidence of cases in urban centres [1,2]. Common presentations include high grade fever, abdominal pain, persistent headache, constipation, diarrhoea, weakness, dizziness and cough. Late diagnosis or failure to respond to antibiotics may lead to complications. Typhoid complications include typhoid intestinal perforation (TIP), gastrointestinal haemorrhage, hepatitis, cholecystitis, myocarditis, shock, encephalopathy, pneumonia and anaemia [3]. The course of illness can range from uncomplicated febrile illness to life threatening sepsis and multiorgan dysfunction. We report a case of previously healthy male with history of travel from Mumbai with typhoid fever complicated by sepsis, encephalopathy and a rare complication, hemophagocytic lymphohistiocytosis (HLH).

Case report

A young male from Malabar, with no previous comorbidities, with recent travel history to Mumbai,

presented with high grade fever with chills and rigor, headache, body pain and loose stools for 4 days. He had multiple fever spikes that subsided with paracetamol along with drenching sweats. Headache was bifrontal and associated with blurring of vision. He had large volume non bloody watery diarrhea. There was history of food intake from outside in last 2 weeks. He had an episode of acute gastroenteritis 2 weeks back that had required admission following which he had complete recovery with treatment.

On admission, he was conscious, confused and had tachycardia and tachypnea with normal blood pressure. Temperature was 101 degrees F and oxygen saturation 95% in room air. Physical examination was remarkable for dry oral mucosa, drenching sweats, mild calf muscle tenderness, hepatosplenomegaly and slurring of speech. There was no icterus, lymphadenopathy, edema, rash or abdominal tenderness. Cardiac examination had tachycardia, no heart murmurs and respiratory system examination was normal except for tachypnea. Laboratory investigations were significant for bicytopenia (Hb: 14, total leucocyte count: 2.2 x 10^3/cu mm, platelet count 32 x 10^3/cu mm) hypokalemia, hyponatremia, elevated transaminases and CRP.

His Human Immunodeficiency Virus test was negative and work up for other infectious etiologies were negative, including Dengue IgM, Leptospirosis serology, Malaria rapid antigen and smear, Scrub typhus IgM, COVID 19 antigen and viral hepatitis A,B,C and E. He was empirically started on intravenous Ceftriaxone and oral Doxycycline. 2 sets of blood culture sent grew Salmonella typhi, sensitive to Ceftriaxone, hence continued it for 10 days and Doxycycline stopped. Urine and stool culture were negative.

Despite on culture sensitive antibiotic, he had multiple fever spikes, tachycardia and tachypnea. Along with it, his sensorium deteriorated, with slurred speech, memory impairment, hallucination, blurring of vision and headache. MRI brain (plain+contrast) showed cytotoxic lesions of corpus callosum, restricted diffusion in bilateral centrum semi ovale and subtle signal alteration in bilateral tempero parietal lobes possibility of encephalitis, probably secondary to salmonella (**Figure 1**). He was shifted to medical intensive care unit in view of persistent tachycardia, tachypnea and worsening of laboratory parameters like leucopenia and thrombocytopenia. There was no evidence of hemolysis.

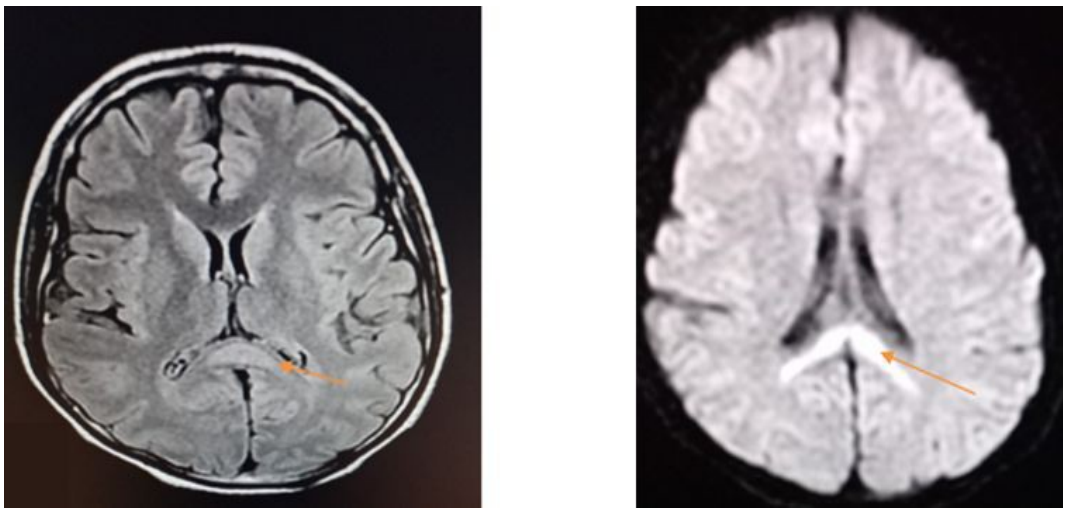

Figure 1: MRI brain (plain+contrast) showed cytotoxic lesions of corpus callosum

Keeping a possibility of HLH, serum ferritin and triglycerides were sent. His Serum Ferritin was significantly elevated (23622.10) and Triglycerides was elevated. At this stage, he had fever, hepatosplenomegaly, bicytopenia, elevated ferritin and elevated triglycerides which satisfied HLH 2004 criteria. A bone marrow study was done and biopsy showed erythrophagocytic histiocytes (**Figure 2**) and granulomas (**Figure 3**), consistent with Salmonella infection. He was started on intravenous steroids. By day 2 of steroids, his fever spikes reduced, his sensorium improved, vitals

improved and his counts started to improve. He was transferred to room and continued on intravenous steroids, which was changed to oral steroids, tapered and stopped in 15 days. On follow up after 2 weeks of discharge, he was doing well, with normal blood counts and mildly elevated transaminases.

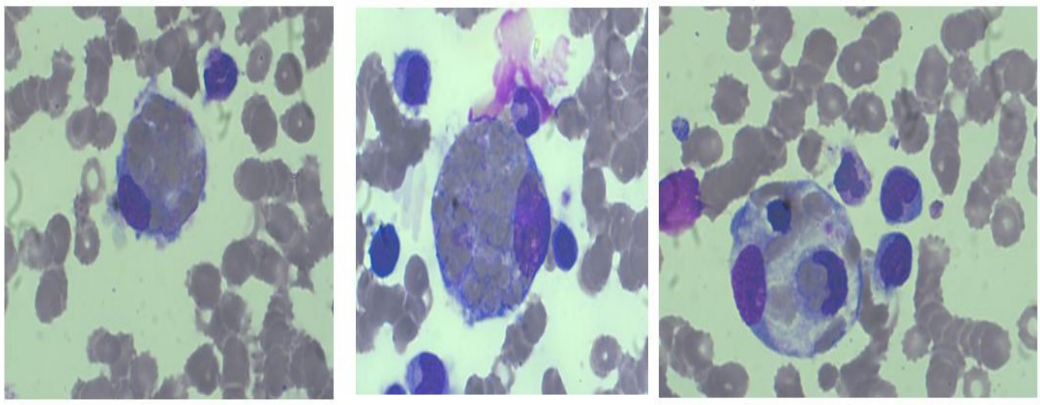

Figure 2: Erythrophagocytic histiocytes

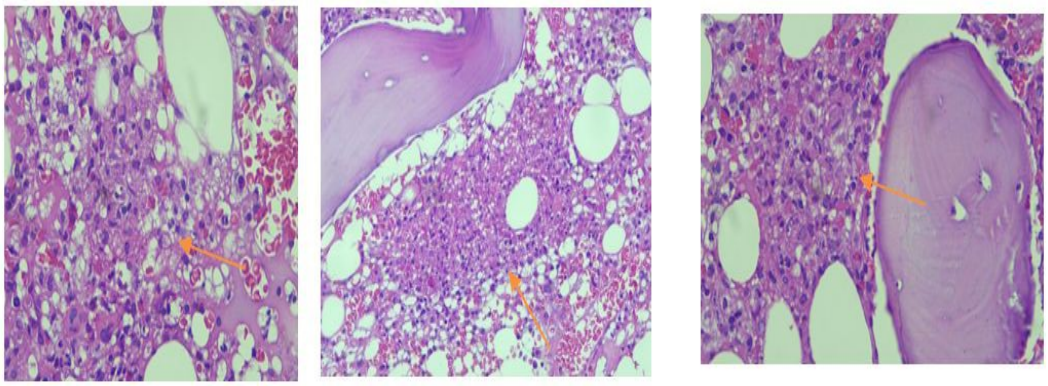

Figure 3: Granuloma formation

Discussion

Typhoid fever is a systemic infection caused by Salmonella enterica serotype typhi (S typhi) or S Paratyphi A, B and sometimes C. Incidence of typhoid is high in south central Asia, south east Asia and southern Africa, with heavy disease burden in India, especially its urban centres. Clinically, the disease can vary from fever with no other morbidity to marked toxemia and complications involving any system. About 10-15% patients develop severe disease, the commonest being gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy. Intermittent confusion, insomnia and dizziness are reported in 3-10% cases. These symptoms are associated with high case fatality. Other rare complications include hepatic, splenic and bone marrow granulomas, splenic and liver abscess, pleural effusion, multiple organ dysfunction syndrome, hemophagocytic syndrome, pseudotumor cerebri, haemolytic uremic syndrome, glomerulonephritis, endocarditis and pericarditis [4]. Keeping a high index of suspicion is necessary while treating complicated typhoid as early recognition and treatment can help to reduce mortality and morbidity.

Hemophagocytic syndrome or hemophagocytic lymphohistiocytosis is a rare disease that is often fatal even with adequate treatment. It is caused by the dysregulation of natural killer T cell function, resulting in activation and proliferation of histiocytes with uncontrolled hemophagocytosis and

cytokine overproduction, characterised by fever, hepatosplenomegaly, cytopenias, liver dysfunction and elevated ferritin. It can be either primary or secondary. Primary HLH is associated with genetic aetiology. Secondary HLH is associated with malignancies, autoimmune disorders or infections [5].

Diagnosis of HLH is based on the diagnostic guidelines proposed by Histiocyte Society which was updated in 2004. It has both clinical and laboratory criteria. Clinical criteria include fever, splenomegaly, hepatomegaly, lymphadenopathy, skin rash and neurological findings. Laboratory abnormalities include anaemia, thrombocytopenia, neutropenia, hypertriglyceridemia, hypofibrinogenemia, hypertransaminasaemia, hyperbilirubinemia, elevated lactate dehydrogenase and hyperferritinemia. Increased plasma concentration of alpha chain of interleukin 2 receptor (sCD25) and impaired NK cell activity. On histopathology, activated macrophages with engulfed leucocytes, erythrocytes, platelets and other precursors are the typical finding [5]. However, the diagnosis may be challenging due to the lack of specificity of clinical and laboratory abnormalities, which can also appear in the context of sepsis or malignancy. Since HLH has high mortality, it is unnecessary to satisfy all criteria to initiate treatment [6]. 60-70% patients with IAH responded to supportive care and treatment of underlying infection, but severe cases, especially those associated with EBV, required immunosuppressive therapy [5,7].

Infection Associated HLH (IAH) is usually caused by viruses like EBV, but bacterial, fungal and parasites have been reported. The pathophysiology of acquired HLH is not fully understood, but it is postulated to be the deficiency of cytolytic activity that results in persistent activation of lymphocytes and histiocytes [8]. In a case series of 30 patients in India, two of IAH cases were in patients with TF [9]. A few case reports from India with young adults who had typhoid fever complicated by HLH has been reported [9-11] and a case report of Indian native with typhoid fever complicated by HLH has been reported from USA [13].

This patient had features of encephalopathy and cytopenias. Blood culture showed drug sensitive Salmonella typhi, but his HLH did not improve with antibiotics and supportive care. Initiation of dexamethasone was necessary to prevent worsening of HLH. Patient responded well to steroids and his bicytopenia normalised. Prompt intimation of corticosteroids was life saving. We stress the importance of keeping a high index of suspicion in complicated infections with cytopenias, multidisciplinary course of action and instituting necessary immunosuppressive agents to prevent mortality.

Conclusion

Typhoid fever is common infectious disease in Indian subcontinent. Any patient who is not responding to culture specific antibiotic must be evaluated for underlying complications. Rare complications like HLH can happen in Typhoid fever and must be suspected in patients with ongoing fever, worsening sensorium, hepatosplenomegaly, disproportionately elevated transaminases and persistent low blood counts. Early recognition and prompt treatment may revert this life threatening complication.

References

1. Cao Y, Karthikeyan AS, Ramanujam K, Raju R, Krishna S, Kumar D, Ryckman T, Mohan VR, Kang G, John J, Andrews JR, Lo NC. Geographic Pattern of Typhoid Fever in India: A Model-Based Estimate of Cohort and Surveillance Data. J Infect Dis. 2021 Nov 23;224(224 Supple 5):S475-S483.

2. Buckle GC, Walker CLF, Black RE. Typhoid fever and paratyphoid fever: systematic review to estimate global morbidity and mortality for 2010. J GlobHealth. 2012;2:10401.

3. Christian S Marchello, Chuen Yen Hong, John A Crump, Global Typhoid Fever Incidence: A

Systematic Review and Meta-analysis, Clinical Infectious Diseases, Volume 68, Issue Supplement_2, 15 March 2019, Pages S105-S116.

4. Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. Lancet. 2005 Aug 27-Sep 2;366(9487):749-62.

5. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. Lancet. 2007;7:814-822.

6. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007 Feb;48(2):124-31.

7. Saevels K, Robert D, Van den Broeck S, Malfait R, Gadisseur A, Jorens P, Verlinden A. EBV-associated hemophagocytic lymphohistiocytosis complicated by severe coagulation disorders and opportunistic infections: case report of a survivor. Clin Case Rep. 2017 Nov 29;6(1):115-118.

8. Abbas A, Raza M, Majid A, Khalid Y, Bin Waqar SH. Infection-associated Hemophagocytic Lymphohistiocytosis: An Unusual Clinical Masquerader. Cureus. 2018 Apr 12;10(4).

9. Singh ZN, Rakheja D, Yadav TP, Shome DK. Infection-associated haemophagocytosis: the tropical spectrum. Clin Lab Haematol. 2005;27:312-315.

10. Ray U, Dutta S, Bandyopadhyay S, Mondal S. Uncommon presentation of a common tropical infection. Indian J Pathol Microbiol 2020;63:161-3.

11. Arora, Navneet & Singla, Neeraj & Jain, Aleena & Sharma, Prashant & Sharma, Navneet. (2021). Secondary haemophagocytic lymphohistiocytosis (HLH) triggered by Salmonella typhi. Postgraduate Medical Journal. 98. postgradmedj-2021. 10.1136/postgradmedj-2021-139999.

12. George N, Sethi P, Nischal N, Kumar A, Siripurapu G, Wig N, Vyas S. A Catastrophic Presentation of Enteric Fever with Secondary Hemophagocytic Lymphohistiocytosis. J Assoc Physicians India. 2018 Dec;66(12):11-12.

13. Non LR, Patel R, Esmaeeli A, Despotovic V. Typhoid Fever Complicated by Hemophagocytic Lymphohistiocytosis and Rhabdomyolysis. Am J Trop Med Hyg. 2015 Nov;93(5):1068-9.