ORIGINAL RESEARCH PAPER

Paediatrics

KEY WORDS:

HLH (HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS): A RARE COMPLICATION OF ENTERIC FEVER- A CASE REPORT

Dr. Ashna Kumar Junior Resident SMGS Hospital Jammu

Dr. Pooja Bharti* Senior Resident SMGS Hospital Jammu *Corresponding Author

ABSTRACT

Typhoid fever is a systemic infection with protean manifestations caused by Salmonella and leads to various life threatening complications, of which HLH (Hemophagocytic Lymphohistiocytosis) is one such uncommon complication. We report a case of HLH in enteric fever who presented with fever and petechial rash.

INTRODUCTION

Typhoid fever remains an important etiology of fever in the developing countries. According to a recent systematic review, the estimated prevalence of laboratory confirmed typhoid and paratyphoid among individuals with fever across hospital studies was 9.7% and 0.9% respectively[1].

The course of typhoid fever can range from an uncomplicated febrile illness to life threatening sepsis and complications like HLH with multiorgan involvement.

Here we report a case of secondary HLH in a girl with typhoid fever.

Case Report

A previously heathy 16 years old female presented to our institute with the history of fever and fatigue since past 7 days. She also complained of rash over neck and 2 episodes of black coloured stools. She denied any history of travel, bone pains, drug intake and contact with animals. No other family member or immediate contacts had similar complaints.

On admission, her temperature was 101 F, HR 124/min, RR 26/min, BP 110/68 mmHg and SPO_2 97% on room air. General physical examination revealed dry tongue, petechial spots at the root of tongue. There was no organomegaly, lymphadenopathy, abdominal tenderness. Laboratory investigations showed bicytopenia Hb was 10.0 g/dl (nadir of 8.5 g/dl), platelet count 89000/mm^3 (nadir of 5000/mm^3), TLC 5800/mm^3 (ANC 3800), transaminitis SGOT 217 IU/L, SGPT 102 IU/L, serum ferritin > 2000 ng/dl, Serum B_{12} 200 pg/ml, triglycerides 346 mg/dl, CPK 182, normal coagulation profile PTI 92.8%. She was HIV non-reactive and other infectious markers HBsAG, anti- HCV, anti HAV, anti HEV were negative. Chest X-ray was normal, Sputum for CBNAAT was negative for M.Tb and mantoux was negative after 72 hours. Rapid testing for malaria was negative.

She was started on injectable ampicillin, while her blood cultures were awaited. She continued with high grade fever and worsening bleeding manifestations in the form of newly appearing petechial spots and ecchymotic patches at sites of cannulation. She was planned for bone marrow examination in view of worsening clinical symptoms. Meanwhile her antibiotics were changed to injectable Azithromycin in view of resistant strains of Salmonella typhi grown on blood culture. Bone marrow examination showed findings of prominence of histiocytes and evidence of phagocytosis secondary to some infective pathology.

The patient fulfilled the criteria for secondary HLH (fever, cytopenia, raised serum ferritin, elevated triglycerides and bone marrow examination suggestive of hemophagocytosis). She was continued on injectable Azithromycin and after 48 hours of starting azithromycin she became afebrile and the platelet count began to improve and hemoglobin started rising, liver functions began to improve. Her general condition and appetite improved. All this is expected in infection related HLH. She was discharged after 7 days of injectable azithromycin for enteric fever. She was called for follow up after one week along with the fresh CBC and on subsequent visit her blood counts were normal and her petechiae had disappeared. She was normal and free of any symptoms.

DISCUSSION

Typhoid fever caused by Salmonella typhi can cause severe disease with complications in as many as 10-15% of patients including GI bleeding, intestinal perforation, hepatitis, pancreatitis,typhoid encephalopathy, DIC, HUS, endocarditis, pneumonia and rarely HLH [2,3].

Infections are potential triggers for primary and sporadic HLH cases. Viruses are the most common cause but many other bacterial, fungal and tropical infections have been associated [4]. Secondary HLH is a complication of typhoid fever which has been described in adults and a few cases in pediatric population.

HLH is a generalized disease, most often presenting as fever (90-100%), maculopapular or petechial rash (10-60%), weight loss and irritability, as was in our case. The pathophysiology of HLH is poorly understood but it involves a state of uncontrolled hemophagocytosis and uncontrolled activation of inflammatory cytokines resulting in end organ damage and death.

When HLH is familial, it presents early in younger age, which is due to the underlying genetic abnormality. Secondary HLH indicates disorder secondary to autoimmune, rheumatological, immunosuppressive states or infections (as in our case), which can present later in life [5].

The diagnosis of HLH is fulfilled by one of the following 2 criteria [6]:

1) A molecular diagnosis consistent with HLH(PRF or SAP mutations)
2) Presence of 5 of the following 8 symptoms, signs or laboratory abnormalities

- Fever
- Splenomegaly
- Cytopenia (affecting ≥ 2 cell lineages; hemoglobin ≤9g/dl [or ≤10g/dl for infants <4 wk of age], platelets < 100,000/μL, neutrophils <1000/μL)
- Hypertriglyceridemia (≥265 mg/dl) and/ or hypofibrinogenemia(≤150mg/dl)
- Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
- Low or absent natural killer cell cytotoxicity
- Hyperferritinemia (≥500ng/mL)

- Elevated soluble CD 25 (IL-2Rα chain;≥400U/mL)

Sixty of the seventy percent of the patients with secondary HLH respond to supportive care and the treatment of the underlying infection but severe cases especially those associated with EBV have required chemotherapy [4].

The diagnosis in our case was also based on the clinical features and laboratory findings (fever, cytopenias, hypertriglyceridemias, hyperferritinemia and hemophagocytosis on bone marrow examination) alone owing to the paucity of molecular diagnostic tests that can confirm the disease. The delay in diagnosis was due to the rarity of the disease and absence of consanguinity. The isolation of Salmonella species indicative of typhoid fever guided our management.

Consanguinity has been reported to account for nearly 24% of the HLH cases [7]. All the clinical and laboratory findings are readily linked to the pathophysiology of HLH. Fever is the result of the inflammatory activity. Cytopenias, hypertriglyceridemia and bone marrow suggestive of hemophagocytosis may be the direct result of the infiltration of lymphocytes as well as macrophages and hemophagocytes. Elevated ferritin has been demonstrated to be 90% sensitive and 96% specific for HLH [8].

For a patient with secondary infection related HLH, supportive care and treatment of the underlying infection is associated with recovery in 60-70% [9,10], since in most patients treating the underlying cause will be enough to withdraw the immune activation stimulus and control the inflammatory cytokine storm [11] as is seen in most pediatric cases of HLH and as was the scenario in our case.

Specific immunomodulatory therapy for HLH can be based on the recommendations by the Histiocytic society HLH 2004 using a combination of etoposide, cyclosporine, corticosteroids and intra-thecal methoteraxate. IvIg can be used in secondary HLH, as it has been shown to be effective as the HLH 2004 protocol with fewer adverse effects [12].

CONCLUSION

Typhoid fever should be suspected in a patient presenting with severe febrile illness complicated by cytopenias which could be secondary HLH. The recognition of the illness is important for prompt diagnosis and treatment with appropriate antibiotics to prevent complications and mortality. Treating the trigger of HLH as the first-line measure would be an effective measure to control the disease process. Only those not responding to these measures or having a fulminant course may benefit from IvIg +/- steroids to control the immune response.

Conflict of interests: none
Source of funding: none

REFERENCES :

1) John J, Van Aart CJ, Grassly NC. The burden of typhoid and paratyphoid in India: systematic review and meta analysis. PLos Negl Trop Dis. 2016; 10(4):15.
2) Bhan M, Bahl R, Bhatnagar S. Typhoid and paratyphois fever. Lancet 366: 749-762.
3) arry CM, Thompson C, Vinh H, Cninh NT, Phuong le T, Ho VA, Hien TT, Wain J, Farrar JJ, Baher S. Risk factors for the development of severe typhoid fever in Vietnam. BMC Infect Dis. 2014; 14:73.
4) Rouphel NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with hemophagocytic syndrome. Lancet Infec Dis. 2007; 7(12):814-822.
5) Pande V, Agarkhedkar SR, Tandon A, Agarwal A. Hemophagocytic Lymphohistiocytosis(HLH) in a case of Enteric Fever. Intl Jour of Bioassays. 2016; 5.3: 4882-4884.
6) Verbsky JW, Grossman WJ: Hemophagocytic lymphohistiocytosis: diagnosis, pathophysiology, treatment and future prospectives, Ann Med. 2006 ;38:20-31.
7) Arico M, Janka G, Fischer A. et al., Hemophagocytic lymphohistiocytosis. Report of 122 children from the international registry. FHL Study Group of the Histiocyte Society. Leukemia. 1996; 10(2):197-203.
8) George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. Journal of Blood Medicine. 2014; 5:69-86.
9) Reiner A, Spivak J. Hemophagocytic histiocytosis: a report of 23 new patients and a review of the literature. Medicine. 1988; 67: 369-388.
10) Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection and malignancy associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am. 1998; 12:435-444.
11) Lehmberg K, McClain KL, Janka GE, Allen CE. Determination of an appropriate cut off value for ferritin in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatric Blood and Cancer. 2014; 61(11):2101-2103.
12) Filipovich AH. Hemophagocytic lymphohistiocytosis(HLD) and related disorders. Hematology. 2009; 2001(1):127-131.