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SPLENOMEGALY IN A TROPICAL COUNTRY- A CLEVER IMPERSONATOR

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ABSTRACT

Hemophagocytic lympho-histiocytosis (HLH) is a potentially fatal disorder of Immune dysregulation which causes considerable morbidity and increased burden to healthcare in tropical and developing nations since it arises as one of the complications of Typhoid fever. By learning about its Pathogenesis and clinical presentation, preventive measures can be undertaken in clinical and epidemiological grounds. HLH due to Typhoid fever is a rare clinical presentation yet it warrants enough suspicion to reduce Morbidity and thus improve Quality of life. In this article we describe about one of the rare complications of Typhoid fever – Hemophagocytic Lympho-histiocytosis and Rhabdomyolysis in a 21 year old female from a Tropical country – India

INTRODUCTION

Typhoid fever is important etiology of Fever in tropical countries which can range from an uncomplicated febrile illness to life-threatening sepsis with multiorgan involvement. As the organism responsible for it – Salmonella Typhi spreads through feco-oral route, Typhoid fever is a major health concern among developing nations. Typhoid fever is one of the major causes of morbidity and mortality in crowded and unhygienic areas. We report a previously healthy female with severe Typhoid fever complicated by sepsis with Hemophagocytic Lympho-histiocytosis (HLH) and Rhabdomyolysis

Case Report

A 21 years female from South India presented with fever, fatigue and confusion for the past 5 days. She also complained of fatigue, body ache, and non-bloody, watery diarrhoea about 4-5 episodes/day for the past 3 days. Her History revealed that she had consumed one of her meals in a road side shop a week back. A provisional diagnosis of Typhoid fever was made and the patient was admitted. On admission her vitals were recorded as Temperature – 100.7°F (38.1°C), Blood Pressure - 98/56 mm of Hg, Heart Rate – 125 beats/minute, Respiratory Rate – 31 breaths/minute, Oxygen saturation 96% on room air. On examination ,patient was drowsy, disoriented, and had dry mucous membrane, moderate muscle tenderness, and mild splenomegaly. Otherwise no edema, lymphadenopathy, abdominal tenderness , skin rashes and meningeal signs. Laboratory investigation showed Pancytopenia with white cell count 1,800 /ml, Hemoglobin 7.9g/dl ,Platelet count 47,000 /ml . USG abdomen showed Moderate splenomegaly with no free fluid. Chest X ray – Normal, HIV 1&2-Negative , HBsAg and anti-HCV negative, Dengue IgM Negative, MSAT – Negative , IgM scrub – Negative, QBC and MP/MF – Negative, Widal O Ab positive in 1:400 dilution, and H Ab positive in 1:400 dilution, Serology reports for EBV & CMV were negative, DCT negative, CT brain showed evolving Cerebral edema possibly meaning meningitis/encephalitis, CRP – 110mg/L, LDH- 2207 U/L, ANA,ENA,ASO – Negative, Serum Ferritin - 4288mcg/L, Triglycerides 278mg/dl, Fibrinogen 1.2gm/L, CK -4186 U /L. Blood culture-positive for S .Typhi. Bone marrow biopsy – showed aggressive large histiocytes seen engulfing the erythroid and neutrophilic precursor which pointed to the diagnosis of HLH. Her Rhabdomyolysis and Pancytopenia improved with hydration, Antibiotics and low dose Steroids. She was discharged on Trimethoprim-sulfamethoxazole 160/800mg two tablets twice daily for a duration of 2weeks

DISCUSSION

Salmonella Typhi serovar *typhi* is a feco-orally transmitted Bacteria that can cause Typhoid fever which results in severe complications including Gastrointestinal bleeding, Intestinal perforation, Hepatitis, Pancreatitis, Typhoid encephalopathy, Disseminated Intravascular Coagulation, Hemolytic Uremic Syndrome, Endocarditis, Pneumonia, and rarely, Reactive HLH and Rhabdomyolysis[1] such as in our patient. The epidemiological burden of Typhoid fever is significantly high in populous and developing country like India. As Humans are its only Host, it is only transmitted from Person to Person. With the help of its flagellar Antigen H these bacteria attach themselves to the gut mucosa. With further Invasion and recruitment of other Mononuclear cells these cause Proliferation of Peyer's Patches and eventual Mucosal necrosis. This worsens the clinical condition and these Bacteria gain access to Reticulo-endothelial system and cause Multi-system Inflammation especially in Liver, Spleen and Gallbladder[2]. This presents as Fever with Hepatosplenomegaly in Tropical and Temperate Countries. However, Splenomegaly is also caused by one of its complications, namely Hemophagocytic Lympho-histiocytosis (HLH)

HLH is a rare still potentially fatal non-neoplastic disease resulting from dysregulated activation and proliferation of Lymphocytes, Natural Killer cells, and T cells. This dysregulation causes Immune hyperactivation, Increased Cytokines release, Hemophagocytosis and bone marrow suppression[3]. The bone marrow suppression is believed to be due to a maturity arrest of the myeloid series, eythroblasts and megakaryocytes with excessive phagocytic activity of the histiocytes in the marrow. This spectrum presents clinically as Fever, Hepatosplenomegaly, Liver dysfunction, increased Serum Ferritin levels and Phagocytosis of blood cells throughout the Reticuloendothelial system. This condition shares many clinical features with uncomplicated Typhoid fever hence serves as a Impersonator. Extreme clinical suspicion is required to diagnose this and subsequently treat it appropriately. This potentially fatal condition is classified as Primary and Secondary hemophagocytic syndrome. Primary HLH is familial, autosomal recessive and is usually diagnosed within the first

two years of life. Secondary HLH can occur at any age and it is usually due to immune system dysfunction caused by Malignancies, Autoimmune disorders, Rheumatological diseases and infections. Viruses are most frequently associated with secondary HLH, particularly Epstein-Barr virus but Tuberculosis, Malaria, Leishmaniasis, and

Typhoid are important tropical infections especially in the Indian subcontinent. Secondary HLH due to Typhoid fever is reported rarely in Tropical Countries like India and Colombia. HLH is diagnosed with a Molecular evidence or when five out of these signs and symptoms are present.

Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
Fever
Splenomegaly
Cytopenia in ≥ 2 CELL LINES
Hypertriglyceridemia / Hypofibrinogenemia
Low or absent natural killer cell cytotoxicity
Hyperferritinemia (≥500 ng/ml)
Elevated soluble CD25

Most cases respond to supportive care and treatment of the underlying infection, but severe cases, especially those associated with EBV, have required chemotherapy. As treatment of HLH warrants Steroids, a prompt diagnosis and distinction from uncomplicated Typhoid fever is needed.

The second unusual feature about this case is Rhabdomyolysis seen in the setting of Typhoid fever. Rhabdomyolysis has been reported in bacterial Sepsis, and in a retrospective study in 103 patients from India, 33% were noted to be in patients with gram-negative sepsis. However, S. Typhi was not isolated in their cohort[4]. There have been 22 case reports of Salmonella infection in the United States causing Rhabdomyolysis, but only two of these were due to S. Typhi, with the majority being caused by non-typhoidal strains. Mechanisms proposed include tissue hypoxia, direct muscle invasion by bacteria, and altered metabolic activity of involved muscles. Despite low incidence, Typhoid fever should be included in the differential diagnoses of Fever with Myalgia and should promptly be managed with treatment of an appropriate antibiotic to treat the underlying Infection and adequate hydration to prevent complications.

CONCLUSION

Typhoid fever should be suspected in endemic regions presenting with severe febrile illness complicated by pancytopenia and myalgia, which could be Secondary HLH and Rhabdomyolysis[5], respectively. As Multi-drug resistant strains of S.Typhi is seen prevalently in Indian subcontinent, judicial use of appropriate Antibiotics is warranted. Bone Marrow Biopsy is needed when there is a clinical suspicion of secondary HLH due to Typhoid Fever. Adequate Hydration and Corticosteroids are required to treat these rare complications in addition to treating underlying Infection. Health Education and Sanitary measures may improve the clinical outcome and subsequently reduce the Morbidity and Mortality associated with Typhoid Fever.

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