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Case Report: Typhoid Fever Complicated by Hemophagocytic Lymphohistiocytosis and Rhabdomyolysis

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Abstract. Hemophagocytic lymphohistiocytosis (HLH) and rhabdomyolysis are rare complications of typhoid fever from *Salmonella enterica* serovar Typhi. Herein, we describe the clinical features in a 21-year-old female from India who presented to the intensive care unit with fever, severe pancytopenia, and rhabdomyolysis.

INTRODUCTION

Typhoid fever (TF) remains to be an important etiology of fever in developing countries, with an estimated 13.5 million episodes in 2010.[1] The course of TF can range from an uncomplicated febrile illness to life-threatening sepsis with multiorgan involvement. We report a previously healthy Indian female with severe TF complicated by sepsis with multiple organ dysfunction syndrome, rhabdomyolysis, and hemophagocytic lymphohistiocytosis (HLH).

CASE REPORT

A previously healthy 21-year-old Indian woman from southern India presented to our hospital with fever and confusion that began 2 days after her arrival from India. She also complained of fatigue, myalgia, and non-bloody, watery diarrhea, occurring three to five times a day. She denies eating uncooked food and food prepared outside her home, or any contact with animals. No other family member or immediate contacts in India or in the United States developed similar symptoms. Her journey began from Vijayawada to Chennai, India, and her airline transit occurred through London, United Kingdom.

On admission, her vital signs were: temperature 39.5°C, blood pressure 88/44 mmHg, heart rate 158 beats/minute, respiratory rate 39 breaths/minute, and oxygen saturation of 95% on room air. Physical examination was remarkable for dry mucous membranes, mild muscle tenderness, splenomegaly, tea-colored urine, and disorientation. Otherwise, she had no edema, lymphadenopathy, abdominal tenderness, or skin rash. Laboratory investigations were significant for pancytopenia with white cell count 0.9×10^9/L (absolute neutrophil count 500/mm^3), hemoglobin 11.6 g/dL (nadir of 7.9), and platelet count 6×10^9/L, acute kidney injury with an elevated serum creatinine of 1.37 mg/dL (peak of 1.64), hypokalemia (nadir of 2.6 mmol/L), serum bicarbonate of 12 mmol/L, rhabdomyolysis with creatine phosphokinase (CPK) of 83,550 U/L, and urinalysis showing 3+ blood. She was human immunodeficiency virus negative, and workup for other infectious etiologies were negative, including *Ehrlichia* PCR; dengue IgM; *Leptospira* serology and urine culture; hepatitis A, B, C, and E panel; and malaria rapid antigen and smear. She was started empirically on intravenous vancomycin, cefepime, and doxycycline. Two sets of blood culture and stool culture grew *Salmonella enterica* serovar Typhi (*Salmonella typhi*), and her antibiotics were eventually de-escalated to intravenous ceftriaxone. Disk diffusion method for susceptibility performed by the Center for Disease Control disclosed the *S. typhi* to be susceptible to ampicillin, ceftriaxone, cefazolin, chloramphenicol, and trimethoprim–sulfamethoxazole, but had intermediate resistance to ciprofloxacin.

With regard to her pancytopenia, patient had a negative workup for hemolysis, however, she fulfilled the diagnostic criteria for HLH: presence of fever, splenomegaly, ferritin level of 838 ng/mL, and a soluble interleukin-2 receptor (IL-2R) level of 2,939 U/mL (reference range 45–1,105 U/mL). Her pancytopenia eventually improved with antibiotics as is expected for infection-associated HLH (IAH). Her renal function also improved with hydration and antibiotics. She was discharged on trimethoprim–sulfamethoxazole 160 mg/800 mg two tablets twice daily to complete a total of 2 weeks.

DISCUSSION

TF 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, hemolytic uremic syndrome, endocarditis, pneumonia, and rarely, reactive HLH and rhabdomyolysis such as in our patient.[2,3] Host factors associated with severe disease have been reported in younger individuals (birth through 1 year of age), the immunosuppressed, females, and those infected with resistant *S. typhi*.[3,4] Specific genetic polymorphisms in major histocompatibility complex class II and III genes have also been found in individuals with severe TF.[5,6]

IAH has been most commonly associated with viral infections, especially Epstein–Barr virus (EBV), but has also been reported with pyogenic infections.[7,8] IAH as a complication of typhoid is rarely reported. The incidence is unknown in the United States, but in a case series of 30 patients in India, two of IAH cases were in patients with TF.[8] The pathophysiology of IAH is poorly understood, but it is suggested to be due to hypersecretion of cytokines by persistently activated lymphocytes and histiocytes. HLH is diagnosed using clinical and molecular criteria. Five of eight clinical findings required are fever; splenomegaly; cytopenia; hypertriglyceridemia and/or hypofibrinogenemia; demonstration of hemophagocytosis 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.[7] Sixty to seventy

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percent of patients with IAH respond to supportive care and treatment of the underlying infection, but severe cases, especially those associated with EBV, have required chemotherapy.[7]

The second unusual feature about this case is the degree of rhabdomyolysis seen in the setting of enteric 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, and the mean serum CPK of 7,114 IU/L was much lower than in our patient.[9] In a review of literature from 1996, *Salmonella* spp. was found to be the fourth most commonly cited cause of bacteria-induced rhabdomyolysis, with 67% of the cases leading to acute kidney injury.[10] 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.[11,12] It should be noted that in all the cases, rhabdomyolysis was noted when patients were bacteremic. Mechanisms proposed include sepsis causing tissue hypoxia, direct muscle invasion by bacteria, and altered metabolic activity of involved muscles.[13] Despite its rarity, TF should be included in the differential diagnosis of myositis or rhabdomyolysis in foreigners or returning travelers and should be managed with treatment of an appropriate antibiotic and adequate hydration to prevent complications.

CONCLUSION

TF should be suspected in returned travelers or foreigners from endemic countries presenting with severe febrile illness complicated by pancytopenia and myalgia, which could be IAH and rhabdomyolysis, respectively. Recognition is important for prompt diagnosis and treatment with an appropriate antibiotic to prevent complications and increased mortality.

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