Typhoid Fever Complicated by Rhabdomyolysis with Acute Hepatitis, Splenic Infarct, Pancreatitis, and Acute Kidney Injury

Abstract

Typhoid fever is a potentially life-threatening infectious disease that presents itself with a wide array of symptoms ranging from uncomplicated fever to sepsis with multiorgan dysfunction syndrome. An 18-year-old male college student presented with progressively increasing fever with abdominal discomfort, anorexia, and persistent vomiting. Typhoid fever was suspected in view of clinical findings along with leukopenia, grossly elevated transaminases, and acute kidney injury. He was managed with intravenous (IV) antibiotics, which resulted in the resolution of fever and other symptoms. Rhabdomyolysis is an extremely rare complication in typhoid fever, which is a very common cause of fever in tropical countries, leading to acute renal failure, causing very high morbidity and mortality.

Keywords: *Hepatitis, myoglobinuric renal failure, pancreatitis, rhabdomyolysis, splenic infarct, typhoid*

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Introduction

Typhoid fever is an important cause of fever, morbidity, and mortality in developing countries. Its wide clinical spectrum can range from uncomplicated febrile illness to life-threatening sepsis with multiorgan dysfunction. Rhabdomyolysis as a complication of typhoid fever is rather extremely rare. This case report describes a young male with *Salmonella enterica* serovar *typhi*, complicated by rhabdomyolysis, pancreatitis, and multiorgan dysfunction.

Case History

An 18-year-old college student was brought to the emergency with a history of progressively increasing fever from the last 8–10 days, associated with abdominal discomfort, anorexia, and persistent vomiting. He was normal before the onset of symptoms and had no significant past medical history. He gave no history of alcohol intake or any drug abuse or blood transfusions. Physical examination revealed generalized abdominal mild tenderness. He was febrile (102°F), dehydrated, having tachycardia (132/min), and had a toxic look. His blood pressure was 90/60 mmHg. He also gave history of decreased urine output for 1 day. He was carrying reports of some blood tests done a day before the presentation, which showed thrombocytopenia (7000/L), leukopenia (2.9 × 10^9/L), and grossly elevated transaminases (aspartate aminotransferase [AST]- 2312 U/L, alanine aminotransferase [ALT]- 512 U/L). Hemoglobin was 12 g/dL, and bilirubin was within normal limits. The patient was admitted to the intensive care unit (ICU) with an initial working diagnosis of possibly enteric fever or malaria or leptospirosis. His labs on day 1 of admission revealed normal hemoglobin 13.2 g/dL, with leukopenia white cell count of 3.5 × 10^9/L, thrombocytopenia (40,000/L), and grossly deranged liver function tests (ALT- 468 U/L, AST- 2464 U/L, lactate dehydrogenase- 3873 U/L, and international normalized ratio (INR) of 1.4).

His kidney function tests were also grossly deranged with urea 208 mg/dL, creatinine 12.2 mg/dL (estimated glomerular filtration rate [eGFR] 5), and uric acid 16.5 mg/dL. The patient was started on hemodialysis urgently. His tests for malaria, IgM anti-HAV, IgM anti-HEV, and HBsAg, and dengue serology were negative. Urinalysis showed

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3+ proteinuria, 2+ hematuria, 10 white blood cells (WBC), and no casts. Chest X-ray and 2D-echocardiography were normal. Ultrasound abdomen showed hepatosplenomegaly with splenic infarcts, bulky distal body and tail of pancreas, and mild ascites. Amylase and lipase were also raised (amylase- 278 U/L, lipase- 432 U/L). Based on these initial reports, it was clear that the patient had multiorgan involvement. His autoimmune workup was negative. Other causes of acute febrile illness with acute kidney injury, like rickettsia and post streptococcal glomerulonephritis (PSGN), were ruled out. Weil–Felix and ASO titer were negative. Coronavirus disease (COVID) reverse transcriptase polymerase chain reaction (RT-PCR) was also sent in view of the ongoing pandemic, which was negative. Leptospiral serology and urine culture were negative. During admission, the patient complained of myalgia and leg pains, and so, creatinine phosphokinase levels were checked, which were astonishingly high (58,011 U/L). On day 4 of admission, his blood culture grew *S. enterica* serovar *typhi*. So here, we had a case of a young male with a classic book-like clinical spectrum of enteric fever complicated by acute hepatitis, acute pancreatitis, splenic infarcts, and acute renal failure secondary to rhabdomyolysis. Later, on the fifth day of admission, he also had lower gastrointestinal bleeding and his hemoglobin dropped down to 5.5 g/dL, yet another known complication of enteric fever, especially in the third week of illness, as seen in this patient. He was started on intravenous antibiotics as per culture reports, blood transfusions, and hemodialysis. Subsequently, after 4 days of treatment in the hospital, he became afebrile, had no gastrointestinal bleed, and hemoglobin stabilized to 9 g/dL, with a good urine output and creatinine of 2.4 mg/dL.

He was discharged on intravenous antibiotics. His serial creatinine phosphokinase levels showed a progressive decline as his clinical condition improved. On follow-up, 5 days post-discharge, he was doing well, and his kidney function, transaminases, and creatinine phosphokinase levels were within normal limits.

Discussion

Rhabdomyolysis is destruction of skeletal muscle fibers with the release of cellular elements into the systemic circulation.[1] Common causes are traumatic, metabolic, gram-negative toxemia, and enzymatic. Rhabdomyolysis has been reported in bacterial sepsis, and in a retrospective study of 103 patients from India, 33% of the cases were noted to be in patients with gram-negative sepsis.[2] However, *S. typhi* was not isolated in their cohort. *Salmonella* species is found to be the fourth most common cited cause of bacteria-induced rhabdomyolysis, with the majority caused due to nontyphoidal strains.[3]

Rhabdomyolysis caused by typhoid fever is a rare entity.[4] Out of 22 cases of typhoid infected Rhabdomyolysis, only 2 were caused by S.typhi over a span of 40 years in USA.[5] It should be noted that in all the cases, rhabdomyolysis was noted when patients were bacteremic. Serum creatinine phosphokinase (CPK) levels are a hallmark of rhabdomyolysis, and five times the normal levels is diagnostic.[6] Several poorly understood mechanisms have been proposed by which *Salmonella* induces rhabdomyolysis, which include tissue hypoxia caused by sepsis, direct bacterial invasion of muscle, toxin release, activation of lysosomal enzymes, and low oxidative and glycolytic enzyme activity.[7] An increase in intracellular concentration of calcium ions has been established as the final common pathway for the development of rhabdomyolysis.[8]

In most cases, rhabdomyolysis is followed by acute renal failure. Renal involvement is a rare manifestation of typhoid fever, occurring in only 2%–3% of cases.[9] The renal involvement is acute, transient, and reversible glomerulonephritis with proteinuria and hematuria. Renal complications in typhoid fever include cystitis, pyelitis, pyelonephritis, mild proteinuria, and less commonly, mild to severe glomerulonephritis, acute tubular necrosis, and interstitial nephritis. Even though the causes of renal failure in many patients are still uncertain and a multifactorial etiology cannot be ruled out, the most likely causes are dehydration, shock, and rhabdomyolysis.[10] Clearly, the most likely explanation of the renal failure in our case is rhabdomyolysis; however, the combination of proteinuria and hematuria suggests that acute nephritic syndrome may also have contributed to it. Acute nephritic syndrome in typhoid fever as the likely cause of acute renal failure has been reported by Hayashi *et al.* in Japan.[11] Hemodialysis was required frequently before renal failure was resolved.

Pancreatitis has been infrequently described in typhoid fever. In a case report by Kadappu *et al*., they reported two cases of *Salmonella* pancreatitis.[12] Similarly, Khan *et al*. also reported cases of *Salmonella* pancreatitis with rhabdomyolysis and renal failure.[13] In the lack of an exact mechanism linking typhoid fever and acute pancreatitis, the suggested explanation is direct pancreatic localization of bacteria, which could have entered through the hematogenous route, lymphatic route, and transmural migration via the biliary duct system or from the duodenum via the main pancreatic duct. Biliary stasis due to cholelithiasis, choledocholithiasis, and biliary tract abnormalities predispose an individual to the above mechanisms,[14] but none of this was present in our patient. Toxin-induced and immune-mediated pancreatitis have also been postulated as other possible explanations.[15]

Salmonella hepatitis is commonly seen and is usually asymptomatic and mild, causing only slightly elevated AST and ALT levels.[16] More than one-third of patients have jaundice. Studies from the Thailand have documented the incidence of *Salmonella* hepatitis to be from <1% to 26% of patients.[17] The factors probably associated with enteric hepatitis are virulence of the organism, delayed treatment,

and poor health of patients. Our patient had high levels of transaminases, with AST levels much higher than ALT levels, but since he also had associated rhabdomyolysis, it can be difficult to distinguish true hepatitis from leakage of muscle cell transaminases. Our patient had a rare coexistence of acute hepatitis with coagulopathy (INR 1.4) and acute pancreatitis, which was reported earlier in one of the patients from Korea.[18] Our patient also developed lower gastrointestinal bleed during the third week of his illness as per the history and time of presentation, as evident by a fall in hemoglobin to 5.6, requiring blood transfusions, which is a frequent and known complication of typhoid fever in this week. Fresh frozen plasma transfusions and vitamin k injections promptly corrected this complication.

This case had an additional finding of multiple splenic infarcts, which was not seen in any of the above-mentioned case series and is one of the abdominal complications of late treatment of typhoid fever.[19] Abdominal ultrasound and computed tomography (CT) are very helpful in the early detection of the splenic lesion. Mechanism of typhoid splenic abscess includes bacteremia in immunocompromised individuals and in patients whose spleen architecture is already altered (e.g., splenic infarction in sickle cell disease or vasculitis) and extension of infection from contagious areas (e.g., intestinal perforation).[20]

Treatment and prognosis of myoglobinuric renal failure and acute pancreatitis associated with typhoid fever remain unclear. According to our review of reported cases, in addition to our case, it seems to have a benign course. The most important aspect of treatment is to recognize the condition promptly, initiate early proper antibiotics, and provide good supportive care. Monitoring any complications and instituting appropriate therapy is critical. The interesting fact is that most of the reported cases of rare complications are among young adults, like that of our case, probably because they did not receive adequate treatment or due to robust immune reactions.[13]

Conclusion

Typhoid fever has potentially serious complications that might involve multiple organs simultaneously in the same patient. Early recognition, supportive care, and adequate antimicrobial treatment are mandatory for these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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