

# Salmonella Hepatitis: An Uncommon Complication of a Common Disease

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### ABSTRACT

Typhoid fever is a very common infectious disease of tropics, associated with high morbidity and mortality. Typhoid fever is often associated with hepatomegaly and mildly deranged liver functions; a clinical picture of acute hepatitis is a rare complication. We report a young patient who presented with fever and jaundice and was found to have acute hepatitis secondary to typhoid fever. Recognition of Salmonella hepatitis is of clinical importance as it can mimic acute viral hepatitis. Early institution of specific therapy can improve the prognosis in these patients.

**Keywords:** Enteric fever, Salmonella hepatitis, *Salmonella typhi*, typhoid fever, typhoid hepatitis

### Introduction

Typhoid fever is a very common infectious disease of tropics, associated with high morbidity and mortality.<sup>[1]</sup> It usually starts as an acute systemic disease without localization, and is clinically indistinguishable from other infections, including malaria, bacterial, and viral infections. Multiple organs are known to be affected by the disease. Hepatic involvement could be considered important, as it may be associated with a higher relapse rate.<sup>[2,3]</sup> Typhoid fever is often associated with hepatomegaly and mildly deranged liver functions; a clinical picture of acute hepatitis is a rare complication. We report a young patient who presented with fever and jaundice and was found to have acute hepatitis secondary to typhoid fever.

### Case Report

A 16-year-old male patient presented in medical outpatient department with history of high-grade fever with chills and an ill-defined abdominal pain of 7 days duration in October 2011. There was no history of cough, chest pain, dyspnea, dysuria, skin rashes, pruritus, dark color urine, clay color stool, or any hemorrhagic manifestations. He had no significant history of medical illness, drug ingestion, surgical procedures, blood

transfusion, sexual promiscuity, and intravenous drug abuse or alcohol consumption. On examination, he was ill looking, mildly dehydrated, and febrile. He had tachycardia with normal blood pressure and respiration. Abdominal examination revealed soft, tender liver, 2 cm palpable below the costal margin at the midclavicular line. Rest of the general and systemic examination was unremarkable. His laboratory investigations showed borderline leukopenia (3800/mm<sup>3</sup>). Peripheral smear for malarial parasite was negative. Biochemical evaluation showed normal renal functions and electrolytes, albumin, and coagulation parameters. Transaminases were elevated with aspartate aminotransferase (AST) 263 U/l, alanine aminotransferase (ALT) 382 U/l, and alkaline phosphatase (ALP) 126 U/l. Total and conjugated serum bilirubin were 1.8 and 1.2 mg/dl, respectively. The blood, urine cultures, hepatic viral markers and serology for enteric fever, dengue and leptospirosis were sent. The patient was treated empirically with antimalarials chloroquine + lumefantrine and flouroquinolone (levofloxacin). Two days later, he was admitted in the emergency ward with vomiting and continuation of high-grade fever. His liver enzymes showed worsening (AST level was 792 U/l and ALT level was 1247 U/l). The icterus was apparent clinically, with a total bilirubin level of 3.6 mg/dl. The serum ALT:Lactate dehydrogenase (LDH) ratio (expressed in multiples of upper limit of normal) was found to be less than 9. The serology for viral hepatitis, dengue, and leptospirosis sent earlier was negative. Widal test was strongly positive in 1:640 dilution for

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both “O” and “H” antigens. Patient was treated with ceftriaxone 1 g intravenous twice daily and azithromycin 1g oral daily for 1 week. His blood culture yielded a growth of *Salmonella typhi* after 5 days incubation, with antibiotic sensitivity to ciprofloxacin (MIC < 0.5 mg/l) and ceftriaxone (<0.25 mg/l). The strain was resistant to ampicillin and amoxicillin + clavulanic acid. With treatment, the patient showed rapid clinical improvement along with decline in liver transaminases levels. He was discharged after 7 days of hospitalization.

## Discussion

Typhoid fever continues to be a common infection in the developing countries. William Osler initially reported hepatic involvement of typhoid fever in 1899.<sup>[4]</sup> Hepatomegaly and moderate elevation of transaminase levels are the common findings that occur in 21–60% of cases<sup>[6,7]</sup> of typhoid fever. However, severe hepatic derangement simulating acute viral hepatitis is very rare. The presentation with marked elevation of transaminases similar to that of acute viral hepatitis, as observed in this case, has been reported by others.<sup>[8-10]</sup> Recognition of this clinical condition is particularly important in tropical countries where malaria and viral hepatitis are quite common. El-Newihi *et al.*<sup>[9]</sup> did a retrospective analysis to compare clinical, biochemical picture, and the outcome of patients with Salmonella hepatitis and acute viral hepatitis. They concluded that the clinical picture of Salmonella hepatitis is frequently indistinguishable from that of viral hepatitis. Other clues that raise the possibility of Salmonella hepatitis include high fever, relative bradycardia, and left shift of WBCs. Despite long hospitalization, Salmonella hepatitis responds to proper antibiotic therapy and has an excellent prognosis.

The admission ALT/LDH ratio is the best discriminator between both entities, which was also advocated by Balasubramanian *et al.*<sup>[10]</sup> in their study of 100 consecutive children with typhoid fever. The serum ALT: LDH ratio levels (expressed in multiples of upper limit of normal) was found to be less than 9 in typhoid hepatitis and more than 9 in acute viral hepatitis.

In viral hepatitis, nonspecific prodromal illness precedes jaundice and the fever usually subsides with the appearance of jaundice, while in typhoid, jaundice usually occurs within the first 2 weeks of febrile illness and the fever persists despite the appearance of jaundice.<sup>[11]</sup>

Pramoolsinsap *et al.*<sup>[12]</sup> in their comprehensive review of Salmonella hepatitis suggested that typhoid fever is often associated with abnormal liver biochemical tests, but severe hepatic involvement with clinical features of acute hepatitis is a rare complication. The documented incidence varies widely from less than 1% to 26% patients with enteric fever. The clinical course can be severe with a mortality rate as high as 20%, particularly with delayed treatment or in patients with other complications of *Salmonella* infection. The factors predisposing to varying degrees of hepatic injury in typhoid fever are not exactly known. Possibly, there is an interplay of the micro-organism factors and

the immunity, which cause liver injury.<sup>[13]</sup> The pathophysiological mechanism by which Salmonella produces hepatic dysfunction, although not fully known as yet, is postulated to be either due to direct invasion or by endotoxemia with immune-mediated liver damage.<sup>[2,7]</sup> Histopathologic study of the liver reveals typhoid nodules, cloudy swelling, ballooning degeneration, moderate fatty change, and mononuclear cell infiltrate in few focal areas.<sup>[2,6]</sup> In addition, intact bacilli have been demonstrated in the parenchyma of the liver by immunohistochemistry and have been cultured from liver biopsy.<sup>[5]</sup>

Although hepatitis-like picture with fever and jaundice is unusual and infrequently reported in the pediatrics literature,<sup>[13]</sup> in tropical areas, the differential diagnosis of a child presenting with fever and jaundice should include typhoid hepatitis. Cholestasis secondary to typhoid fever has only been reported in a few instances.<sup>[14]</sup> In a study of 254 patients with typhoid fever, Ahmad *et al.*<sup>[15]</sup> found that clinical manifestations of typhoid fever are often non-specific and clinically indistinguishable from other infections, including malaria and other bacterial and viral infections, and can pose a significant diagnostic problem, especially in the tropics where jaundice in the febrile patient can be due to malaria, amebic or viral hepatitis. In many parts of the world, diagnosis is still based entirely on clinical features because conclusive laboratory confirmation of the infection is not usually available. They also reported significant rise in serum bilirubin without a corresponding increase in serum ALT, which is unusual in viral hepatitis but common in typhoid. So, typhoid should be considered in any febrile patient who develops jaundice about a week after the onset of illness and at the peak of fever with or without hepatomegaly. There are studies showing higher relapse rate associated with Salmonella hepatitis as compared to the general population.<sup>[2,3]</sup>

Since typhoid fever is a common illness, the recognition of Salmonella hepatitis is of clinical importance as it can mimic viral, malarial, or amebic hepatitis. Early institution of specific therapy can improve the prognosis in these patients.

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