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Cholestatic hepatitis due to *Salmonella typhi*

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Abstract

Salmonella infection occurs worldwide and is still an important public health problem in many developing countries. The infection can affect almost all major organs including the liver. Severe hepatic involvement with a clinical feature of acute hepatitis is a rare complication. In this paper, a 39-year-old male with acute cholestatic typhoid hepatitis is presented. The case had a tender hepatomegaly and elevated serum alanine and aspartate transaminase, alkaline phosphatase, and gamma glutamyl transferase levels; these features cannot been distinguished from those of acute viral hepatitis. Serological and viral markers of acute viral hepatitis were negative. No pathology could be determined in abdomen Ultrasonography (USG) or Magnetic Resonance (MR) Cholangiography. As enteric fever is a common infection, the recognition of salmonella hepatitis is of clinical importance. When patients from an endemic or outbreak area present acute febrile hepatitis, typhoid fever should be a consideration.

Introduction

Typhoid fever is an acute systemic disease caused by the ingestion of food or water contaminated with the organism *Salmonella enterica* subsp. *enterica* serotype Typhi. The infection occurs worldwide and is still an important public health problem in many developing countries.[1] It is estimated to cause more than 21 million illnesses and 216,000 deaths worldwide annually.[2] The clinical manifestations of typhoid fever are usually nonspecific, such as sustained fever with fatigue, headache, abdominal pain, vomiting, or anorexia. Various organs, including the liver, have been involved in the course of typhoid fever, resulting in a wide spectrum of presentations.[3]

The usual pathological site of salmonella infection is the lymphoid tissue of the gastrointestinal tract. Hematogenous dissemination of the organism or its endotoxin results in systemic involvement that can affect almost all major organs, including the liver, central nervous system, gall-bladder, kidney, lung, and heart.[1,3] Liver involvement is commonly observed in patients with typhoid fever, but severe hepatic involvement with a clinical feature of acute hepatitis is a rare complication.[3]

Case Report

In this paper, a patient with acute cholestatic typhoid hepatitis is presented. A previously healthy 39-year-old man was admitted from Pasinler/Erzurum, where there was a limited outbreak of *Salmonella typhi* infections in the summer of 2010. Seven days before admission, he had a temperature of 39.2°C, with a headache, fatigue, loss of appetite, and a nonproductive cough. Amoxicillin and acetaminophen provided by his doctor did not reduce the patient's temperature. General physical and systemic examinations were unremarkable, except for fever and mild tenderness in right upper abdominal region.

On investigation, the patient's hemoglobin level was 15.2 g/dL, total leukocyte count was 7400/µL (polymorphs 58%, lymphocytes 31.8%, monocytes 10%, basophils 0.1%, and eosinophils 0.1%,), and platelet level was 128,000/µL. Liver tests showed increase in aspartate transaminase (AST) (277 U/L; range 4-37), alanine transaminase (ALT) (657 U/L; range 0-42), gamma-glutamyl transferase (GGT) (322 U/L; range 5-50), alkaline phosphatase (ALP) (1111 U/L; range 0-270), total bilirubin (1.15 mg/dL; range 0.2-1.1), and direct bilirubin (0.96 mg/dL; range 0.00-0.30). Salmonella test of the patient was found positive. In addition, salmonella was produced in blood culture. Serological and viral markers of acute viral hepatitis were negative (markers for the hepatitis C virus, hepatitis A virus, hepatitis B virus, hepatitis E virus, cytomegalovirus, and Epstein-Barr virus). The C-reactive protein (CRP) level was 199 mg/dL (range 0-6). Urinalysis showed normal features. Changes in laboratory results after the patient's hospitalization are given in Table 1.

Abdominal sonography resulted in normal findings. The Magnetic Resonance (MR) Cholangiography findings requested as a result of the consultation with the gastroenterology clinic were also normal.

The patient was treated initially with ceftriaxone (CEF) 2 g given intravenously once daily. On the fourth day of the treatment, blood culture yielded the growth of S.typhi. The isolate was susceptible to cefotaxime and CEF, but resistant to ciprofloxacin and levofloxacin.

The patient remained febrile for 5 days. Then, after treatment with CEF on the sixth day, the patient was feeling better, and we observed the progressive improvement of liver enzymes and CRP. In addition, blood and stool cultures were tested, respectively, after 10 days of CEF, and were negative. The patient left the hospital after 10 days, well and fully recovered.

Discussion

Salmonella typhi infection is still a major health problem in tropical and developing countries. In the developed world, enteric fever is uncommon and predominantly a disease of returning travelers.

Typhoid fever is often associated with abnormal biochemical tests on the liver, but severe hepatic involvement with a clinical feature of acute hepatitis is a rare complication. Hepatic complications of typhoid fever were first reported by William Osler in 1899.[4] He documented eight cases with hepatomegaly and jaundice out of 1500 cases of typhoid fever. Since then, several reports of typhoid hepatitis have been described.[4] The extent of liver involvement in typhoid fever may be a dramatic presentation with a picture indistinguishable from viral hepatitis in 1-26% of cases.[5-7] Our case had elevated serum alanine and aspartate transaminase, alkaline phosphatase, and gamma glutamyl transferase levels; these features cannot been distinguished from those of acute viral hepatitis.

Four cases whose acute renal failure and hepatitis complications had been followed were presented in a study conducted in South Africa, and the AST value in these cases was found to be a maximum of 830 U/L. As the course of this case was cholestatic, AST increased to a maximum of 248 U/L.[3]

In another study,[5] data from 27 patients with typhoid hepatitis were compared to those of 27

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Table 1. Hematological and biochemical profile of patient.

	Normal range	30.09.2010	04.10.2010	06.10.2010	11.10.2010	22.12.2010
Hemoglobin	13.5-15.5 (g/dL)	15.2	13.6		14	16.2
Leukocyte count	4.8-10.8 (103/µL)	7.4	6.7		9.7	8.7
Platelet	130-400(103/µL)	128	190		443	269
AST	4-37 U/L	277	233	248	64	24
ALT	0-42 U/L	657	338	425	148	41
ALP	0-270 U/L	1111	1144	1787	675	260
GGT	5-50 U/L	322	271	267	176	30
Total bilirubin	0.2-1.1 mg/dL	3.15	4.35	5.37	2.46	0.25
Direct bilirubin	0.0-0.3 mg/dL	2.96	3.13	4.60	2.03	0.01
CRP	0-6 mg/L	199	38.9	20.6	12.7	3.25

AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CRP, C-reactive protein

acute viral hepatitis cases. In this study, the ALT increase of the transfused cases of patients with typhoid hepatitis was less than that found in those with viral hepatitis and AST; the increases in ALP levels were found to be more apparent. Again, while bilirubin levels were found to be higher in patients with acute hepatitis, they were lower in patients with salmonella hepatitis. However, a small increase was determined in the bilirubin levels. No pathology could be determined in abdomen Ultrasonography (USG) or MR Cholangiography.

In an extensive examination made on typhoid hepatitis in Thailand, it was noted that cases similar to acute hepatitis clinic were seen quite rarely; and it was emphasized that virulence of the factor, delay in treatment, and the patient's general state of health being bad may cause this picture to emerge. Typhoid nodules characterized by an apparent hyperplasia in reticuloendothelial cells were mentioned in the pathological examination. It was claimed that typhoid hepatitis pathogenesis was multi-factored and endotoxins, local inflammatory response, and/or immune response of the host can be effective.[1]

The recent demonstration of intact S.typhi in the liver tissue of patients with typhoid fever suggests that organisms are phagocytosed by the reticuloendothelial system but overcome the cells' killing action and produce hepatic injury by liberating cytotoxic substances *in situ*.[4]

Acetaminophen is known to cause toxic hepatitis mostly in a closed dependent manner and with hepatocellular damage. The occurrence of hepatitis approximately 1 week after the use of low dose of acetaminophen (1500 mg/day) in the subject and with the treatment specific to salmonella (ceftriaxone) which is thought to have caused this picture, improvement in cholestatic hepatitis case (cholestasis enzymes and bilirubin levels had reduced) with the symptoms of the patient have made us diagnose salmonella induced cholestatic hepatitis on the subject. No certain toxic hepatitis is usually expected with the use of acetaminophen in daily therapeutic doses and it is too rare in cholestatic type (excluding idiosyncratic cases). In a recent study about the use of acetaminophen in daily therapeutic doses and covering more than 2500 patients where the patients were followed for more than one year, it was stated that only 181 of the patients had their ALT values above normal limits. In the study, three times height of ALT and the height of bilirubin level were not determined together in any of the patients.[8] Also, none of the patients' ALT levels were found higher than 10 times of normal limits. As our patient used normal therapeutic dose of acetaminophen (1500 mg/day), the cholestatic form of the hepatitis incurred and ALP, GGT, ALT and direct bilirubin (DBIL) rise being in the foreground, ALT levels rising approximately 15 times more the higher limit of the normal as well as the visible improvement in the cholestasis table after ceftriaxone treatment made us think of salmonella induced cholestatic hepatitis in the patient.

The prognosis is usually good, as salmonella hepatitis responds well to specific antibiotic therapy. 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.[1] Treatment with appropriate antimicrobial agents is important in reducing the mortality of invasive infection. Fluoroquinolones (e.g., ciprofloxacin), which have been available since the 1980s, have become a mainstay of therapy for invasive salmonellosis. However, resistance against quinolones has gradually been seen in increasing rates.[9,10] Reduced ciprofloxacin sensitivity has become increasingly prevalent and is associated with high rates of clinical and microbiological failure.[11] Therefore, alternative antimicrobials, including third generation cephalosporins and azithromycin, are increasingly used as first-line therapy.[11] There was quinolone resistance in our case as well, and the patient was treated by ceftriaxone.

Conclusions

As enteric fever is a common infection, the recognition of salmonella hepatitis is of clinical importance. When patients from an endemic or outbreak area present acute febrile hepatitis with or without diarrhea, typhoid fever should be a consideration. Blood culture and serological tests for salmonella in these patients will lead to early diagnosis and appropriate treatment.

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