Abstract

During the course of typhoid fever, the usual histologic finding of the liver is “nonspecific reactive hepatitis.” Hepatic granuloma (HG) is a rare complication of typhoid fever. We present two cases of typhoid fever with HG and review the relevant literature. Case 1 (a 53-year-old female) was found to have both hepatic and splenic granulomas. This is the first case of typhoid fever with splenic granulomas in the English language literature. Case 2 (a 66-year-old male) developed granulomas in the bone marrow in addition to HG. It should be considered that typhoid fever may lead to granulomas in several organs.

Case Report

Case 1

A 55-year-old woman was admitted with a 2-week duration of fever, chills, loss of appetite, fatigue, headache, myalgias, colicky periumbilical pain, jaundice, nausea, and diarrhea. She had used ampicillin irregularly for five days before admission but without response. Her past and family histories were unremarkable. Physical examination revealed a temperature of 39.5°C, blood pressure of 110/60 mmHg and pulse rate of 80/min. She had a decrease in skin turgor, jaundice on scleras, increased bowel sounds and tenderness on abdomen.

Laboratory investigations showed hematocrit 30%, white blood cells 5,000/µl (differential count: stab 5%, PMN leucocyte 60%, lymphocyte 30%, and monocyte 5%), platelets 250,000/µl, erythrocyte sedimentation rate (ESR) 100 mm/h, ALT 323 IU/l, AST 250 IU/l, alkaline phosphatase 790 IU/l (normal range: 64–306), γ-GT 70 IU/l (N: 0–190), LDH 919 IU/l (normal range: 225–450), total bilirubin 2.9 mg/dl, direct bilirubin 2.3 mg/dl, total protein 5.7 g/dl (N: 6.20–8.50), albumin 2.68 g/dl (normal range: 3.63–4.91). Chest X-ray was normal. During the clinical follow-up, she developed intermittent-type fever rising up to 40°C. Painless diarrhea without blood and mucus continued. She developed hepatomegaly of 4 cm and splenomegaly at the costal margin. She lost 6 kg. Stool investigation revealed 7–8 white blood cells, without erythrocytes and parasites. Stool cultures yielded no pathogens as did blood cultures. Widal test and Brucella agglutination test repeated within 2 weeks remained negative. Anti-HAV IgM, HBsAg, anti-HBeIgM, EBV IgM and IgG, CMV IgM and IgG, Brucella IgM and IgG remained negative. Repeated chest X-ray did not show miliary pattern; repeated tuberculin skin test remained negative and fundoscopic examination was normal.

Her anemia was of the chronic inflammation type. White blood cells and lymphocytes changed in ranges of 3,700–6,500/mm³ and 1,500–3,000/mm³ respectively. Aspiration of

Introduction

Typhoid fever is a systemic infectious disease caused by a Gram-negative agent Salmonella typhi. While hepatomegaly is encountered in ~80% of the patients, ~60% of the patients have some abnormalities in liver function tests (generally a moderate rise in AST level, prolonged prothrombin time in ~25%, and hyperbilirubinemia in ~17%) (1, 2). Severe hepatic involvement with a clinical feature of acute hepatitis can be seen in 1–26% of patients with typhoid fever (3). In contrast, hepatic granuloma (HG) is rarely seen. Here, we report two cases of typhoid fever with HG and review the relevant literature.
bone marrow was normal. ESR persisted in value of $\sim 100$ mm/h. Gynecologic examination and double-contrast colon studies were normal. Abdominal and pelvic CT revealed splenomegaly and interaorto-caval lymph nodes measuring $\sim 1$ cm. A diagnostic laparotomy was planned with her informed consent; wedge biopsy of liver and splenectomy were performed. Non-caseating granulomas were observed in both specimens (Figs. 1 and 2). The second sets of blood samples taken just before laparotomy cultured *S. enterica* serovar *Typhi* sensitive to chloramphenicol, ampicillin, trimethoprim/sulfamethoxazole, and ciprofloxacin with disk-diffusion method. She responded well to chloramphenicol.

**Case 2**

A 66-year-old man was admitted with a 7-day duration of constipation, 5-day duration of fever and chills. His past and family histories were noncontributory.

He looked ill. Physical examination revealed a temperature of 39.2°C, blood pressure of 110/70 mmHg and pulse rate of 68/min, the remaining findings of examination were unremarkable.

Laboratory investigations showed hematocrit 33%, white blood cells 1,300/µl (differential count: PMN leukocyte 60%, lymphocyte 40%), platelets 80,000/µl, ESR 45 mm/h, AST 162 IU/l, ALT 139 IU/l, alkaline phosphatase 228 IU/l (N: 64–306), $\gamma$-GT 101 IU/l (normal range: 0–190), LDH 1,064 IU/l (normal range: 225–450), CPK 101 IU/l (normal range: 0–190), total bilirubin 0.5 mg/dl. The remaining laboratory results, urinalysis and chest X-ray were normal.

During clinical follow-up, he had night fevers rising up to 39.2°C with chills. We detected a positivity of 1/160 to O antigen and 1/320 to H antigen by Widal test. *Brucella* agglutination tests (Rose-Bengal and Wright) remained negative. Blood and bone marrow samples taken during admission cultured *S. enterica* serovar *Typhi* sensitive to chloramphenicol, ampicillin, trimethoprim/sulfamethoxazole, and ciprofloxacin with disk-diffusion method. Stool cultures yielded no pathogens.

He responded well to ciprofloxacin (500 mg, twice daily oral) within 4 days. Bone marrow biopsy revealed two tubercules with small foci of noncaseating necrosis (Fig. 3). Liver biopsy showed microvesicular steatosis in the parenchyma, mild inflammatory response and a microgranuloma in a portal region.

Abnormalities in blood count and liver function tests improved well within 2 weeks. The patient has been doing well for 18 months.
Discussion

Salmonella infections may affect many sites, although the gastrointestinal tract is primarily affected (4). During the course of typhoid fever, the usual histologic finding of the liver is “nonspecific reactive hepatitis.” (1–3, 5, 6). Previously, increased activity of the reticuloendothelial activity in the liver and spleen has been detected in typhoid fever (7). The most frequent changes are the presence of areas of focal hepatocyte necrosis with mononuclear cell infiltration (the typhoid nodules), dilation and congestion of sinusoids, and hyperplasia of Kupffer cells. HG is a rare complication of typhoid fever (4, 7, 8). Three cases of typhoid fever with HG have been reported in the English language literature (6, 7). The present cases represent the 4th and 5th cases. The features of these patients are summarized in Table 1. Paris (8) reported 5 cases of typhoid hepatitis in 1984. Liver biopsy was performed for cases numbered 2, 3, and 4 and the first two revealed HG. Satti et al (9) reported a series of 59 patients with HG. The etiology was typhoid fever for one case. This patient had fever, hemoptysis, and hepatomegaly raising the suspicion of tuberculosis, but the results of serology were consistent with typhoid fever. Liver biopsy revealed noncaseating granulomas rather in loose texture. The patient improved rapidly with the treatment of typhoid fever. But the authors did not thoroughly discuss typhoid fever as a cause of HG.

El-Newihi et al (5) reviewed 27 cases with Salmonella hepatitis. They performed liver biopsy in two patients: HGs were not encountered.

In Turkey, the main etiologies of HGs are tuberculosis, sarcoidosis, and brucellosis (10–12). These and other disorders were excluded for both of our patients. Case 1 had granulomas without necrosis in liver and spleen. To our knowledge, no cases of typhoid fever with splenic granulomas were reported in the literature. In animal models, Salmonella infections were shown to cause splenic granulomas in addition to HG (13, 14). This patient is the first typhoid fever with splenic granulomas. Case 2 had granulomas in the bone marrow additionally. This finding also represents a very rare complication of typhoid fever (15, 16).

In conclusion, typhoid fever should be considered among the etiologies that may lead to granulomas in several organs.

References

Typhoid Fever and Bone Marrow Granulomas