

Acute Brucellar Hepatitis: Report of Two Cases

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Introduction: Brucellosis is a common zoonotic disease which has a wide spectrum of clinical manifestations and complications in humans. Brucellosis is an endemic disease in Iran. The aim of this case report was to introduce acute hepatitis as a rare complication of acute brucellosis.

Case Presentation: First case, a 25-year-old man, who complained from fever, chilliness, nocturnal sweating, nausea, vomiting, jaundice, and right upper quadrant pain, and was admitted to the hospital. Laboratory tests showed a five-fold increase in alanine aminotransferase and aspartate aminotransferase levels, and increased total and direct bilirubin and alkaline phosphatase levels. Second case, a 63-year-old man, who complained from fever, chilliness, weight loss, malaise and nocturnal sweating, and was admitted to the hospital. Laboratory tests showed an eight-fold increase in alanine aminotransferase and aspartate aminotransferase levels, and increased total and direct bilirubin and alkaline phosphatase levels. The patient had jaundice at the third day of admission. The results of seroagglutination tests, Wright and 2-mercaptoethanol (2ME) were positive for both patients. The patients were diagnosed as having acute brucella hepatitis and were treated with standard regimen of anti-brucella drugs and improved completely after six weeks of treatment.

Conclusions: Brucellosis must be considered in the differential diagnosis of acute hepatitis in patients with jaundice and fever manifestations especially if there is a history of unpasteurized dairy products ingestion and life in endemic areas because early diagnosis and treatment of the patient can decrease complications and mortality rate.

Keywords: Brucella; Hepatitis; Jaundice

1. Introduction

Brucellosis or undulant fever is a common zoonotic disease and is endemic in many countries, especially in Mediterranean areas, India, Saudi Arabia, in parts of south and Central America and east and western Africa. The disease has been eradicated in some developed countries but it is endemic in Middle Eastern countries such as Iran (1, 2). The incidence rate of brucellosis in Iran was 21 per 100000 individuals in 2012. Hamadan is one of the most populated regions in Iran, with incidence rates of 62.9 and 81.4 per 100000 individuals in 2012 and 2013, respectively (3). Brucellosis is transmitted from infected animals to humans via various pathways such as consumption of contaminated dairy products or direct contact with animals (4, 5).

Brucellosis has a wide spectrum of clinical manifestations and complications in humans. It may involve various organ systems including the liver, gastrointestinal tract, nervous system, lungs, blood vessels, heart, skin, eyes and joints. Liver involvement is frequent in both acute and chronic brucellosis and a slight increase in transaminase levels develops frequently, and mild hepatosplenomegaly occurs in 20% to 30% of cases. However, acute hepatitis is a rare clinical presentation of brucellosis (5, 6). Definitive diagnosis of brucellosis is based on

culture (positive in 15% to 90%), serologic tests or both (5). The aim of this case report was to introduce acute hepatitis as a rare complication of acute brucellosis.

2. Case Presentation

2.1. Case 1

The first case was a 25-year-old male farmer, who lived in Malayer city and was admitted to the hospital because of fever, chills and jaundice. He had complained from fever, chilliness, sweating and malaise during the one month before admission, and nausea, vomiting and yellow skin for the previous 10 days. The patient had a history of unpasteurized dairy consumption and also recurrent abortions in his livestock. Moreover, his mother and brother had brucellosis several months ago. Physical findings included fever (temperature of 39°C), jaundice and tenderness in the right upper quadrant of the abdomen. He was diagnosed as having acute hepatitis due to viral, bacterial or collagen vascular diseases.

The laboratory data were as follows; leukocyte count: $4.2 \times 10^3/\mu\text{L}$ with 55% polymorphonuclear, serum alanine aminotransferase (ALT): 171 U/L, serum aspartate amino-

transferase (AST): 250 U/L, serum alkaline phosphatase: 381 U/L and total bilirubin level: 3.4 mg. Serological tests for brucellosis, and blood and urine cultures were negative. Abdominal sonography showed mild splenomegaly and no hepatomegaly.

Serological markers for hepatitis A, B, and C and antibody to human immunodeficiency virus (HIV antibody) were negative. Serological tests for collagen vascular diseases were negative, and C3, C4 and CH50 were in the normal ranges. At the second day of admission, repeated standard agglutination tests were positive: Wright at 1/160, Coombs Wright at 1/320 and 2-mercaptoethanol (2ME) at 1/80. Acute brucella hepatitis was diagnosed, and a combination of streptomycin (1 g/day IM) and doxycycline (2 × 100 mg/day orally) were started for the patient. The pathology of bone marrow biopsy was normal and the blood culture in Castaneda media after 12 days of incubation was positive for *Brucella spp.* The patient was discharged after seven days of admission and was completely cured and the liver function tests returned to normal at the end of six weeks of antibiotic therapy. At the 24-month clinical follow-up, the patient had not relapsed.

2.2. Case 2

The second case was a 63-year-old male farmer, who lived in a rural area (Kandolan) of Malayer city, and was admitted to the hospital with clinical manifestations of fever, chilliness, and bone and joints pain. He had complained from lower extremities and left knee pain during the three previous weeks before admission and also had fever, chilliness, nocturnal sweating, anorexia, and malaise and weightloss (5 kg) for the previous five days. The patient had a history of unpasteurized dairy consumption and also recurrent abortions in his livestock. In physical examination, the vital signs were, temperature of 39°C, blood pressure = 130/90 mmHg, respiratory rate = 12/minute and pulse rate = 100/minute. He had pain and tenderness in the left knee and mild splenomegaly, but the other organs were normal.

The laboratory results before the admission were as follows: leukocyte count: $5.5 \times 10^3/\mu\text{L}$ with polymorphonuclear of 71%, hemoglobin: 14.1 g/dL, platelet: $143 \times 10^3/\mu\text{L}$, serum ALT: 51 U/L, serum AST: 141 U/L, serum alkaline phosphatase: 334 U/L and erythrocyte sedimentation rate (ESR) of 3 mm/h. The standard agglutination tests and 2 ME titers were 1/160 and 1/80, respectively. The patient was diagnosed as having acute hepatitis due to brucellosis and treatment with doxycycline (2 × 100 mg/day oral) and gentamicin (280 mg/IV/daily) was started. The patient progressed to jaundice on the third day of admission. The laboratory results at the admission were as follows: leukocyte count: $5.4 \times 10^3/\mu\text{L}$ with polymorphonuclear of 84%, hemoglobin: 13 g/dL, platelet: $118 \times 10^3/\mu\text{L}$, serum ALT: 727 U/L, serum AST: 449 U/L, serum alkaline phosphatase: 785 U/L, total bilirubin level: 1.82 mg/dL and direct bilirubin level: 1.23 mg/dL, ESR 35 mm/h and C-reactive

protein (CRP) 2+. At the fifth day of admission, Coombs Wright and 2ME titers were 1/1280 and 1/640, respectively. Viral hepatitis markers and blood cultures were negative. The patient was discharged after seven days of admission and he was completely cured and the liver function tests returned to normal at the end of six weeks of antibiotic therapy. At the three-month clinical follow-up Wright and 2ME tests declined to 1/320 and 1/80, respectively and the patient had not relapsed.

3. Discussion

Brucellosis is a zoonotic infection with protean manifestation. Pathological changes in the liver and slight increased serum level of liver enzymes are the outcomes of clinical brucellosis. However, isolated acute hepatitis rarely occurs as a presentation of localized brucellosis.

In the present report, we described two cases of acute brucellar hepatitis with presentation of fever, jaundice, and marked elevation of liver enzymes; one being an adolescent and another aged man.

In a study of 158 cases of brucellosis in our hospital, during the period between 1996 and 1997, jaundice was observed in 11 (7%) patients. However acute hepatitis with jaundice, nausea, vomiting, and right upper quadrant pain with more than five-fold increase in liver enzymes were found in three (1.9%) patients. All of them recovered with successful treatment (7).

Another report of 809 cases of brucellosis, during 2000 - 2004, showed hepatomegaly in 25 (3.09%) and jaundice in nine (1.11%) patients (8). In our report both patients had splenomegaly but no hepatomegaly, while both presented jaundice and a fivefold increase in liver enzymes.

Asef Zadeh et al. (9) in 2008 reported on a 35-year-old butcher with fever, jaundice and right upper abdominal pain accompanied by more than a ten-fold increase in liver enzymes, standard tube agglutination (STA) titre of 1/320 and 2ME titre of 1/160. He responded to the combination of doxycycline and rifampin for eight weeks.

Ulug et al. (10) in 2010 reported on a 33-year-old woman with fever, jaundice and hepatosplenomegaly, who was diagnosed as having acute hepatitis with positive blood culture and serology for brucellosis. Doxycycline plus streptomycin were used and complete recovery was observed after receiving a six-week course of treatment. This case is compatible with case 1 in the current study, in which both culture and serology were positive and the patient responded to a doxycycline plus streptomycin regimen.

Losurdo et al. (11) also reported on a 20-year-old Italian boy with acute brucellar hepatitis and STA of 1/160, who had recovered after receiving anti-brucella therapy.

Erdem et al. (12) reported on a 35-year-old man who complained from fever, headache, nausea and dark urine for the previous ten days. On clinical examination there were no pathological findings except a yellow sclera. The laboratory results were as follows: serum alanine trans-

ferase level of 370 U/L, serum aspartate transferase of 582 U/L, serum alkaline phosphatase of 1073 U/L, and serum total bilirubin concentration of 3.05 mg/mL. Viral hepatitis markers and immunologic markers of autoimmune hepatitis and Mono spot test were negative. The Wright agglutination titer was positive at 1:1280 titer. He was treated with doxycycline and rifampin, and completely cured at the end of the treatment.

Another case report by Sunmez et al. was on a 61-year-old male patient with complaints of fever, chills, cough and dyspnea. His temperature was 39°C and his physical examination revealed yellow sclera and hepatomegaly. The laboratory test results showed serum alanine transferase of 750 U/L, serum aspartate transferase of 445 U/L, serum alkaline phosphatase of 395 U/L, and total bilirubin concentration of 3.6 mg/dL. Viral hepatitis markers were negative. The patient had a positive history of fresh cheese ingestion and Wright test result was positive at 1:160. His liver biopsy reported a mild fibrosis in the portal septal area, mononuclear cell infiltration and piecemeal necrosis. He received doxycycline and streptomycin and on follow-up, the hepatic enzymes had returned to normal. He was cured completely after six weeks (13).

The proper drug regimen for the treatment of acute brucella hepatitis is not definite. A complete cure of brucella hepatitis was seen in our patients with doxycycline and aminoglycoside. A combination of doxycycline and rifampin was also used successfully in some other reports. However, because of the potential risk of hepatotoxicity of rifampin, we recommend the combination of doxycycline and aminoglycoside as the first choice for treatment of brucellar hepatitis.

In conclusion, brucellosis must be considered in the differential diagnosis of acute hepatitis in patients with jaundice and fever manifestations especially if there is

a history of unpasteurized dairy products consumption in endemic areas because early diagnosis and treatment of the patient can decrease its complications and mortality rate.

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