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CASE REPORT

Acute Brucella Hepatitis in an Urban Patient

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A 35-year-old man was referred to our center because of low grade fever, vomiting, yellow sclera, and tenderness in the upper-right quadrant of his abdomen. Laboratory tests showed a white blood cell (WBC) of 7100/µL, a platelet of 184,000/µL, an erythrocyte sedimentation rate (ESR) of 4 mm/h, an alanine aminotransferase (ALT) of 525 U/L, an aspartate aminotransferase AST of 142 U/L, a total bilirubin level of 4.23 mg/dL, and a direct bilirubin level of 3.16 mg/dL. Viral hepatitis markers, immunoglobuline M antibody to cytomegalovirus (anti-CMV IgM), Ebstein-Barr virus (EBV) IgM, and immunologic markers of autoimmune hepatitis were negative. The patient was diagnosed with acute hepatitis. Alkaline phosphatase was in the normal range throughout the course of the disease. Because of the patient's occupation as a butcher and his history of eating semi-cooked sheep testes, serologic tests of brucellosis were conducted; the tests came out positive. We were concerned about the hepatotoxicity of standard regimens; therefore, we started treatment with streptomycin and ciprofloxacin regimens. Although liver enzyme had fallen and fever discontinued, the total and direct bilirubin concentrations in the patient's serum both increased in spite of using 2 weeks of the abovementioned drug regimen. The elevation of bilirubin could have been due to drug hepatotoxicity. Alternatively, a regimen containing ciprofloxacin may have not have been efficient enough and may have had effects on the direct bilirubin concentration. Fortunately, within 8 weeks, progressive recovery was noticed. Brucellosis should be considered in the differential diagnosis of fever and hepatitis for those who live in endemic areas, especially if his/her job was at high risk for acquiring brucellosis. We recommend taking a careful occupational and behavioral history for patients with acute hepatitis syndrome. We assumed that ciprofloxacin was not suitable for brucella hepatitis treatment and also it may cause liver damage. The most appropriate treatment is a standard regimen containing doxycycline.

Keywords: **Brucella, Hepatitis, Alkaline Phosphatase, Hyperbilirubinemia, Ciprofloxacin**

Introduction

Brucellosis is an endemic zoonosis in the Mediterranean region, including in many parts of Iran [1, 2]. In the Islamic Republic of Iran, brucellosis represents a major health problem [2]. Incidence of brucellosis in the Qazvin province, in the northern part of the country, is considered low in comparison with other heavily infected provinces. According to data derived from active surveillance, the incidence of brucellosis in the Qazvin province was 65, 49, 62, 62, and 36 per 100,000 people in the years 2002-2006, respectively [3].

Normally brucellosis infection is caused by consuming dairy products. However, the bacteria can enter the body through contacting infected animals' reproductive tissues and ingestion [4]. Human brucellosis is a multisystemic disease with a wide range of clinical symptoms. Brucellosis can present

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Table 1. Total and direct bilirubin concentrations in patient's serum

Test / Date	2008/2/19	/2/27	/3/1	/3/3	/3/18	/3/26	/4/3	/5/1	2008/6/17
Total bilirubin (mg/dl)	4.23	9.93	13.25	15.16	18.18	22.73	16.27	4.1	0.79
Direct bilirubin (mg/dl)	3.16	7.83	10.57	11.91	14.38	13.18	9.8	1.9	0.26
Indirect bilirubin (mg/dl)	1.07	2.1	2.68	3.25	3.80	9.55	6.47	2.2	0.53
ALT (U/L)	525	207	172	116	96	91	102	53	17
AST (U/L)	142	67	74	39	43	52	59	28	17

with various manifestations and any organ in the body may be involved. Hepatosplenomegaly, elevated liver enzymes, and increased bilirubin levels have been reported in brucellosis patients. However acute hepatitis is a rare manifestation [5]. We report one case, a 30-year-old male with acute brucella hepatitis, which demands attention because there is rare case in the literature about direct hyperbilirubinemia even after treatment.

Case Report

In January 2008, a 30-year-old man was brought to the physicians' clinic (Bu-Ali University Hospital, Qazvin, Iran) with a history of fever, nausea, vomiting, fatigue, and pain in the upper-right quadrant of his abdomen. The patient had been complaining of these symptoms incessantly for the previous 10 days, and his temperature was 37.8°C. A clinical examination revealed no pathologic findings except yellow sclera and tenderness in the upper-right quadrant of the abdomen. The laboratory results were as follows: leukocyte count: 7.1×103/µL, platelet count: 184×103/µL, Hemoglobin: 5.6 g/dL, erythrocyte sedimentation rate: 4 mm/hour, serum alanine aminotransferase (ALT): 525 U/L, serum aspartate aminotransferase (AST): 142 U/L, and total bilirubin level: 4.23 mg/dL (direct: 3.16 mg/dL). Serum glucose, lipids, urea, creatinine levels, and prothrombin time were normal. γ-glutamyl transpeptidase (GGT) and serum alkaline phosphatase (ALP) were within the normal ranges throughout the course of the disease (ALP patient value: 195-218 IU/L). Tests of viral hepatitis markers (hepatitis B surface antigen [HBsAg], hepatitis B core immunoglobuline M antibody [anti-HBc IgM], antibody to hepatitis C virus [anti-HCV], hepatitis A virus IgM antibody [anti-HAV IgM]) and antibody to human immunodeficiency virus (anti-HIV) were negative.

In the second stage of the patient's evaluation, it was observed that the other tests (IgM antibody to Ebstein-Barr virus [anti-EBV IgM], antibody to cytomegalovirus [anti-CMV], and anti-Fasciola) were negative, too. In the third step, tests of immunologic markers of autoimmune hepatitis (antinuclear antibody [ANA], antimitochondrial antibodies [AMA], anti-smooth muscle antibody [ASMA], perinuclear-staining antineutrophil cytoplasmic antibodies [p-ANCA], and antibody to liver-kidney microsome type 1 [anti-LKM1]) were conducted and came out negative. Because of the patient's occupation as a butcher and his history of eating semi–cooked sheep testes, serologic tests of brucellosis were conducted. The standard agglutination test (Wright) and 2-mercaptoethanol (2ME) titers were 1/320 and 1/160, respectively. These results indicated that the patient had acute hepatitis due to brucellosis.

In treating the patient, we were concerned about the hepatotoxicity of standard regimens; hence, we started streptomycin (1g/day IM) and ciprofloxacin (2×500 mg/day orally) treatments. On the fifth day of treatment, the serum ALT level had fallen to 116 U/L and fever discontinued, while the total and direct bilirubin concentrations in the patient's serum both increased (Table 1). In spite of the reported hepatotoxicity of the standard regimen, we had to change the treatment to a standard regimen (doxycycline and rifampin). Fortunately, within 8 weeks, we noticed progressive recovery of the patient in signs, symptoms, and normalized liver-function tests. At the 6-month clinical follow-up, our patient had not relapsed and Wright and 2ME titers had declined.

Discussion

Brucellosis is a systemic infection in which any organ or system of the body may be involved. Because the signs and symptoms of brucellosis are nonspecific, and isolation of the causative organism is difficult, the diagnosis often depends on serologic

techniques. However the absolute diagnosis of brucellosis requires isolation of the bacterium from blood or tissue samples [4, 6]. In daily practice, the diagnosis of brucellosis is established by a positive Wright's agglutination test in a titer of ≥ 1/160 in association in an appropriate clinical setting [7]. Due to several barriers we did not perform a blood culture test. First, we did not have access to the BACTEC blood culture system for rapid diagnosis. Secondly, a routine blood culture is time consuming and the results can take 3-4 weeks. Thirdly, there is low percentage of positive blood culture for brucellosis patients in the reported results in our region.

The brucella infection in our patient was demonstrated with positive serology (standard tube agglutination test). Agglutination in the presence of 2-ME was used to distinguish specific IgG (suggestive of active disease) from IgM reactivity [7]. Our patient demonstrated a high titer of 2ME, which was due to active disease. Although bovine brucellosis is caused mainly by *brucella abortus* and is still the most prevalent, *brucella melitensis* is the principal cause of brucellosis in sheep, goats, and camels [8]. Because *Brucella abortus* has not been reported in humans in our country [2] and given the patient's history of eating semi-cooked sheep testes; we assumed that the etiologic agent in the patient was *brucella melitensis.*

The liver is frequently involved in both acute and chronic brucellosis, and consequently the patient experiences a slight increase in transaminase levels and mild hepatosplenomegaly, and, more rarely, acute hepatitis [1, 4, 9]. Increased direct bilirubin usually means that the biliary ducts are obstructed. ALP levels in our case were not in the range of a typical cholestatic case (3 times the upper normal limit). Normally an increase in ALP/AST and ALP/ALT ratios indicate a cholestatic component. Although in the case study these ratios were not elevated, our findings suggest that the increased direct bilirubin level may not have been due to bile duct injury [10]. Although liver enzyme had fallen and fever discontinued after treatment containing ciprofloxacin and streptomycin, the total and direct bilirubin concentrations in the patient's serum increased in spite of 2 weeks of the abovementioned drug regimens. The elevation of bilirubin could be due to drug hepatotoxicity. Alternatively, inadequate efficiency of the abovementioned drug regimens may have had effects on the direct bilirubin concentration. The aminoglycosides (including streptomycin) are not hepatotoxic [11], and ciprofloxacin is known to have a relatively low occurrence of adverse side effects. However, increasing evidence suggests that ciprofloxacin may cause severe liver damage [12, 13]. Approximately 1.7% - 1.9% of patients taking ciprofloxacin show elevated AST and ALT levels, 0.8% have an increased ALP concentration, and 0.3% have enhanced bilirubin levels. Because Jaundice resulting from ciprofloxacin toxicity is transient [14], we didn't perform a liver biopsy.

The proper drug regimen for the treatment of acute brucella hepatitis is not definite. Our literature search failed to find any report in relation to the efficacy of brucella hepatitis treatment regimens. Because users of doxycycline tend not to have an increased risk of developing hepatotoxicity, it is appropriate to begin a standard regimen containing doxycycline rather than ciprofloxacin [15, 16]. Brucella hepatitis can be resolved with antimicrobial therapy, and in the absence of other causes (e.g., hepatitis C or alcoholism), cirrhosis does not occur despite the severity of the inflammation [17]. A complete cure of brucella hepatitis was seen in our patient.

Conclusions

In our case study, acute hepatitis was the only manifestation of brucellosis. Thus, brucellosis should be considered in the differential diagnosis of fever and hepatitis for those who live in or have visited endemic areas, especially if the patient's job put him/her at high risk for acquiring brucellosis [18]. We recommended a careful occupational and habit history taking of our patient, who had acute hepatitis syndrome. People at high risk are livestock handlers, slaughter industry workers, and veterinarians. Although most people become infected by consuming raw milk or unpasteurized dairy products, eating semi-cooked testes of infected animals may cause infection, too. This case study showed that a regimen containing ciprofloxacin is not appropriate for brucella hepatitis treatment and a regimen containing doxycycline is the preferable option for the abovementioned disease course.

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