

Brucellosis as a rare cause of granulomatous hepatitis with hepatic and bone marrow granulomas: A case report

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Abstract

Brucellosis is a zoonotic infection that may involve the liver in a variety of ways, however, data on the histopathology of liver effects in brucellosis are limited. Brucellosis is generally characterized by a high fever, joint or back pain, and hepatosplenomegaly. This report illustrates a case of granulomatous hepatitis with granulomas in the liver and bone marrow in a patient who presented with non-specific symptoms, hepatomegaly, splenomegaly, digital clubbing, and laboratory signs of intrahepatic cholestasis. Granulomas were detected in the bone marrow and hepatic specimens. The diagnosis of brucellosis was based on the isolation of *Brucella mellitensis* in a blood culture and serum agglutination titers of 1:640. Treatment for brucellosis led to improved laboratory and clinical findings. Brucellosis should be considered in regions where it is endemic in cases of an elevated transaminase level and related clinical findings. Brucellosis should also be considered in the differential diagnosis of intrahepatic cholestasis and/or granulomas in hepatic and bone marrow biopsies. This case report provides valuable histopathological features and detailed information of liver involvement in a case of brucellosis.

Keywords: Brucellosis; bone marrow; granulomatous disease; liver.

Introduction

Hepatic granulomas are chronic inflammatory lesions consisting of enlarged, modified macrophages (epithelioid histiocytes), which are generally surrounded by fibroblasts and lymphocytes. Hepatic granulomas are detected in 2% to 15% of hepatic biopsies. The many causative factors of hepatic granuloma include common infectious factors of tuberculosis, hydatid cyst, syphilis, brucellosis, typhoid fever, chronic hepatitis B and C, Epstein-Barr virus infection, HIV, fungal infections, sarcoidosis, primary biliary cirrhosis, Hodgkin's disease, drug reactions, and polymyalgia rheumatica.^[1,2]

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Brucellosis can be transmitted to human beings through occupational contact or contaminated animal milk.^[3,4] The clinical appearance may mimic many diseases. It may cause localized disease involvement in nearly all organs, though it is most frequently seen in the bones, joints, central nervous system, heart, lung, spleen, testes, liver, gallbladder, kidneys, prostate or skin. It may lead to granulomatous hepatitis in cases of liver involvement.^[5,6]

The present case emphasizes that reactive hepatitis is not always the cause of the elevations in liver functional tests observed in brucellosis, and that, while rare, granulomatous hepatitis should also be considered. In addition, this report aims to encourage further investigation of the histopathological features of liver involvement in brucellosis, as the current data are limited.

Case Report

A 54-year-old, male freelance worker was admitted with the complaints of abdominal pain, headache, knee pain, fatigue, and weight loss that had increased in the month and a half prior to presentation. The patient reported that he had lost weight (10 kg) in the previous 4 months. There was nothing significant in his medical history, other than a smoking habit of 2 packs/day.

His general status was good, and the patient was conscious and cooperative. His vital sign values were a blood pressure of 80/60 mmHg, a heart rate of 98 beats/minute, a respiratory rate of 14/minute and a temperature of 37°C. A physical examination revealed pale conjunctivas, the presence of both hepatomegaly and splenomegaly 5-6 cm below the costal margin and crossing the midline, and digital clubbing.

Laboratory test results at the time of admission were hemoglobin: 9 gr/dL, hematocrit: 26%, leukocyte count: 3600/mm³, platelet count: 151,000/mm³, mean corpuscular volume: 82 fL, erythrocyte sedimentation rate (ESR): 41 mm/hour, serum iron level: 19 ug/dL, serum iron binding capacity: 153 ug/dL, C-reactive protein level: 34 mg/dL, and rheumatoid factor level: 71. Baseline biochemical findings were alanine aminotransferase: 41 U/L, aspartate transaminase: 72 U/L, alkaline phosphatase: 523 U/L, gamma-glutamyl transferase: 62 U/L, albumin: 2.6 g/dL, globulin: 4.1 g/dL, total bilirubin: 0.8 mg/dL, fasting blood glucose: 83 mg/dL, urea: 28 mg/dL, creatinine: 0.8 mg/dL, lactate dehydrogenase: 394 U/L, total cholesterol: 135 mg/dL, sodium: 132 mmol/L, potassium: 4.8 mmol/L, chloride: 103 mmol/L, and calcium: 7.6 mg/dL. Upper abdominal ultrasonography revealed that the liver was enlarged (190 mm), as well as hypochoic parenchyma, and an enlarged spleen (150 mm) with normal structure. Doppler ultrasonography indicated that the vascular structures were within normal limits. Upper gastrointestinal system endoscopy and posteroanterior chest X-ray results were normal.

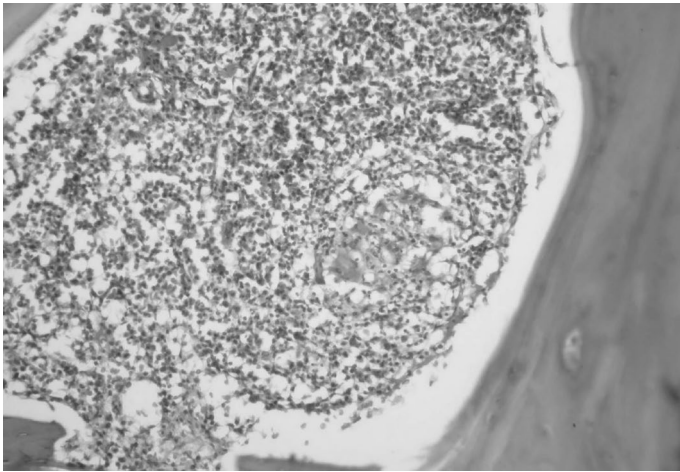


Figure 1. Bone marrow biopsy. Granulomatous myelitis: granuloma consisting of multinuclear giant cells, epithelioid histiocytes, fibroblasts, and lymphocytes are visible between bone lamellae. (Hematoxyline-eosin, x20).

Physical and laboratory findings related to hepatomegaly, splenomegaly, digital clubbing, anemia, leukopenia, a high ESR, and intrahepatic cholestasis were observed. The patient was evaluated for hematological diseases (lymphoma, leukemia) and intrahepatic cholestasis (infiltrative and infectious causes). A peripheral blood smear and bone marrow aspiration were performed. Hypochromatic microcytic anemia was diagnosed based on the peripheral blood smear with no sign of hemolysis. The bone marrow aspiration results were non-diagnostic. Anti-toxoplasma immunoglobulin M (IgM), anti-cytomegalovirus IgM, anti-Epstein-Barr virus IgM, anti-rubella IgM, hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs), anti-hepatitis B core antibody (HBc) IgG, anti-hepatitis C virus (HCV), anti-hepatitis A virus (HAV) IgM, venereal disease research laboratory test (VDRL), and anti-HIV results serological analysis results were all negative. A tuberculin skin test was also negative.

Hemoglobin electrophoresis, hemolysis tests, and thyroid function test findings were all normal. Only a mild increase in the tumor marker CA 19.9 (77 U/mL) was observed. Protein electrophoresis revealed a peak gamma globulin band of 24.2%. Autoimmune markers of anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), liver kidney microsome type 1 (LKM-1), antimitochondrial antibodies (AMA), anti-mitochondrial M2 antibody (AMA-M2), perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibodies (P-ANCA and C-ANCA) were negative.

A bone marrow biopsy was performed and revealed signs of granulomatous myelitis (Fig. 1). No dilatation in the intra- or extrahepatic bile ducts with elevated levels of transaminases and cholestatic enzymes was observed. The rationale for performing a liver biopsy was first to rule out a hepatic disease and then to exclude other causes of liver pathology in the setting of intrahepatic cholestasis. The patient provided written, informed consent for the liver biopsy.

The biopsy was reported as granulomatous hepatitis without caseous necrosis or Langerhans-type giant cells (Fig. 2a, b). Other biopsy findings included patchy proliferation areas in the bile ducts (signs of intrahepatic cholestasis), dense mononuclear inflammatory cell infiltrations in the portal areas, bile pigment accumulation, mild mononuclear cell infiltration in local areas of the parenchyma (focal lytic necrosis), and minimal interface hepatitis. A hepatic biopsy specimen was evaluated

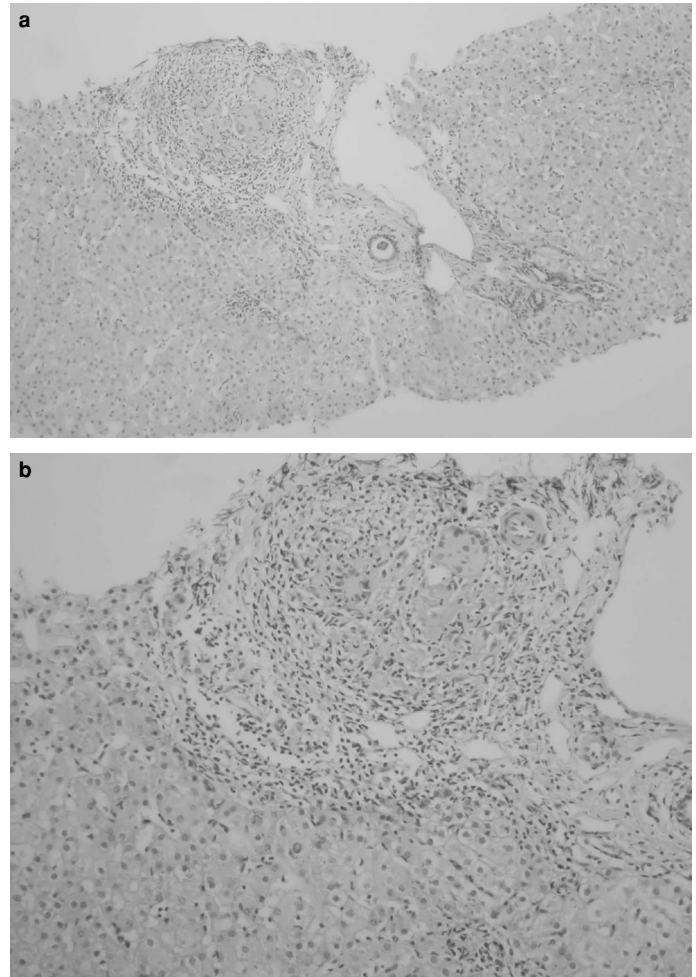


Figure 2. Granulomatous hepatitis findings of epithelioid histiocytes, fibroblasts, lymphocytes, and multinuclear giant cells without caseous necrosis. Other biopsy findings were patchy proliferation areas in the bile ducts (signs of intrahepatic cholestasis), periportal bile pigment accumulation, dense mononuclear inflammatory cell infiltrations in the portal areas, mild mononuclear cell infiltration in local areas of the parenchyma (focal lytic necrosis), and minimal interface hepatitis [(a) Hematoxyline-eosin, x10; (b) Hematoxyline-eosin, x20].

with Ziehl-Neelsen staining and no acid resistant bacilli were detected. Rose bengal stain and brucellosis agglutination test results were positive (1:640). *Brucella melitensis* grew in the blood cultures. Lumbo-sacral and pelvis graphies demonstrated signs of sacroileitis. Rifampicin 600 mg/day and doxycycline 200 mg/day was administered for 6 weeks. Improvements in the clinical, hematological, and biochemical parameters included resolution of the laboratory signs of cholestasis. The patient was in complete clinical remission and free of symptoms during 6 months of follow-up.

Discussion

Hepatic granulomas are chronic inflammatory lesions that develop due to late-type hypersensitivity reactions to antigenic stimulation. Hepatic granulomas are generally detected in 12% to 15% of hepatic biopsies.^[1,2] Sarcoidosis, Hodgkin's disease, drug reactions, polymyalgia rheumatica, tuberculosis, brucellosis, typhoid fever, hydatid cyst, syphilis,

chronic hepatitis B and C, Epstein-Barr virus infection, HIV, and fungal infections should be considered in the differential diagnosis in patients with granulomatous hepatitis and hepatic granuloma in the hepatic histology. Nonetheless, some 10% to 15% of cases are idiopathic.

The primary laboratory tests used in the differential diagnosis are tuberculin skin test, assessment of serum angiotensin converting enzyme level, AMA, posteroanterior chest graphy and computed tomography (if necessary), VDRL, HIV, *Brucella* agglutination tests, and anti-HCV and HBsAg evaluation. Additionally, it is important to ask about possible hepatotoxic agents. In the present case, after the appropriate tests were conducted for the differential diagnosis, the patient was diagnosed with brucellosis and appropriate treatment resulted in a cure. The patient in this case report presented with complaints of non-specific symptoms like headache, abdominal pain, knee pain, and fatigue, rather than classic signs of brucellosis, such as fever and sweating.

Brucellosis, primarily being a disease of wild and domestic animals, is transmitted to human beings through contact via animal breeding, butchering, or consumption of contaminated dairy products.^[3,4] Brucellosis is generally characterized by a high fever, night-sweats, fatigue, joint-back pains, and hepatosplenomegaly. Although the morbidity of brucellosis in Turkey is considerably high, it is a disease with a very low mortality. Brucellosis is a widespread and serious public health problem in the Anatolian regions of Turkey.^[7-9]

A definitive diagnosis of brucellosis is made with blood, bone marrow, or infected tissue cultures. Although growth in blood cultures has shown variations (15-70%), as it is an intracellular microorganism, the culture growth rate is around 90% in bone marrow. The disease is mainly diagnosed using indirect methods since patients may have used various antibiotics before the brucellosis diagnosis, and there are often no culturing facilities in rural healthcare units. Therefore, various serological tests, such as serum agglutination tests (SAT), Rose Bengal staining, immunofluorescence antibody tests, and enzyme-linked immunosorbent assay tests are used.^[3,4] SAT appears to be a standard method. While values of $\geq 1:160$ can be diagnostic, this test can also yield false negative results. Ozkurt et al.^[10] reported a SAT positivity rate of 96% in a series of 50 patients: 100% in 30 patients with acute brucellosis, 94.1% in 17 patients with subacute brucellosis, and 66.6% in 3 patients with chronic brucellosis.

Hepatic involvement is variable in brucellosis.^[11] In some papers, hepatic involvement has been reported to be 10%. However, this is generally in reactive hepatitis form. Hepatitis, expressed as a modest increase in serum transaminase levels, is observed in some 25% of patients, ranging from 5% to 40%.^[11,12] Involvement of the liver is common in human brucellosis but liver brucellosis or pseudotumor necrotizing granuloma is a very uncommon negative effect of this infection, observed only in 1.7% of individuals. Sometimes there may be non-caseified granulomas, and a pyogenic *Brucella* abscess has also rarely been reported. Although the presence of a progressive hepatic disease has been reported, this is very rare.^[11]

Granulomas are frequently encountered in the liver because of its rich blood supply and dense reticuloendothelial cell content. Granulomas develop as a response of the immune system to indigestible foreign substances by inflammatory cells and macrophages. These substances are typically infectious microorganisms (mycobacterias, cystosomas, etc.) and materials injected or ingested orally (talk, rock oil, drugs, etc.).^[13]

Sarcoidosis and tuberculosis constitute more than one-third of granulomatous hepatic diseases. Despite a detailed examination, 10%

of cases remain undiagnosed.^[6] In Turkey, it has been demonstrated that infectious causes were responsible for more than half of hepatic granuloma cases (tuberculosis, hydatid disease, brucellosis, and typhoid fever).^[14] Hepatic granuloma in varying proportions has been reported in histological examination of chronic viral hepatitis.^[15,16] It was reported in 2 studies conducted in Turkey that rarely, hepatic granulomas have been encountered in chronic hepatitis B (1.5%) and C (1.3%) patients.^[17,18] Brucellosis may present in different clinical forms through involvement in various organs; atypical cases with peritonitis, meningitis, and ascites have been reported.^[2,19] The present patient presented with non-specific symptoms and intrahepatic cholestasis signs in addition to hepatic and bone marrow involvement. Since this patient's intra- and extrahepatic bile ducts were not dilated, but the transaminase and cholestatic enzyme values were elevated, an intrahepatic cholestasis pattern was suspected. A hepatic biopsy to differentiate between infiltrative and infectious causes was performed. The biopsy allowed for a differential diagnosis between various autoimmune diseases (primary sclerosing cholangitis), infiltrative diseases (amyloidosis, sarcoidosis, lymphoma, and granulomatous diseases) and Stauffer syndrome (Hodgkin's disease, renal cell carcinoma), and is accepted as the gold standard for intrahepatic cholestasis. *Brucella abortus* (*B. abortus*) is the most common species responsible for hepatic granulomas. Histopathologically, histiocytic granulomas are present, often with central necrosis, portal and peripheral infiltration, and hyperplasia of the Kupffer cells. These granulomas result from caseation within the macrophages. Although *B. abortus* tends to establish a granulomatous form of hepatitis, *Brucella melitensis* may cause both diffuse and granulomatous lesions in the liver. In addition to progressive clinical improvement, we observed improvements in biochemical and hematological parameters in this patient following treatment for the final diagnosis and the laboratory signs of cholestasis disappeared.

Reactive hepatitis signs, granulomatous hepatitis, hepatic granuloma formation, parenchymal necroses, Kupffer's cell hyperplasia, and cholestasis may be observed in cases of hepatic injury due to a *Brucella melitensis* agent.^[11,13] Despite many reported cases of human brucellosis, the extent, severity, and histopathological features of liver involvement are still unclear.^[11,20] This case supplies additional information for the literature of this area of study.

Brucellosis can be a cause of intrahepatic cholestasis, and should be considered in cases with mildly increased transaminases along with prominently increased cholestasis enzymes. Improvement in both clinical outcome and hepatic injury can be achieved with the administration of early and effective chemotherapy. This case report presents different histological patterns and provides valuable detailed information of liver involvement of brucellosis.^[21]

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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