CLINICAL VIGNETTE

Brucellosis Beyond Borders

Judy Y. Choi, M.D.[1], Joseph Zaky, M.D.[2]
[1]University of California Los Angeles, Department of Family Medicine, Santa Monica, California USA;
[2]Olive View-UCLA Medical Center, Department of Internal Medicine, Sylmar, California USA

Abstract

We present a patient who was admitted repeatedly to the hospital with recurrent or persistent brucellosis. Presenting symptoms were non-specific, and initial treatment was likely inadequate. While brucellosis is more commonly diagnosed outside the United States, greater migration of infectious disease makes this disease an important consideration in the work-up of a fever of unknown origin.

Case Report

A 45-year-old Hispanic female presented to the emergency room with fevers and chills for two weeks that were associated with headache. Ibuprofen and Amoxicillin temporarily resolved her symptoms. However, her fevers returned one week later and were associated with fatigue, myalgias, abdominal pain, and right flank pain. Sick contacts included her son, who recently recovered from an upper respiratory infection, and her father-in-law, who was recovering from bronchitis or pneumonia after a recent trip to Tijuana, Mexico. Her only reported sexual activity was with her husband. She denied international travel but acknowledged consuming dairy products from Mexico four weeks prior to admission.

On exam, she was afebrile, tachycardic to 108 bpm, blood pressure of 97/40 mm/Hg, with a respiratory rate of 15/min. Her exam was remarkable for neck stiffness, abdominal tenderness in the right upper quadrant and bilateral lower quadrants, and right costovertebral angle tenderness. A pelvic exam revealed suprapubic and cervical motion tenderness. The remainder of the exam was unremarkable.

Initial labs revealed a white blood cell count of 5.6, hemoglobin of 12.3, and platelets of 281. She had transaminitis of AST 236, ALT 178, alkaline phosphatase 131, bilirubin 0.6. ESR was 40 and CRP 31. Wet mount was normal. Chest x-ray revealed a small cyst in the left lung. Abdominal and pelvic ultrasounds revealed cholelithiasis, enlarged fatty liver, and a corpus luteum cyst in the right ovary; no abscess was seen. CT abdomen and pelvis confirmed fatty liver, cholelithiasis, and a 1.5 cm portacaval lymph node with small lymph nodes in the porta hepatis, retroperitoneum, and mesentery. Echo-cardiogram was normal. The patient refused a lumbar puncture.

The patient's fevers persisted despite negative blood and urine cultures. To further evaluate the fever, additional testing included Influenza, EBV, HIV, gonorrhea, chlamydia, RPR, Coxiella, brucella titers, coccididiomycosis, serologies and stool studies. All returned within normal limits. To further evaluate the transaminitis, a hepatitis panel, ESR, CRP, ANA, and anti-smooth muscle antibodies returned normal. A liver biopsy of the right hepatic lobe revealed poorly-formed granulomas, lobular inflammation with minimal necrosis, stage I fibrosis, and fatty changes. Cefoxitin and doxycycline were started while awaiting the results of her brucella titers. Brucella IgG was elevated (2.17) while IgM was equivocal (0.9). Her antibiotics were switched to ceftriaxone and doxycycline, and her fevers resolved within 24 hours. She was discharged on doxycycline 100 mg po BID and rifampin was held due to transaminitis.

After one week, she followed up in the infectious disease clinic, reporting right upper quadrant abdominal pain, flank pain, and hematochezia. Her transaminitis resolved with AST 29, ALT 61, and alkaline phosphatase of 107. She returned again in four weeks while continuing doxycycline. Her brucella titers were elevated: IgM to 1.8 and IgG to 3.22. A confirmatory agglutination test was unavailable. After four more weeks, her brucella serologies decreased but remained positive (IgM 1.09; IgG 2.88), without transaminitis. In light of her hepatic granulomas and positive titers, she was restarted on doxycycline with rifampin and returned in two weeks to monitor her liver enzymes, which

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remained normal. She was instructed to complete the eight-week course of doxycycline and rifampin.

One month after completion of her antibiotics, her abdominal pain recurred. However, she did not follow up and presented to the ER three months later and was re-admitted with fevers, chills, cough, pleuritic chest pain, myalgias, and hematocheizia. Brucella IgG titers were elevated to (3.3) with declining IgM titers (0.5), which suggested chronic infection or relapse. Two out of four blood culture samples returned positive for gram negative organisms consistent with brucella. In light of her chest pain and bacteremia, a trans-esophageal echocardiogram was ordered after empirically starting bactrim, intravenous gentamicin, doxycycline, and rifampin. Her echocardiogram returned normal and bactrim and gentamicin were discontinued. Her fever resolved and she was discharged with another eight-week course of doxycycline and rifampin.

Discussion

The global burden of human brucellosis remains enormous, causing more than 500,000 infections per year worldwide[1]. While control of Brucella in zoonotic reservoir species has reduced the incidence of human brucellosis in North America, many areas of the world still have high prevalence of disease. Thus, enhanced awareness of this disease is important when evaluating a fever of unknown origin in a diverse patient population.

Human brucellosis is a zoonotic infection caused by small gram negative aerobic coccobacilli of the genus *Brucella*, transmitted most commonly through direct contact with infected animals or through ingestion of unpasteurized dairy products. The species that cause human brucellosis are *B. melitensis* (sheep and goats*), B. abortus* (cattle), *B. suis* (swine) and *B. canis* (dogs). Brucellae are taken up by tissue lymphocytes and transferred through regional lymph nodes, where they can seed the rest of the body and persist in tissues of the mononuclear phagocyte system, including spleen, liver, lymph nodes, and bone marrow[1]. The bacteria can also target the skeletal system and reproductive tract. A rare, but fatal, complication of brucellosis is infective endocarditis.

Humans present with a febrile illness that is difficult to diagnose on the basis of clinical presentation alone. The asymptomatic latency period of two to four weeks from the time of exposure adds to the difficulty of diagnosis. The infected persons may not correlate their symptoms with the exposure to infected animals products. Diagnosis is often established by isolation of Brucella species from blood or bone marrow cultures. If blood cultures are negative but suspicion is high, serologic tests can be performed. A positive serology for brucella serum agglutination testing or a four-fold increase in brucella antibody titer in two weeks, is considered definitive[2]. ELISA is the second most common serologic diagnostic method – it is highly sensitive, specific, and rapid. In relapsing brucellosis and those with persistent infection, Coombs and immunocapture agglutination tests are preferred. The 2-mercaptoethanol (2-ME) agglutination test that measures IgG antibodies only may be useful to evaluate response to therapy[3]. The 2ME test is superior to the standard tube test in determining the adequacy of therapy, and a negative 2ME test is strong evidence against a diagnosis of chronic brucellosis.

Relapse usually occurs within the first six months of treatment but can be seen up to twelve months following completion of treatment. The rate of relapse following treatment is between 5 to 15 percent[4]. Patients with chronic brucellosis have clinical features and/or relapse with elevated antibody titers and/or isolation of species from blood or tissue cultures for more than one year after the initial diagnosis[3]. Interpretation of serologic tests can be difficult, especially in differentiating relapse, chronic infection, and re-infection. Our patient's reoccurrences may be a manifestation of chronic brucellosis or relapse. Serological tests may stay persistently elevated after recovery in those treated, making it difficult to distinguish between active and past infection.

We propose various explanations may be responsible for the persistence of infection in our patient. Studies have shown that Brucella species use both passive and active mechanisms to evade detection by the innate immune system[2]. Another explanation for the initial reoccurence can be explained by a subop
timal treatment regimen – she was treated with doxycycline alone due to the risk of worsening transaminitis with rifampin, yet monotherapy shorter than six weeks is considered inadequate treatment. The World Health Organization recommends the following for patients older than 8 years: doxycycline 100 mg PO bid and rifampin 600-900 mg/d PO; for 6 weeks OR doxycycline 100 mg PO bid for 6 weeks and streptomycin 1 g/d IM daily for 2-3 weeks. Gentamicin can be used in place of streptomycin and ciprofloxacin-based regimens have also shown equal efficacy to doxycycline-based

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regimens[5]. Multidrug antimicrobial regimens are the mainstay of therapy because of high relapse rates reported with monotherapy. After an adequate course of treatment, persistent or recurrent symptoms of brucellosis should prompt a search for localized suppurative lesions. In our patient, it is unclear whether or not the liver granulomas seen on her liver biopsy represent a manifestation of brucella hepatitis or lesion responsible for relapse. Finally, chronic infection may be due to poor medication compliance or unreported consumption of new unpasteurized milk products.

As patient's case demonstrates, the symptoms of brucellosis are vague and non-specific, making clinical diagnosis of extremely difficult. While this infection is much more commonly contracted outside the United States than within its borders, one must account for brucellosis in the work-up of a fever of unknown origin particularly with the increasing globalization of both humans and infectious disease. This case demonstrates the importance of timely recognition of the infection and its proper treatment.

REERENCES

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Submitted on December 26, 2012

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