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ID CASE

Brucella Endocarditis in Persons Who Inject Drugs

John M. Cafardi,[1] Douglas Haas,[1] Thomas Lamarre,[1] and Judith Feinberg[2]

[1]The Christ Hospital, Cincinnati, Ohio, USA, and [2]West Virginia University, Morgantown, West Virginia, USA

We report 2 cases of infective endocarditis in injection drug users due to *Brucella* infection. Although cardiac involvement is a frequent sequela of brucellosis and endocarditis is often seen with injection drug use, *Brucella* endocarditis in persons who inject drugs without zoonotic exposure has not been reported to date.

Keywords. *Brucella*; culture-negative endocarditis; infective endocarditis; injection drug use.

In the last 10 years, the United States has seen a dramatic increase in injection drug use and its associated infectious sequelae. These include HIV, hepatitis B, and hepatitis C, as well as suppurative complications, including endovascular and musculoskeletal infections. The rate of infective endocarditis, in particular, has risen dramatically, having increased from 6% between 2000 and 2008 to 12% in 2013 [1]. Furthermore, endocarditis often serves as a sentinel marker for the introduction of injection drug use in a given area [2].

Most cases of infective endocarditis associated with injection drug use are due to *Staphylococcus aureus*; however, streptococci, enterococci, gram-negative organisms, and *Candida* spp. are also observed [3]. Culture-negative disease in this population, while uncommon and typically due to obtaining cultures after administration of antibiotics, has been reported and is most commonly due to infection with *Bartonella* spp. [4].

Here, we present what is, to our knowledge, the first 2 cases of culture-negative infective endocarditis due to *Brucella* in injection drug users without identifiable zoonotic exposures.

CASE 1

A 24-year-old woman with a complicated medical history including injection heroin use, tricuspid valve replacement following endocarditis due to methicillin-susceptible *Staphylococcus aureus,* and hepatitis C infection was admitted with fever.

Multiple blood cultures obtained before antibiotic therapy were without growth, and transesophageal echocardiography demonstrated a vegetation on the tricuspid prosthesis with associated regurgitation and stenosis. She was evaluated by cardiac surgery, and surgical intervention was recommended but was deferred due to injection drug use while hospitalized. She was treated with empiric vancomycin, cefepime, and levofloxacin and refused therapy with buprenorphine for opioid use disorder. She left the hospital against medical advice after 11 days.

Over the next several months, she intermittently presented to multiple facilities with dyspnea and lower-extremity edema, although she repeatedly left against medical advice. Five months after her initial presentation, she returned to our institution with ongoing complaints of dyspnea and edema; repeat echocardiogram demonstrated multiple vegetations on the prosthetic tricuspid valve as well as tricuspid stenosis and regurgitation. Cultures of blood obtained on admission for bacterial, fungal, and acid-fast pathogens were without growth. Serologic testing for *Bartonella henselae, Legionella pneumophilia,* and *Coxiella burnettii* was negative, whereas serologic testing for *Brucella* spp. at Quest Diagnostics (San Juan Capistrano, CA, USA) demonstrated a positive IgM, negative IgG, and a positive serum agglutination test (SAT) at 1:640. The SAT was repeated 2 weeks after the initial test and was again positive with a titer of 1:320. Serologic and nucleic acid testing for HIV were negative, whereas additional testing showed immunity to hepatitis B without evidence of prior infection, positive hepatitis C antibody, and undetectable hepatitis C RNA. Testing for *Tropheryma whipplei, Histoplasma,* or *Aspergillus* was not performed.

She reported living in urban areas in the Midwest and repeatedly denied any zoonotic exposures, including cats, dogs, sheep, or goats, as well as consumption of unpasteurized milk or cheeses. She denied any visits or periods of residence in rural areas or exposures to farm animals. She was unwilling to discuss her source of opioids or injection equipment despite repeated requests.

Therapy for brucellosis with rifampin and doxycycline was initiated. She again refused buprenorphine therapy for opioid use disorder and was discharged on oral doxycycline and rifampin, as outpatient parenteral therapy with gentamicin was judged to be unacceptably high risk. She has followed up intermittently with cardiology, cardiac surgery, and infectious diseases. At her most recent follow-up visit 2 months after discharge, she reported ongoing adherence to doxycycline and

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Correspondence: John M. Cafardi, MD, Department of Infectious Diseases, The Christ Hospital, MOB Suite A44, Cincinnati, OH 45219 (john.cafardi@thechristhospital.com).

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rifampin, although she has refused follow-up serologic testing. She has not returned for further visits.

CASE 2

Approximately 8 months after the initial presentation of Case 1 and 6 months after her second admission, a 44-year-old man with a history of injection drug use and chronic hepatitis C presented with several months of subjective fevers, malaise, night sweats, back pain, weight loss, and intermittent abdominal pain. Evaluation revealed anemia, thrombocytopenia, and hepatosplenomegaly with enlargement of the portocaval and porta hepatis lymph nodes. Transesophageal echocardiography demonstrated mitral valve vegetation with associated mitral regurgitation. Multiple sets of blood cultures obtained before initiation of antibiotics were negative. Testing for HIV, hepatitis B, and syphilis was negative, whereas infection with hepatitis C, genotype 3, was confirmed. Rheumatoid factor was elevated at 58 IU/mL, whereas antinuclear antibody testing was negative. He was evaluated by Hematology and started on glucocorticoids for presumed autoimmune hemolytic anemia and thrombocytopenia. Vertebral magnetic resonance imaging showed no evidence of osteomyelitis or discitis, and cerebrospinal fluid analysis revealed normal glucose and protein levels without pleocytosis.

Serologic testing for *Brucella* species was performed at Quest Diagnostics (San Juan Capistrano, CA, USA) and demonstrated positive IgM, negative IgG, and positive serum agglutination titer (SAT) at 1:320. Further testing for culture-negative endocarditis, including *Bartonella, Coxiella, Aspergillus, Histoplasma, Legionella,* or *Tropheryma whipplei,* was not performed.

He reported living in urban areas in the Midwest and repeatedly denied any zoonotic exposures, including cats, dogs, sheep, or goats. He denied any visits or periods of residence in rural areas or exposures to farm animals, as well as consumption of unpasteurized milk or cheeses. He was unwilling to discuss the source of his opioids or injection equipment despite repeated requests.

Therapy with doxycycline, rifampin, and gentamicin was initiated; however, he left against medical advice after 10 days of antibiotic treatment. He was not considered a candidate for outpatient parenteral antibiotic therapy or cardiac surgery due to his poor compliance and ongoing injection drug use. He subsequently returned to the hospital after ~24 hours and was restarted on doxycycline, rifampin, and gentamicin to complete an additional 7 days of aminoglycoside therapy. He was discharged to complete 6 weeks of doxycycline and rifampin as well as a prednisone taper and has since been lost to follow-up.

DISCUSSION

Brucellosis is the most common zoonotic infection worldwide and is acquired by ingestion of contaminated food or contact with infected tissues [5]. It is endemic in Western Europe, North and Sub-Saharan Africa, Central and South America, and the United States [6], with ~2.5 billion people living in regions where *Brucella* is endemic; there is a worldwide burden of disease of ~500 000 cases annually [7].

Brucellosis typically presents with nonspecific symptoms, including fevers, malaise, arthralgia, and night sweats. After this initial prodrome, focal disease with osteoarticular, genitourinary, neurologic, or cardiovascular involvement develops in 30%–90% of infected individuals [5].

Endocarditis is a rare complication of systemic *Brucella* infection, occurring in 2%–3% of cases, with <400 cases reported in the literature since 1966 [8] and no reported cases in which injection drug use was the sole risk factor for endovascular infection. Despite its rarity, infective endocarditis is responsible for 80% of the deaths due to brucellosis [9]. To date, infective endocarditis due to *Brucella* has been exclusively reported in individuals with a clear history of exposure to animal sources. Definitive diagnosis requires isolation of *Brucella* species in cultures of blood, body fluid, or tissue samples or a 4-fold increase in antibody titer obtained ≥2 weeks apart while a presumptive diagnosis is made by isolation of *Brucella* DNA in a tissue sample or a SAT ≥1:160 in a symptomatic individual [10].

The preferred treatment of brucellosis is 6 weeks of doxycycline with either 3 weeks of streptomycin, 1 week of gentamicin, or 6 weeks of rifampin. The treatment of *Brucella* infective endocarditis is complex and, due to the limited number of cases, poorly defined. In general, a combination of medical and surgical therapy is required for cure [11], although management via successful medical therapy alone has been reported [12].

We believe these are the first cases of *Brucella* infective endocarditis associated with injection drug use without identifiable zoonotic risk factors. Although the possibility of false-positive serologic testing or unidentified zoonotic exposure exists, we were unable to identify any zoonotic risk factor despite repeated inquiry. Although attempts to determine the source of the drugs and/or injection equipment were unavailing, it is possible that there was a zoonotic source for these infections that occurred in the same area and during a narrow time frame and that it may have been connected to the source of the drugs and/or injection equipment. Given these cases, we suggest consideration of brucellosis when evaluating culture-negative infective endocarditis in persons who inject drugs.

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