CLINICAL VIGNETTE

Bartonella henselae Bacteremia in an HIV-Positive Patient

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Case Report

A 44-year-old male with AIDS and recent diagnosis of pneumocystis pneumonia presented to the emergency room with one day of decreased appetite, night sweats, fevers, cough, generalized weakness, and altered mentation with slow responses. He otherwise denied nausea, vomiting, abdominal pain, diarrhea, dysuria, shortness of breath, headache, paresthesias, vision changes, focal muscle weakness, and rash. Past medical history includes syphilis, pancytopenia, and heart failure. The patient lives in a home with a dog with fleas. He takes bictegravir/emtricitabine/tenofovir alafenamide and atovaquone.

His initial vitals were notable for temperature of 39.5°C, heart rate 130, and blood pressure of 72/40 mm Hg. His physical exam was positive for oral thrush, regular tachycardia, crackles in the right base, slowed speech, and a raised violaceous 1cm lesion on the right dorsum of the hand. Otherwise, he was alert and oriented x 4 with a normal abdominal, neurologic, and lymph node exam. His labs were pertinent for a white blood cell (WBC) count of 5.3 K/cumm, hemoglobin of 7.0 g/dL, platelets of 176 K/cumm, CD4 count of 17/cumm, sodium of 129 mmol/L, creatinine of 2.5 mg/dL (baseline 0.9 mg/dL), alanine transaminase of 38 U/L, aspartate transaminase of 67 U/L, alkaline phosphatase of 333 U/L, gamma-glutamyl transferase of 105 U/L, and total bilirubin of 1.7 mg/dL, albumin 2.3 g/dL. Computed tomography without contrast of the chest, abdomen, pelvis, and brain was remarkable for improved bilateral lung opacities and cholelithiasis without evidence of cholecystitis.

He was admitted for sepsis without a clear source and treated empirically with vancomycin and cefepime. Blood and urine cultures were negative. Lumbar puncture on hospital day 3, had a normal opening pressure, normal cerebrospinal fluid analysis, and negative gram stain and culture. Dermatology consulted for biopsy of the violaceous skin lesion, which showed Kaposi sarcoma. The patient remained persistently febrile so empirical treatment for disseminated Mycobacterium avium complex started on hospital day 4 with no improvement. Polymerase chain reaction testing for *Bartonella henselae* of the blood was positive on hospital day 7 and he was started on oral doxycycline 100mg twice a day. Transthoracic and transesophageal echocardiograms were negative for endocarditis. The patient continued to have fevers and repeat abdominal imaging showed new hepatosplenomegaly. The diagnosis of hemophagocytic lymphohistiocytosis (HLH) was suspected with fever, cytopenias, elevated ferritin, and splenomegaly. Further testing including interleukin-2 receptor level and natural killer cell activity, confirmed the diagnosis of HLH. The patient however opted to pursue home hospice and was discharged on hospital day 17.

Discussion

Bartonella spp. can produce a wide variety of clinical syndromes with notable distinctions between immunocompetent and immunocompromised individuals. Immunocompetent individuals most often develop cat scratch disease (CSD), characterized by a primary inoculation lesion followed by regional lymphadenopathy in 90% of patients.[1] The lymphadenopathy typically resolves within several months but can persist over 6 months to as long 12-24 in some patients. An estimated 5-25% of patients with CSD develop atypical manifestations, including Parinaud's oculoglandular syndrome, neurologic illness, hemolytic anemia, hepatosplenomegaly, glomerulonephritis, pneumonia, arthralgia, and osteomyelitis, relapsing bacteremia, and endocarditis.[1,2]

Immunocompromised individuals, however, often present in more diverse ways with more nonspecific symptoms, potentially due to bacteria-induced dysregulation of cytokines and growth factors in the setting of immunodeficiency.[1,3] One of the most common manifestations of *Bartonella* infection in immunocompromised patients is bacillary angiomatosis, characterized by vascular proliferative lesions that classically present as angiomatous cutaneous lesions but can also involve visceral tissue.[1,2] Bacillary peliosis hepatis, which involves dilatation of sinusoidal blood-spaced cavities in the liver, is another well documented sequela of *Bartonella* infection.[1,2]

Immunosuppressed individuals, especially those with HIV, can develop *B. henselae* bacteremia with variable presentation, ranging from relapsing fever and weight loss to endocarditis, rheumatologic symptoms, neurologic manifestations, and even epithelioid hemangioendothelioma.[1,4–6] The prevalence of *B. henselae* bacteremia on PCR was 10% in a sample of 188 HIV-positive patients and as high as 18% via culture, indirect fluorescent antibody testing, or PCR in a group of mostly HIV-positive individuals presenting with fever.[7,8] *B. henselae* bacteremia has also been reported in immunocompetent patients with CSD-like symptoms or no symptoms at all. One study found 16% of healthy blood donors seropositive for *B. henselae*; however, presence of antibodies in serum was poorly associated with true infection.[9–11]

Infection by *Bartonella* spp. species can be diagnosed through a variety of methods. Cutaneous lesions concerning for bacillary angiomatosis can be biopsied and distinguished from Kaposi's sarcoma by H&E and Warthin-Starry staining with a characteristically protuberant appearance of endothelial cells.[1] Histopathological examination can also diagnose bacillary peliosis hepatis, classically characterized by dilated capillaries with enlarged, blood-filled, cystic spaces with adjacent clumps of bacilli best visualized with Warthin-Starry staining.[1]

Bacteremia can also be identified through various laboratory techniques. *Bartonella* is a particularly fastidious genus to culture and requires specific protocol and culture conditions for isolation. Both Isolator tubes and EDTA blood tubes have been used with one study finding Isolator tubes to be more sensitive for *B. henselae* isolation than EDTA tubes.[1,12] Certain enriched agars without the addition of antibiotics are preferred for culture, and *Bartonella* spp. been identified via BACTEC and BacT/Alert automated blood culture systems with acridine orange staining after extended incubation.[1,13]

Serology via indirect immunofluorescence assay (IFA) represents an alternative method for *Bartonella* diagnostic testing. One study found IFA to have a sensitivity of 88% and specificity of 94% of detecting CSD, using an antibody titer cutoff of at least 1:64.[14] A similar IFA assay with the same 1:64 antibody titer level was utilized to diagnose *Bartonella* bacteremia in asymptomatic, immunocompetent individuals.[9] Lastly, PCR represents a newer method of isolation. Primers against numerous targets have been described, including the 16S ribosomal RNA gene, 16S-23S intergenic spacer region, and the *htrA* gene encoding a heat shock-like protein.[1,10,15] A study comparing these isolation methods in a population of high-risk, immunocompetent individuals found IFA antibodies were not detected in 30.4% of bacteremic patients, while PCR on only extracted blood would not have detected Bartonella infection in 34.7% of bacteremic patients.[15] The authors concluded that independently testing blood, serum, and enrichment blood culture by PCR should to be performed to supplement serologic data to diagnosis *Bartonella* sp. Bacteremia. In our patient, the serum was positive for *B. henselae* by PCR, but the blood culture was negative, highlighting the need for complementary diagnostic approaches to identifying *Bartonella* bacteremia.

No randomized controlled trials evaluating treatment of *Bartonella* infections in patients with HIV have been published. Studies report either doxycycline 100mg PO or IV every 12 hours or erythromycin 500mg PO or IV every 6 hours can be used as first-line antimicrobial treatment for bartonellosis, including *Bartonella* spp. bacteremia.[1,6,8,16,17] Rifampin 300mg PO or IV every 12 hours can be added for severe infections, and duration of antibiotic therapy should continue for at least 3 months.[1,6,16,17] After the positive serum PCR result for *B. henselae*, our patient was started on doxycycline 100mg PO every 12 hours and his fevers initially subsided. It is significant to note that the patient had already been receiving empirical RIPE and azithromycin therapy for TB and disseminated MAC therapy, which may have had activity against the bacteremia prior to diagnosis. The patient continued to have fevers after starting doxycycline and was restarted on RIPE and azithromycin therapy in addition to doxycycline before being diagnosed with HLH and being discharged to home hospice.

Given the prevalence of *B. henselae* bacteremia in both immunocompromised and immunocompetent patients, there should be a low threshold for sending *Bartonella* studies in HIV-positive patients with recurrent fevers of unknown origin or other nonspecific symptoms. A combination of serology, culture, and PCR-based diagnostics should be performed, and prompt treatment be initiated with either doxycycline or erythromycin for positive patients for infection control.

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