CASE REPORTS

Native Valve Endocarditis Due to *Bartonella henselae* in a Middle-Aged Human Immunodeficiency Virus-Negative Woman

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We report the case of a human immunodeficiency virus-negative woman who developed native valve endocarditis of the aortic valve due to *Bartonella henselae* infection. The diagnosis was established using serology and PCR analysis of excised aortic valve tissue.

CASE REPORT

A 38-year-old woman having a remote history of intravenous drug use was admitted to Lyndon B. Johnson Hospital in May 2000 after she presented to the emergency room. She complained of fever, nausea, vomiting, and nonbloody diarrhea over a 2-week period associated with fatigue and generalized weakness. She lived in Texas and owned a fully grown cat and two kittens. Initial examination of the patient revealed a temperature of 39°C, a grade 3/6 diastolic murmur, and splenomegaly. Laboratory evaluation showed the following values: white blood cell count, 2.4×10^9 /liter; hemoglobin level, 11.9 g/dl; platelet count, 62×10^9 /liter. In addition, a chest radiograph showed moderate cardiomegaly but no effusions or infiltrates. Because of a high level of suspicion that the patient had infective endocarditis, transthoracic echocardiography was performed on the day of admission, which demonstrated the presence of a large, mobile vegetation on a bicuspid aortic valve.

Initially, the patient received empirical treatment for infective endocarditis with a combination of vancomycin and gentamicin. Twenty-four hours later, a transesophageal echo test was performed, revealing a 2-cm vegetation attached to both cusps of the bicuspid aortic valve, moderate aortic regurgitation, dilatation of the ascending aorta without evidence of abscess formation, and concentric left ventricular hypertrophy. Two weeks after that, a total of six sets of blood cultures collected by adult isolator tubes prior to and after initiation of antibiotic treatment yielded no growth. Additionally, serum specimens were collected for infectious serology, including agents of culture-negative endocarditis. Subsequently, the patient's hospital course was complicated by the development of glomerulonephritis secondary to her infective endocarditis and nonoliguric acute renal failure due to aminoglycoside toxicity. The serum creatinine level peaked at 3.5 mg/dl. *Bartonella* serology using an indirect immunofluorescence assay (IFA;

Microbiology Reference Laboratory, Cypress, Calif.) showed the following titers: *Bartonella henselae* immunoglobulin M (IgM), 1:20 (reference range, negative, <1:20); *B. henselae* IgG, 1:512 (reference range, negative, <1:64); *Bartonella quintana* IgM, 1:20 (reference range, negative, <1:20); *B. quintana* IgG, 1:512 (reference range, negative, <1:64). When a serology result positive for *Bartonella* species was reported, the patient's antibiotic regimen was changed to ceftriaxone and azithromycin. Serological tests for *Brucella*, *Chlamydia*, and *Coxiella* species, other common etiological agents of culture-negative endocarditis, were negative.

Because of the patient's persistent febrile episodes and the presence of no obvious source other than her infective endocarditis, she underwent aortic valve replacement approximately 8 weeks after being admitted to the hospital. PCR (Microbiology Reference Laboratory) confirmed the presence of *B. henselae* in the vegetation.

Stained sections of the patient's aortic valve cusps with hematoxylin and eosin showed nonvascularization, focal necrosis, and infiltration by a predominance of chronic inflammatory cells, as well as neutrophils. Also, Gram and Grocott-Gomori methenamine silver staining showed that no microorganisms were present in valvular tissues. Culture analyses of the vegetation and cardiac valvular tissue samples by recommended techniques (18) were negative for *Bartonella* species after 28 days of incubation.

The patient's overall clinical condition improved soon after the valve replacement. She became afebrile, and her serum creatinine level gradually decreased over a period of 2 weeks to 1.2 mg/dl. During the second postoperative week, she developed a postpericardiotomy syndrome-related pericardial effusion that was managed medically and did not require invasive intervention. The patient was then discharged, and she completed a 6-week course of oral azithromycin and levofloxacin at home. Seven months after the surgery, the patient remained clinically stable.

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Culture-negative endocarditis remains a diagnostic and therapeutic problem, accounting for 5 to 30% of all endocarditis

cases (13, 19, 20). *Bartonella* was first described as a cause of endocarditis in two separate reports in 1993 (7, 16). More recently, it has been recognized as an important cause of culture-negative endocarditis (4, 14, 17). Three *Bartonella* species, in particular, are known to cause infective endocarditis: *B. henselae*, *B. quintana*, and *B. elizabethae*. In a multicenter international study that evaluated patients having culture-negative endocarditis (14), 22 patients having *Bartonella* endocarditis were found: 5 were infected with *B. quintana*, 4 were infected with *B. henselae*, and 13 were infected with an undetermined *Bartonella* species. More recently, *Bartonella vinsonii* subsp. *berkhoffii* was described as the agent of afebrile culture-negative endocarditis in a 35-year-old male patient having a bicuspid aortic valve vegetation (15). This species had previously been isolated only from blood samples obtained from a healthy dog, as well as a dog suffering from valvular endocarditis (5, 9).

The epidemiologic features of patients having *Bartonella* endocarditis are variable. While almost all reports of *Bartonella* endocarditis have involved adults, two recent cases were reported in pediatric patients (2, 3). Overall, approximately 85 to 90% of the cases have involved men. The clinical features of patients having *Bartonella* endocarditis are similar to those previously reported in patients having infective endocarditis (14). Approximately 90% of patients having *Bartonella* endocarditis have involvement of the aortic valve. Finally, in the largest series (14), approximately 50% of the patients had evidence of a preexisting valvular disease, as did our patient.

Blood cultures from patients with *Bartonella* endocarditis require prolonged incubation before they become positive (if they become positive at all), and they are not considered the optimal diagnostic test for this organism. Indeed, in the multicenter international study described above (14), only 5 (23%) of 22 patients had blood cultures positive for *Bartonella* at any time during their clinical course. The best method for isolation of the organism is the use of pediatric or adult isolator tubes (Wampole, Cranbury, N.J.) or EDTA blood tubes (18). *Bartonella* species also require specific laboratory conditions for optimal growth, making them difficult to isolate and to grow. Recovery of *Bartonella* species from subcultures is enhanced by plating samples onto heart infusion or chocolate agar supplemented with 5% rabbit blood (18). The agar plates should be incubated for at least 21 days in 5% CO₂ at 35 to 37°C.

The histopathology of cardiac valvular tissue may contribute to the etiologic diagnosis of *Bartonella* endocarditis when serology or molecular techniques are not available. Hematoxylin and eosin staining of the involved valve typically shows inflamed connective tissue with focal granulation. Warthin-Starry silver staining may, in some instances, reveal the organisms as dark-stained bacteria. In one study, the cardiac valve pathology of 15 patients having confirmed *Bartonella* endocarditis was compared with that in 25 cases of non-*Bartonella* endocarditis using computerized quantitative image analysis (10). In contrast with the other cases of infective endocarditis, the *Bartonella* endocarditis cases were more fibrotic and calcified, were less vascularized, and had less extensive vegetation and chronic inflammation.

Given the highly fastidious nature of *Bartonella* species, clinicians must rely upon other modalities to diagnose infection. IFA and enzyme-linked immunosorbent assay are the two serologic methods currently used to diagnose *Bartonella* infec-

tions. It is of note that our patient had an indirect IFA titer of 1:512 for *Bartonella* species. On the other hand, in the multicenter international series (14), all but one patient with *Bartonella* endocarditis had titers of $\geq 1:1,600$ as determined by microimmunofluorescence. Because most *Bartonella*-related infections have been described only recently and the number of cases is still relatively small, the titer at which antibody levels become significant for the diagnosis of infection has yet to be determined. Although clearly defined cutoff levels for a *Bartonella*-positive serology test do not exist, some would consider an IgG titer of >100 to be significant (11). In addition, several groups have questioned the specificity of antibody estimation tests. Current serologic tests do not reliably distinguish *B. quintana* antibody responses from *B. henselae* ones. Cross-reactivity between *Bartonella* species and other organisms, including *Coxiella burnetii* (6) and *Chlamydia* species (8), has been reported. Drancourt et al. (8) reported that patients having *B. quintana*-induced endocarditis had IgG titers of >256 against *Chlamydia pneumoniae* and >64 against *Chlamydia trachomatis* and *Chlamydia psittaci*. However, our patient had negative serology results for *Chlamydia* species.

PCR has been a very useful technique for demonstrating *Bartonella* DNA in cardiac valvular tissue, especially when fresh valvular tissue is used (14). In the present case, a PCR assay using the degenerate primers CAT1 and CAT2, which allow amplification of a 414-bp fragment of DNA from *B. henselae* and *B. quintana* (1), was used. It is of note that PCR can distinguish all of the *Bartonella* species.

The optimal antibiotic therapy for *Bartonella* endocarditis is unknown. First, the role of antibiotic therapy is limited by the fact that most *Bartonella* endocarditis patients have undergone valve replacement despite intravenous antimicrobial therapy (8, 14, 17). Second, the literature consists mostly of series of case reports and does not show use of a consistent antibiotic therapy regimen. Finally, it should be noted that *Bartonella*-induced endocarditis usually results in extensive valve damage, requiring replacement (7, 8). A study investigating the bactericidal activity of antibiotics against *Bartonella* species in vitro found only aminoglycosides to be bactericidal against *B. henselae* either in axenic broths or in cocultivation with eucaryotic cell lines (12). An antibiotic regimen for *Bartonella* endocarditis consisting of gentamicin and either ceftriaxone or doxycycline has been suggested, however (11). Based on experience with other *Bartonella* infections, the use of macrolides (erythromycin, azithromycin, and clarithromycin) is a reasonable option, but given their static nature, the addition of a bactericidal agent is recommended.

In summary, we have described a case of native valve endocarditis caused by *B. henselae* in a human immunodeficiency virus-negative woman. The diagnosis was made by using serology (to the genus level) and PCR analysis of surgical tissue samples (to the species level). The patient underwent aortic valve replacement and then received a course of levofloxacin and azithromycin and continues to do well.

Bartonella infection should be included in the differential diagnosis of culture-negative endocarditis. Early use of *Bartonella* serology (as well as *C. burnetii*, *Chlamydia*, and *Brucella* serology) is recommended in those cases in which properly obtained blood cultures do not establish the etiology of the endocarditis. Nonculture techniques such as serology and PCR

analysis of surgical tissue may be the diagnostic methods of choice given the difficulty in culturing these organisms.

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