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The Brief Case: *Bartonella henselae* Endocarditis—a Case of Delayed Diagnosis

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CASE

A 54-year-old male presented to an outside institution with a 2-month history of myalgia, headaches, 10-pound weight loss, fever, and night sweats. His past medical history was notable for rheumatic heart disease and placement of a bioprosthetic aortic valve 7 years prior. The patient was from Iowa, where he previously worked as a roofer, lived near many cattle farms, had a pet dog and cat, and frequently went fishing along the Mississippi river. On presentation, the patient had lower-extremity edema and his creatinine was elevated to 3.2 mg/dl (normal range, 0.59 to 1.04 mg/dl). Transthoracic echocardiogram (TTE) showed a stenotic and calcified aortic valve. Urinalysis demonstrated dysmorphic erythrocytes, and blood cultures drawn prior to initiation of antibiotics remained negative. Further laboratory analysis demonstrated an erythrocyte sedimentation rate (ESR) of 109 mm/ h (normal range, 0 to 29 mm/ h) and markers of vasculitis with a positive cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) with a titer of 1:256 and positive antiproteinase 3 (anti-PR3) levels of >8 U. Screening tests for HIV, hepatitis C virus, hepatitis B virus, and latent tuberculosis by an interferon gamma release assay were all negative. The patient initially responded to a 2-week course of prednisone; however, within 1 month he experienced additional fevers, weight loss, fatigue, malaise, and further worsening of his renal function. The patient was empirically treated with intravenous (IV) vancomycin and ceftriaxone for these symptoms. A renal biopsy was performed and interpreted as consistent with postinfectious glomerulonephropathy.

The patient was subsequently transferred to our medical center for further evaluation. Serologic testing for *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis/Coccidioides posadasii*, and *Brucella* species were all negative. Notably, the patient was seropositive for the following pathogens: spotted fever group *Rickettsia* with an IgG titer of 1:256, *Coxiella burnetii* phase II IgG titer of 1:256 (all other *C. burnetii* IgM and IgG titers were less than 1:16), *Bartonella quintana* IgG titer of 1:512 and an IgM titer of <1:20, a *Bartonella henselae* IgG titer of 1:32,768, and an IgM titer of <1:20. *Bartonella* species and *C. burnetii* real-time PCR (RT-PCR) on blood were negative. A transesophageal echocardiogram (TEE) demonstrated a stenotic aortic valve with thickened leaflets and a calcific, mobile mass. Valvular biopsy was not performed. Based on the results above, a diagnosis of *B. henselae* endocarditis was established. The patient was treated with oral doxycycline, IV ceftriaxone, and gentamicin for 2 weeks, followed by an additional 4 weeks of oral doxycycline and IV ceftriaxone, and remains on oral doxycycline indefinitely. One year after diagnosis, the patient is without further cardiovascular complications or need for surgery, and his *B. henselae* IgG titer has declined to 1:2,048. The patient was advised to have pets tested and treated for fleas.

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For answers to the self-assessment questions and take-home points, see https://doi.org/10.1128/JCM.00123-19 in this issue.

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DISCUSSION

Bartonella spp. are short, fastidious, Gram-negative coccobacilli transmitted to humans via either an insect vector or cats, depending on the species. While upwards of 30 species have been identified, 12 have been linked to human infection, among which three are most commonly encountered clinically. These include the causative agents of Oroya fever (*Bartonella bacilliformis*), trench fever (*Bartonella quintana*), and cat scratch disease (CSD; *Bartonella henselae*) (1). Oroya fever is endemic to the Andes Mountains and limited to specific elevations inhabited by its vector, the sand fly. This acute form of *B. bacilliformis* infection presents as a febrile illness with marked anemia (1). The chronic form of *B. bacilliformis* infection, verruga peruana, is more common among persons native to the region where it is endemic and presents as nodular skin lesions months after initial infection (1). Trench fever draws its name from World War I, when more than a million soldiers fighting in close quarters developed a recurrent episodic febrile illness associated with bone pain, headache, and rash, transmitted by lice. Modern outbreaks are associated with poor living conditions among the homeless population and in refugee camps (1, 2) Transmission of *B. henselae* is associated with cats and cat fleas. Weeks after a scratch or bite, a pustule will form at the site of inoculation with associated localized lymphadenopathy. Commonly, this is a self-limiting disease (1, 3). *B. henselae* and *B. quintana* have a global distribution and are associated with culture-negative endocarditis in approximately 12% to 28% of cases. *Bartonella* spp. are the second most common cause of culture-negative endocarditis, after *Coxiella burnetii* (4, 5). Definitive diagnosis of *Bartonella* endocarditis can be challenging and typically involves consideration of clinical presentation, echocardiography findings, and laboratory results with respect to the modified Duke criteria for infective endocarditis (6). In a study of 101 patients with *Bartonella* endocarditis, echocardiography findings included the presence of vegetation in 90% of cases, with a predominance of aortic valve involvement identified in 59% of patients, whereas multiple valves were involved in only 18% of the cohort (7).

Serology is the single most informative, noninvasive test to aid in the diagnosis of *Bartonella* endocarditis. Immunofluorescence assays (IFAs) and enzyme-linked immunosorbent assays (ELISAs) for detection of IgG and IgM are commercially available for *B. quintana* and *B. henselae*, although classically, IFA is preferred due to its better performance characteristics and ability to provide semiquantitative titers. IFA results of $\geq$1:64 for IgG-class antibodies to *B. henselae* are considered positive, with sensitivity ranges of 88% to 98% reported across different assays (8). Notably, however, seroprevalence studies performed across multiple countries have shown that anywhere from 3% to 30% of otherwise healthy individuals may be seropositive for IgG-class antibodies to *B. henselae* using this threshold titer. However, the majority of these positive results are at titers of $\leq$1:128, and for this reason a single-time-point, low-level positive IgG titer should be interpreted with caution (Table 1). Reasons for this reactivity are likely due to prior exposure to the bacterium or possibly are the result of cross-reactivity with other *Bartonella* spp. or organisms, including *C. burnetii*, *Chlamydophila pneumoniae*, or spotted fever group *Rickettsia*. Given these findings, IgG titers of $\geq$1:256 and/or a 4-fold rise in IgG antibodies between acute and convalescent-phase samples are considered indicative of current or recent infection. Notably, patients with *Bartonella* endocarditis often present with high IgG titers, and prior studies have demonstrated that IgG levels of $\geq$1:800 correlate with endocarditis in 94% of cases (9). Assays for detection of IgM-class antibodies against *B. henselae* are considerably less sensitive (range, 50% to 62%), with titers of $\geq$1:20 considered positive (8, 10). IgM-class antibodies to *Bartonella* species are typically present early in infection and wane 8 to 10 weeks thereafter, suggesting that IgM testing may not be helpful during later stages of disease (8). The reported specificity of IgM assays is high (95%), and notably higher than that reported for IgG assays (69% to 89%), although false-positive results may still occur with *C. burnettii* and *C. pneumoniae* infections (11). Notably, a positive anti-*Bartonella* IgM result alone should be considered cautiously and interpreted alongside

TABLE 1 Advantages and limitations of methods for detection of *Bartonella* species endocarditis

Method	Advantages	Limitations
Serology	High sensitivity in cases of endocarditis Seroconversion or increasing IgG antibody titers indicate active infection Noninvasive	False positives due to cross-reactivity Mildly elevated baseline IgG antibody titers (<1:128) in the general population
Bartonella-specific RT-PCR	High sensitivity and specificity from tissue	Low sensitivity from blood
16S rRNA PCR and sequencing	Broad-range bacterial DNA amplification reduces the need for targeted pathogen testing	Lower sensitivity than pathogen-specific PCR Risk of identifying a contaminant
Histopathology/immunohistochemistry	Allows for assessment across spectrum of infectious diseases Demonstrates involvement of specific tissue	Lack of pathogen-specific stains Background/nonspecific staining makes interpretation difficult
Culture	Definitive diagnosis Indicates active infection	Poor sensitivity from all specimen types

the timing of the potential exposure and duration of patient symptoms. Convalescent testing of a new specimen collected 2 to 3 weeks later is recommended to show seroconversion of anti-*Bartonella* IgG, to help rule out a false-positive IgM result.

Historically, culture of both blood and heart valve tissue were the preferred microbiologic methods employed for suspected *Bartonella* endocarditis. Even with specialized collection and culture procedures however, including plating on fresh media and incubation in 5% CO_2 at 35 to 37°C for up to 21 days, recovery was poor (Table 1) (12). For this reason, culture has largely been supplanted with nucleic acid amplification tests (NAATs), including *Bartonella*-specific real-time PCR (RT-PCR) assays and/or broad-range bacterial 16S PCR and sequencing (9, 13). While superior to culture, these new methods are not without their own set of limitations, as pretest probability varies greatly with specimen type (4). One study of patients with confirmed *Bartonella* endocarditis showed just 33% sensitivity using a *Bartonella*-specific RT-PCR from blood (9). While less than ideal, this is an improvement over recovery of *B. henselae* in blood cultures, which is approximately 20% among patients with endocarditis (9). *Bartonella*-specific RT-PCR demonstrated improved performance from explanted valve tissue, with a sensitivity of 92% compared to 60% sensitivity using broad-range PCR and sequencing and to just 30% sensitivity achieved using traditional culture methods (9). While positive NAAT results provide definitive evidence of infection with *Bartonella* spp., the highly variable negative predictive value of these assays warrants cautious reliance on a negative result when clinical suspicion remains high (Table 1).

Histopathology of valve tissue commonly accompanies microbiological testing when biopsy is performed. In cases of *Bartonella* endocarditis, visualization of the organism in tissue can be difficult, especially with prior antibiotic treatment. *Bartonella* spp. are not easily observed with routine stains, such as hematoxylin and eosin (H&E), Grocott-Gomori methenamine silver (GMS), or Gram stain (Table 1). Silver stains, such as Warthin-Starry, Steiner, or Dieterle, are preferred, but can be technically challenging to interpret due to high background and nonspecific silver deposition on reticulin or other fibers, mimicking the appearance of coccobacilli (14). Species-specific immunohistochemical stains are also available in specialized laboratories but suffer from poor sensitivity (9).

Finally, the positive c-ANCA result in this case deserves mention, as this finding is not uncommon in cases of *Bartonella* endocarditis. A 2016 case series of 50 patients demonstrated that among 24% of patients diagnosed with any infective endocarditis, 84% had a positive c-ANCA result and 74% of c-ANCA positive patients with infective endocarditis demonstrated renal failure (15). Furthermore, a 2014 case report and literature review of *Bartonella* endocarditis cases reported that 50% of the eight

reviewed cases were c-ANCA positive (16). Although further research is needed to correlate c-ANCA results with infective endocarditis, a positive c-ANCA result may prompt providers to consider culture-negative endocarditis sooner, alongside a detailed clinical assessment and targeted diagnostic testing.

SELF-ASSESSMENT QUESTIONS

1. Which of the following is the most sensitive noninvasive microbiologic assay for detection of suspected *Bartonella* spp. endocarditis?
    a. Blood culture
    b. Culture of heart valve tissue
    c. *Bartonella* sp. IgG-specific serologic testing
    d. Broad-range 16S PCR and sequencing from heart valve tissue
2. A 63-year-old male originally from Brazil and now living in a homeless shelter presents to the emergency department with a fever, headache, rash, and bone pain in the shins, neck, and back. On examination, lice are visible on the patient's clothes and hospital bed sheets. Which of the following is the most likely causative organism?
    a. *Bartonella henselae*
    b. *Bartonella quintana*
    c. *Bartonella bacilliformis*
    d. *Bartonella alsatica*
3. Antibodies to which of the following pathogens can lead to cross-reactivity on serologic assays for detection of *Bartonella* sp. antibodies?
    a. *Anaplasma phagocytophilum*
    b. *Brucella abortus*
    c. *Coxiella burnetii*
    d. *Treponema pallidum*

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