Streptobacillus moniliformis mitral valve endocarditis and septic arthritis: the challenges of diagnosing rat-bite fever endocarditis

Daisy Torres-Miranda,[1] Mahdi Moshgriz,[2] Marc Siegel[1]

[1]Department of Medicine, George Washington University, Medical Faculty Associates, Washington, DC; [2]Department of Pathology, George Washington University Medical Center, Washington, DC, USA

Abstract

Streptobacillus moniliformis, the cause of rat-bite fever (RBF) in the United States, has rarely been reported as a cause of infectious endocarditis. In the majority of previously reported cases, the diagnosis was clinically-based in patients with underlying valvular abnormalities in the setting of positive blood culture for *Streptobacillus moniliformis*. We report a case of native valve endocarditis secondary to *Streptobacillus moniliformis* in a woman with a mitral valve vegetation but negative blood cultures where the diagnosis was established using molecular diagnostics on the valvular tissue.

Case Report

A previously healthy 52 year-old African American female presented to the hospital with confusion. According to her partner, she had been complaining of constant pain in the right knee and ankle for three days, associated with generalized weakness. There was no history of trauma to the extremity. She had no known allergies and was not taking any medications. She had no history of recreational drugs, no recent travel and was only sexually active with one male partner.

On presentation, the patient was lethargic and oriented to self-only. Her temperature on admission was 39.4°C, blood pressure 92/54 mmHg, heart rate 96 beats per minute and respiratory rate 18 breathes per minute, with an oxygen saturation of 96% on ambient air. On examination, the right knee and right ankle demonstrated swelling, warmth, and erythema. A punctate opening in the heel of right foot with no surrounding erythema was noted. Laboratory studies revealed leukocytosis (white blood cell count 22,600 cells/mL, 88% neutrophils, 6% bands), hyponatremia (sodium 125 mEq/L), and hypokalemia (potassium 2.8 mEq/L). Inflammatory markers were elevated (erythrocyte sedimentation rate 85 mm/hr, C-reactive protein >270 mg/dL). Radiography of the right knee and ankle showed osteoarthritic changes with mild soft tissue swelling but no evidence of any acute pathology. Doppler ultrasound was negative for deep vein thrombosis. Arthrocentesis of the right knee yielded purulent synovial fluid (white blood cell count of 73,110 cells/mL, 87% neutrophils). Gram stain showed no organisms. No arthrocentesis was performed on the right ankle.

Intravenous vancomycin and piperacillin-tazobactam were initiated for presumed septic arthritis and the following day the patient was taken to the operating room for washout of the right knee. This again showed purulent synovial fluid (white blood cell count 63,440 cells/mL, 94% neutrophils) and the Gram stain again revealed no organisms. The synovial fluid culture revealed growth of Gram-negative bacilli that could not be speciated using standard laboratory techniques. We used trypticase soy agar (TSA) with 5% sheep blood, chocolate agar, Columbia CNA agar, MacConkey agar, and thioglycollate agar with vitamin K and Hemin. *S. moniliformis* grew best on chocolate agar after 4 days in anaerobic condition. No standardized methods have been established to determine *S. moniliformis* antimicrobial susceptibility, and since *S. moniliformis* there has been no documented resistance to penicillin, susceptibility testing was not performed.

The patient became afebrile on the third hospital day and the intravenous antibiotics were switched to ceftriaxone alone. However the patient had persistent leukocytosis, with a white blood cell count range from 14,000 to 16,000 cells/mL. A new cardiac murmur was subsequently auscultated and a transesophageal echocardiogram revealed a 1.4x1.3 cm mass on the atrial side of the mitral valve with perforation and severe mitral regurgitation (Figure 1). All blood cultures remained no growth after 5 days incubation. Serologies for *Bartonella henselae, Bartonella quintana* and *Brucella* were negative. Polymerase chain reaction (PCR) for *Coxiella burnetii* was negative.

Due to difficulty in speciating the Gram-negative bacillus that grew from the synovial culture, Matrix-Assisted Laser Desorption Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS) was performed on one of the colonies, which identified the organism as *Streptobacillus moniliformis*. The patient was taken for mitral valve repair and the mitral valve leaflet showed rare clumps of bacteria on Brown-Hopps stain. However, there was again no growth on culture. The valve tissue was sent to the Centers for Disease Control and Prevention where 16S rRNA sequencing (Microseq, Applied Biosystems, Foster City, CA) was performed and demonstrated molecular evidence of *Streptobacillus moniliformis*.

On further questioning, the patient and her partner admitted to living in an apartment with a rodent infestation but had no known contact with any rodents. The patient was treated with ceftriaxone 2 g intravenously daily for 6 weeks post valve repair. She was discharged after 5 weeks of hospitalization and made a full recovery.

Discussion

Rat-bite fever (RBF) is caused by *S. moniliformis* in North America, while *Spirillum minus* is the predominant cause in Asia. *S. moniliformis* is a fastidious, facultative anaerobic, pleomorphic, filamentous, Gram-negative rod bacteria found commensally in the throat and nasopharynx of rodents.[1-6] Human infection can result from a bite or scratch from an infected rat or by consumption of contaminated food or water.[7,8] Consistent with our patient, approximately 30% of the patients recall no

Correspondence: Daisy Torres-Miranda, 2150 Pennsylvania Ave, NW, Suite 8-436, Washington, DC 20037, USA.
Tel.: +1.202.741.2234.
E-mail: datorres@gwu.edu

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bite or other exposure.[4,6] Studies suggest that *S. moniliformis* may have a predilection for synovial and serosal surfaces.[4,9]

Symptoms of RBF occur three days to three weeks after infection. Symptoms include malaise, vomiting, fever, a morbilliform rash and polyarthralgias.[1-7] The prevalence of RBF endocarditis is unclear but is considered to be rare. Including this case, there have been only 26 cases of *S. moniliformis* native valve endocarditis reported in the medical literature. In a review of 16 cases of RBF endocarditis, 50% of the patients had preexisting valvular damage, most commonly due to rheumatic heart disease.[10] Embolic phenomena are rarely reported.[6]

The overall mortality rate of untreated RBF ranges from 7% to 13%.[2,4-5] However RBF endocarditis is associated with significantly higher mortality rates, as high as 50% in some reviews.[4,10] We estimated a mortality rate of 43% when we reviewed all the reported cases where patient outcomes were reported. The majority of these deaths occurred in cases that had received either non-targeted antibiotic therapy or inadequate antibiotic dosing.[10-12]

There have been three reviews of all of the previously reported cases of *S. moniliformis* endocarditis from 1915 to 2014.[6-7, 10] Since these reviews, two more cases of RBF infectious endocarditis have been reported.[13,14] The diagnosis of endocarditis was most often established based on the clinical presentation, that included fever, rashes, and joint pains, a cardiac murmur, often without demonstrating a vegetation on echocardiogram, and a positive blood culture for *S. moniliformis*.[6-7]

In the majority of previously reported cases, *S. moniliformis* has grown in routine blood culture bottles. However, it has been reported that sodium polyanethol sulfonate (SPS), the anticoagulant that is in most commercial aerobic blood culture bottles, can inhibit the growth of *S. moniliformis*.[2,4-5] Nevertheless, *S. moniliformis* has been successfully recovered from SPS containing blood culture bottles.[6,15] Agar-based culture of *S. moniliformis* requires incubation with 5-10% carbon dioxide and TSA enriched media, while no serologic tests are currently available, making diagnosis challenging using standard practices.[3,4-5]

Because of challenges in microbiological diagnosis of RBF, molecular diagnostic techniques have been developed to identify *S. moniliformis*. The 16S rRNA gene sequence has been used on a variety of specimens including heart valves, bone and synovial fluid, offering an alternative tool for rapid and efficient diagnosis.[8,16,17] However, identification with this method is only specific to the *Streptobacillus* genus and not the species.[17] As demonstrated in this case, PCR can help to identify *S. moniliformis* in the case of culture-negative mitral native valve endocarditis. Three other cases of both native and prosthetic valve *S. moniliformis* endocarditis were diagnosed using 16S rRNA PCR assays where the blood cultures remained negative after two weeks incubation.[12-13,16]

Although *S. moniliformis* PCR is not commercially available to be performed on blood samples, 16S rRNA sequencing for *S. moniliformis* from preliminary positive blood cultures has been suggested.[3] In comparison to blood cultures, PCR can increase the sensitivity while decreasing the time to obtain results, which can take up to 7 days using standard techniques, although being significantly more expensive.[18] Given the large sequence database of bacteria available from GenBank, the 16S rRNA is the favored target gene for the identification of fastidious organisms. Tak *et al.* compared blood culture with PCR-based methods in patients with definitive or possible endocarditis and showed that PCR almost always identified a bacterium, even when the blood cultures were negative. This method could be particularly useful in cases of endocarditis where prior use of antibiotic might inhibit bacterial growth of the blood cultures.[19]

Due to the rarity of the disease, there are no guidelines on how to treat RBF endocarditis. Dual therapy with high-dose penicillin G for 4 weeks in combination with streptomycin or gentamicin for the initial 2 weeks has been recommended.[4] In our case, since the patient had clinically improved on ceftriaxone before the diagnosis of RBF endocarditis was established, and since the diseased heart valve tissue had been resected, we decided to complete treatment with ceftriaxone alone. Of note, cephalosporins have also been used successfully in the literature.[4,12-13]

Conclusions

In conclusion, RBF should be considered and evaluated for in the workup or cases of culture negative infectious endocarditis in patient with compatible clinical presentations, particularly if they report any rodent exposure. PCR is a reliable and highly sensitive method that can be performed on resected heart valves specimens, since the *S. moniliformis* DNA remains detectable in the infected valve for several weeks after antibiotic therapy is initiated.[19] Although dual therapy with a penicillin and aminoglycoside is recommended, monotherapy has also been shown to be effective in isolated cases.

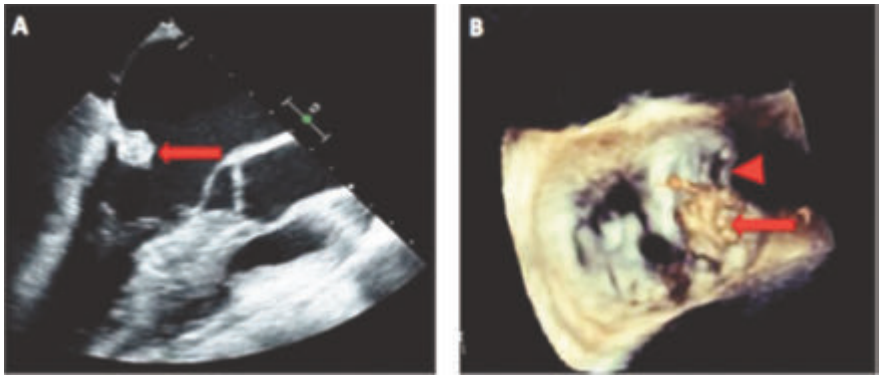

Figure 1. A) Transesophageal echocardiogram image showing a 1.4x1.3 cm mass on the atrial side of the posterior leaflet of the mitral valve (solid arrow). B) Real time 3-dimensional echocardiogram image showing the mitral vegetation (solid arrow) and the 4 mm perforation of the posterior mitral valve leaflet (arrowhead).

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