INTRODUCTION

Francisella tularensis is a gram-negative coccobacillus that can cause zoonotic infection in humans. Transmission occurs most commonly after a bite from an arthropod vector, such as a tick. It is also possible through contact with an infected animal or its feces. Tularemia, also known as rabbit fever, is diagnosed when an infection is clinically present. Six main syndromes are well described: ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, and pneumonic. Clinically relevant tularemia is rare in and of itself, and cardiac involvement is exceedingly rare. We present the case of a patient who experienced prosthetic valve endocarditis due to F. tularensis infection, which, as far as we are aware, is the only documented description of this organism affecting a patient’s bioprosthetic valve.

CASE PRESENTATION

A 58-year-old male veteran with a previous myocardial infarction and a myxomatous mitral valve with associated severe mitral insufficiency, who had undergone coronary artery bypass grafting and valve replacement (31-mm Epic porcine bioprosthesis; St. Jude Medical, St. Paul, MN) 1 year previously, presented with a 6-week history of observed skin ulceration with a small amount of purulent drainage. He resided in a rural community in the upper peninsula of Michigan, where he owned 150 acres of land. He had one dog and owned no other pets or farm animals. He hunted for deer and bear, but had not gone hunting or dealt with any game meat in >6 months. He had not traveled outside of the region for at least the past year. His primary care physician had seen and evaluated him and opted for treatment of possible Lyme disease with a 2-week course of oral doxycycline. Two sets of peripheral blood cultures were also obtained.

When seen at the Milwaukee Veterans Affairs Hospital, the patient was afebrile with a heart rate of about 70 beats/min and normotension. Physical examination was positive for subtle right posterior cervical lymphadenopathy. Skin examination showed a resolving petechial rash over the right flank, with a centralized raised, reddened patch, including a small area of eschar. There was no appreciable murmur, and lung sounds were clear. Examination of the eyes and distal extremities was unremarkable. He denied shortness of breath, cough, chest pain, neurologic deficits or speech issues, and gastrointestinal symptoms, including diarrhea. He denied any current or historical intravenous drug abuse.

Serum chemistry demonstrated normal creatinine, electrolytes, liver function, and lactate. White blood cell count was elevated at 13 K/μL without a left shift, and hemoglobin was slightly reduced at 12.2 g/dL, without any patient-reported evidence of gastrointestinal bleeding. C-reactive protein and erythrocyte sedimentation rate were highly elevated at 247 mg/L and 96 mm/h, respectively. Presenting electrocardiography showed normal sinus rhythm and normal axis, with no evidence of any form of heart block. Within the next 72 hours, serology was negative for Babesia, Ehrlichia, anaplasmosis, and Borrelia burgdorferi. Additionally, peripheral smear was negative for parasites.

The patient was admitted, blood cultures were obtained, and he was treated empirically with ceftriaxone and vancomycin. Fever and presence of a prosthetic heart valve raised suspicion for infective endocarditis. As such, the patient underwent transthoracic echocardiography (TTE). Image quality was suboptimal, but the valve was well seated, with preserved motion of the bioprosthetic leaflets and newly appreciated moderate to severe thickening of both of these leaflets (Video 1). Three-dimensional transesophageal echocardiography was pursued to better illustrate these findings and exclude further cardiac complication. Two large, mobile vegetations were clearly identified: one attached to the anterior leaflet, measuring 14 × 6 mm, and the other attached to the posterior leaflet, measuring 9 × 3 mm (Figures 1-6, Video 2). These images were obtained using a Philips EPIQ 7 with an X8-2T transesophageal probe (Philips Medical Systems, Andover, MA).

No other vegetation was identified, nor was there any valvular insufficiency (figure 7, Video 3) or other evidence of perivalvular spread of infection. Mean gradient across the bioprosthetic valve was 5 mm Hg (Figure 8), comparable with values obtained immediately after surgery, with no other evidence of prosthesis dysfunction.

Within 48 hours of the patient’s admission, previously obtained outside blood cultures returned presumptively positive, three of four outside demonstrating growth of gram-negative rods after 9 to 10 days. Testing was later confirmed by the Wisconsin State Laboratory of Hygiene, speciated as F. tularensis by polymerase chain reaction, with bacterial titer of >1:10,240. Duke criteria were refined with these new data, now consistent with definite infective endocarditis.

The patient had experienced no other clinically apparent complications related to prosthetic valve endocarditis, and his symptoms soon began to abate while on antibiotic therapy. There was no clinical evidence of distal embolization, and further imaging to evaluate for this was not pursued. Cardiothoracic surgery was consulted during this
hospitalization, and in the absence of any current and clear class I or class IIa indication for surgical intervention, medical management and close clinical follow-up were recommended. The patient was transitioned to intravenous ciprofloxacin and gentamicin and was discharged home after placement of a peripherally inserted central catheter.

He completed a 2-week course of intravenous ciprofloxacin and gentamicin and was then transitioned to another 4-week course of oral ciprofloxacin. The patient reported compliance with all doses of antibiotic and experienced no toxicity related to this therapy. No other blood cultures, obtained in relation to the aforementioned hospitalization or afterward, returned positive (10 blood cultures in all).

Repeat TTE, completed 4 weeks after completion of antibiotics, demonstrated persistent vegetations, as well as thickening of both bioprosthetic leaflets (Video 4). There was no appreciable change in gradient across the prosthesis, nor was any valvular insufficiency evident. The patient had returned to his previous activity and perceived level of health.

In subsequent months, cardiology, infectious diseases, and cardiothoracic surgery followed the patient closely, with no new or concerning symptoms reported. Repeat TTE, completed 6 months after hospitalization, showed findings similar to those from the study 4 weeks after completion of antibiotics: persistent vegetations and thickening of both bioprosthetic leaflets, without other evidence of significant dysfunction of the prosthetic valve (Video 5).

Options for surgical intervention were reviewed with the patient. He remained free of any symptoms consistent with distal embolism and continued to experience no high-risk clinical or echocardiographic findings for embolism, including heart failure, significant prosthetic regurgitation, vegetation length > 10 mm, or vegetation hypermobility. Furthermore, the patient was unwilling to consider surgical options with his perceived level of health and thus was continuing expectant management at the time of this writing.

DISCUSSION

Organisms that are difficult to grow in culture represent some of the more unusual or rare causes of infective endocarditis. *F. tularensis* represents one of these organisms, with fastidious growth under standard conditions. Because isolation of *F. tularensis* in blood culture can be difficult to achieve, this delays providers and care teams in arriving at the underlying cause of bacteremia. Specifically, isolate recovery and identification can take up to 2 weeks. Additionally, tularemia is rare in any clinical subtype and is even more rare as a cause of cardiovascular pathology. Finally, symptoms consistent with tularemia tend to be nonspecific, further lending to underrecognition of the causative organism. As discussed, there are only a handful of cases of tularemia causing infective endocarditis, and this presentation summarizes the only experience of prosthetic valve endocarditis definitively caused by this bacterium.

In review, cardiac involvement secondary to *F. tularensis* in other reported cases most frequently involves the native valve. A 2016 summary of cases lists four cases of infective endocarditis secondary to this organism: two cases affecting the native aortic valve, one affecting the native mitral valve, and one affecting the atrial portion of a patient’s permanent pacemaker. Vegetations can be large, even in the setting of prosthetic material. Of these mentioned cases, a 1-cm vegetation was associated with a patient’s atrial pacemaker lead, and the entirety of the patient’s device was
subsequently removed. All other patients were successfully treated with extended courses of antibiotics alone (either 28 or 42 days in total). Still other case reports have described prosthetic joint infection with isolates of *F. tularensis*. Treatment in both cases involved removal of infected prosthetic joints. Finally, three case reports to date detail cases of myocarditis caused by *F. tularensis*. This disease manifestation appears to be clinically unrecognized before the first description of tularemia-associated myocarditis, in 2010.

In our patient’s case, echocardiographic data helped provide a unifying diagnosis, informed the decision to pursue medical therapy, and later allowed monitoring and evaluation of function of the patient’s bioprosthetic valve. At the time of presentation, TTE and three-dimensional transesophageal echocardiography satisfied a major Duke criterion with discovery of prosthetic vegetation. The authors then completed a more exhaustive search for an underlying infectious organism, given a higher index of suspicion for infective endocarditis. In previous published cases, it appears that early use of TTE data, often before positive serologic data become available, aids in the diagnosis of infective endocarditis. Although few cases of tularemia-associated endocarditis exist, it would appear that echocardiographic data play an important role in helping establish this diagnosis. However, few, if any, conclusions can be drawn regarding key echocardiographic characteristics that might suggest the presence of tularemia-associated infective endocarditis.

In a broader review of this bacterium, there are two main subspecies of *F. tularensis*: *F. tularensis tularensis*, which is more virulent and is more prevalent in North America, and *F. tularensis holarctica*, which is found throughout the northern hemisphere. Transmission occurs by sustaining a bite from an arthropod vector (e.g., ticks, flies, mosquitoes), handling infected animals or their feces, or inhalation or ingestion of contaminated soil, water, or plants. Additionally, transmission has been reported after exposure from domesticated dogs and cats. Large outbreaks are not characteristic of this zoonosis.

Mainstays of therapy against *F. tularensis* include aminoglycosides, tetracyclines, and quinolones, and antibiotic treatment.
considerations are more comprehensively addressed in other publications. For our patient, it is plausible that treatment with doxycycline (before the reported hospitalization) affected the yield of the bacterium in culture.

More frequent syndromes of tularemia include ulceroglandular, glandular, ocular-glandular, pharyngeal, typhoidal, and pneumonic subtypes. Our patient’s presentation appears to have started with transmission via tick bite, resulting in the ulceroglandular subtype of disease, which would have then provided a nidus for hematologic spread and subsequent seeding of the patient’s bioprosthetic valve. A key component that contributed to successful care of this patient was maintaining a high index of suspicion for *F. tularensis* in the correct clinical context. Echocardiographic imaging then helped further refine this suspicion and aided in achieving this highly unusual diagnosis.

**CONCLUSION**

The bacterium *F. tularensis* can cause infective endocarditis, including device or prosthesis infection. This case highlights some of the challenges in arriving at this diagnosis and the role of modern echocardiographic imaging aiding prompt diagnosis. Overall, this patient’s presentation contributes to our understanding of this exceedingly rare clinical entity.

**SUPPLEMENTARY DATA**

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2019.10.002.

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**Figure 7** Two-dimensional transesophageal echocardiographic image, midesophageal, two-chamber view, in diastole, including color flow. AML, Anterior mitral leaflet; PML, posterior mitral leaflet; LA, left atrium; LV, left ventricle.

**Figure 8** Two-dimensional transesophageal echocardiographic image, midesophageal, mitral inflow. Mean gradient 5 mm Hg, heart rate 81 beats/min.