A Rare Cause of Prosthetic Valve Infective Endocarditis: *Francisella tularensis holarctica*

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ABSTRACT

Introduction: *Francisella tularensis* subspecies *holarctica* is the most common cause of tularemia in Europe and Japan. Tularemia presents in clinical syndromes, usually as ulceroglandular and glandular syndrome. This entity rarely causes endocarditis. In the United States, only 1 case of a native valve infectious endocarditis has been described to date.

Case Presentation: In this article, we report a case of a patient with several weeks of fevers, night sweats, and myalgias who was diagnosed with prosthetic valve infectious endocarditis secondary to *F tularensis* subspecies *holarctica*.

Discussion: Four previous case reports of *F tularensis* endocarditis have been reported worldwide, with this being the first case of prosthetic valve endocarditis. Antibiotic therapy alone has provided effective treatment in all reported cases of endocarditis.

Conclusion: Infective endocarditis caused by *F tularensis* is an important entity for physicians to understand in areas of endemicity, especially in cases of culture-negative endocarditis.

INTRODUCTION

Francisella tularensis is the etiologic agent of tularemia, a rare zoonotic infection that affects mostly the Northern Hemisphere.[1,2] This highly infectious gram-negative coccobaccillus can be transmitted to humans through multiple mechanisms that include arthropod bite (ticks, flies), animal bite, inhalation, and consumption of contaminated food or water.[1] The natural reservoir is small mammals, including rabbits, squirrels, and muskrats. Currently there are 4 recognized species of *F tularensis*. The two more commonly associated with disease are *F tularensis tularensis* (type A) found in North America and *F tularensis holarctica* (type B), mainly seen in Europe and Japan.[1] Approximately 125 cases have been reported annually in the United States during the past 2 decades.[3] In 2016, the US states with highest incidence were South Dakota, Wyoming, and Arkansas. It is more common during the summer months between May and September.[4] It can be divided into 6 distinct syndromes, including ulceroglandular, glandular oculoglandular, oropharyngeal, pneumonic, and typhoidal. Rarely, tularemia can cause meningitis, pericarditis, and endocarditis.[5]

Endocarditis due to *F tularensis* has been reported 4 times in English literature. Of those, just 1 case has been reported in the United States.[6] Previously, a Canadian patient presented with infection of a pacemaker lead with *F tularensis*.[7] We present the second case of tularemia endocarditis in the United States and the first associated with a prosthetic valve.

CASE PRESENTATION

A 58-year-old man from the Upper Peninsula of Michigan sought medical care in Milwaukee, Wisconsin in the fall due to nighttime fevers for 1 month. He also noticed a right flank skin lesion that appeared 2 days after fever onset. The lesion was pustular in

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Table 1. Summary of Previous Cases With *F tularensis* Endocarditis Reported in the Literature and the Current Case Report

Characteristic	Case 1[6]	Case 2[7]	Case 3[5]	Case 4[5]	Current Case
Age	42	63	75	66	58
Sex	Male	Female	Male	Male	Male
Cardiovascular history	Hypertension	None	None	MVR, AVR, PPM	MVR, CAD
Exposure	Unknown	Domestic pet	No	No	Tick
Geography	United States (Arkansas)	Canada (Ontario)	France	France	United States (Michigan)
Initial presentation	Febrile, cough	Febrile, cough, fatigue, new valvular murmur	Febrile, cough, new valvular murmur	Febrile, fatigue	Febrile, ecchymotic skin lesion
Temperature	39.8°C	Febrile	40°C	39°C	37.1°C
Adenopathy	None	None	None	None	None
Cardiac localization	Mitral	Posterior aortic cusp	Posterior aortic cusp and tricuspid valve	Pacemaker lead	Mitral prosthesis
Secondary localization	None	Pulmonary	Pulmonary	None	None
Serology (IU/mL, titer)	1:80 on day 7 1:800 on day 14	1:400	IgM 1:50 andIgG negative on day 2; IgM 1:100, IgG 400 on day 19	1:2560 on day 14 1:14,640 on day 60	1:10,240 on day 11
Culture	BC positive day 9	BC positive	Negative	BC positive day 8 negative on PPM	BC positive day 5
PCR	Not performed	Not performed	16s DNA PCR positive on blood	16s DNA PCR positive on blood	DNA detected in blood
Subspecies treatment	Unspecified	Holarctica	Unspecified	Holarctica	Holarctica
Treatment	IV gentamicin	Moxifloxacin (28 days) + IV gentamicin (14 days)	IV amoxicillin/clavulanate + gentamicin (19 days), then levofloxacin (23 days)	Ciprofloxacin (42 days) + IV gentamicin (14 days)	IV gentamicin + ciprofloxacin (14 days) + PO ciprofloxacin (28 days)
Treatment duration	28 days	28 days	42 days	42 days	42 days
Outcome	Satisfactory	Satisfactory	Satisfactory	Satisfactory	Satisfactory, Repeat MVR

Abbreviations: MVR, mitral valve replacement; AVR, aortic valve replacement; CAD, coronary artery disease; PPM, pacemaker; BC, blood culture; PCR, polymerase chain reaction; PO, oral.

appearance with a central bite mark that he attributed to a recent tick bite.

One week prior to presentation, the patient also developed diffuse myalgias and generalized weakness. His medical history was significant for being a former smoker, coronary artery disease status post multiple coronary stents, coronary artery bypass and bioprosthetic mitral valve replacement 2 years prior to presentation, as well as hypertension and ulcerative colitis (on mesalamine). He owned a pet dog and had a remote history of hunting and skinning both deer and bear. On exam, his vital signs were normal; he was edentulous and had a small right subconjunctival hemorrhage. On his right flank, he had a small eschar surrounded by an ecchymosis 3 inches in diameter. Initial laboratory workup demonstrated hemoglobin of 12.2 g/dL and leukocytosis of 13,000 cells/µl. Three initial blood cultures were all positive for growth on day 5, revealing gram-negative coccobacillus on gram stain. The organisms were found to be oxidase negative, urease negative, and weakly catalase positive, raising concerns for *F tularensis.* The specimen then was sent to the Wisconsin state lab, which confirmed *F tularensis* subspecies *holarctica* by polymerase chain reaction (PCR). Repeat blood cultures on day 5 were negative. Francisella antibody titer returned positive on day 11 with a titer of 1:10,240. Serological tests results for babesiosis, Lyme, erlichosis, and anaplasmosis were negative. A transesophageal echocardiogram showed 2 mobile echodensities measuring approximately 1.4 x 0.6 cm and 0.9x0.3 cm attached to the mitral prosthesis consistent with a vegetation, which were new compared to 2 years prior

The patient was initiated on dual therapy, with ciprofloxacin 400 mg intravenously every 12 hours and gentamicin 5mg/kg/day intravenously (using ideal body weight and Hartford nomogram for dosing), planned for 14 days, followed by ciprofloxacin 750 mg orally every 12 hours for another 14 days (total of 28 days duration). Unfortunately, he left the hospital against medical advice and missed 3 doses of intravenous (IV) gentamicin; however, he was able to resume daily IV gentamicin (dosed every 24 hours) at a facility near his home approximately 48 hours after discharge. He subsequently required readmission due to a pulmonary embolism, and his antibiotics were continued. Ultimately, he received approximately 2 weeks of IV gentamicin and 6 weeks of ciprofloxacin. The ciprofloxacin course was extended to 6 weeks given his potential medication nonadherence and missed doses early in therapy. His serum *F tularensis* titer continued to decrease to 1:1280; however, about 1 year later, his titer rose to 1:5120 and repeat transesophageal echocardiogram showed a 1.7 x 0.78 cm vegetation on the mitral valve with some inflow restriction but no mitral valve regurgitation. He was placed back on ciprofloxacin perioperatively and taken for repeat mitral valve replacement. The explanted valve was

found to have dense pannus formation surrounding the entire sewing cuff as well as vegetations on the atrial side of the leaflets. Valve culture and 16 S rRNA bacterial sequencing were negative. The specimen was sent to the CDC for microscopic pathologic review, which demonstrated significant lymphohistiocytic inflammation, collagen fiber alteration, and adherence of fibrin to the endocardial surface. *F tularensis* immunohistochemistry assay, Warthin-Starry, and Grocott's methenamine silver stains were negative. He did well and was given 2 weeks of gentamicin and another 6 weeks of oral ciprofloxacin 750 mg by mouth twice daily.

DISCUSSION

Our patient had the classic risk factors for tularemia (animal exposure, tick bite, and involvement in hunting and skinning animals). Michigan is not a high-incidence area of tularemia,[4] making an epidemiological diagnosis difficult. The presence of an ulcerative lesion in the skin suggested ulceroglandular tularemia; however, he lacked lymphadenopathy. His clinical course did not fit cleanly into any of the 6 typical manifestations of tularemia; however, he did not seek medical attention upon onset of symptoms, and it is possible he failed to notice lymphadenopathy or other symptoms.

Of the 4 endocarditis cases reported in the literature, 2 reported the subspecies as *F tularensis* subspecies *holarctica*: 1 in Canada[7] and 1 in France.[5] Our patient is subspecies *holarctica*, an uncommon species in North America. Although there has been a reported case of cardiac device infection with tularemia before, this is the first report of prosthetic valve infectious endocarditis.

F tularensis is a fastidious bacteria that grows poorly on standard culture media; usually resulting in a diagnostic delay. Risk factors for tularemia should be taken in account when evaluating a patient with fever of unknown origin in endemic areas. If risk factors are present, the lab should be notified that *F tularensis* is suspected so appropriate biosafety precautions are implemented. Patient blood should be inoculated on chocolate agar with cysteine/cystine that facilitates bacteria growth.[6] Definitive diagnosis is made by culture or serology; either a single titer >1:160 by standard tube agglutination or a fourfold or greater increase in titer.[7] The patient was treated initially with ciprofloxacin and gentamicin intravenously for 14 days with a subsequent course of oral (PO) ciprofloxacin for 28 days. In the previously published reports, patients have been treated with various combinations of antibiotics, including 28 days of IV gentamicin, moxifloxacin for 28 days plus IV gentamicin for 14 days, amoxicillin-clavulanate plus IV gentamicin for 19 days and subsequent levofloxacin for 23 days, and ciprofloxacin for 42 days plus 14 days of IV gentamicin.[5-7] Although optimal antimicrobial therapy for *F tularensis* infective endocarditis remains unknown, antimicrobial treatment is largely successful with no previous cases reporting the need for valvular surgical intervention with the exception of pacemaker extraction.[5]

CONCLUSION

This case demonstrates the challenge of making the diagnosis of prosthetic valve infectious endocarditis due to *F tularensis* and clinicians should be aware of tularemia as a cause of endocarditis in regions where this pathogen is present in conjunction with the risk factors involved in this zoonotic disease.

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