**CASE REPORT**

A 55-year-old African American woman presented with fatigue and unintentional weight loss for six months; otherwise the review of systems was negative. On physical examination she was found to have a new murmur, prompting evaluation with a transthoracic echocardiogram (TTE) which revealed an aortic valvular mass and aortic regurgitation. Subsequent transesophageal echocardiogram (TEE) showed a 2.9 × 1 cm mass on the right aortic valve (AV) coronary cusp (Figure 1A) with associated flail leaflet resulting in severe aortic regurgitation (Figure 1B) and moderate thickening of mitral valve (MV) (Figure 1C) with moderate mitral regurgitation (Figure 1D). Three sets of blood cultures were obtained before empiric vancomycin and ampicillin-sulbactam was initiated. A total of seven sets of blood cultures (collected on four different days) were subsequently negative. Other serologic tests were negative, including Q fever immunoglobulin G (IgG), *Bartonella henselae* immunoglobulin M (IgM)/IgG, *Bartonella quintana* IgM/IgG, *Brucella* IgM, and antinuclear antibody (ANA). Given the severity of aortic regurgitation and the size of the aortic valve vegetation, on hospital day 10 she underwent AV replacement with a mechanical AV prosthesis as well as debridement of MV leaflet vegetations identified intraoperatively. Aortic valve histopathology showed acute inflammation with inflamed fibrinous vegetation. Smear for acid-fast bacilli and Gram stain were negative. Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains were positive and revealed abundant rod-shaped bacteria (Figure 2). *Tropheryma whipplei*-specific polymerase chain reaction (PCR) of the explanted aortic valve was positive.

After PCR detection of *T. whipplei*, the patient was discharged on intravenous (IV) ceftriaxone. She completed four weeks of ceftriaxone and then transitioned to oral trimethoprim-sulfamethoxazole one double strength tablet twice daily. She completed 16 months of maintenance therapy with trimethoprim-sulfamethoxazole, which she tolerated well with no evidence of relapse.

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**Figure 1:** Transesophageal echocardiogram images. (A) Transesophageal echocardiogram (TEE) image shows 2.9 × 1 cm mass (circled) on the right coronary cusp of the aortic valve coronary. (B) TEE image with color Doppler shows severe aortic regurgitation. (C) and (D) TEE image shows moderate mitral valve thickening with mitral regurgitation on color Doppler.
DISCUSSION

Infective endocarditis is a rare endovascular infection with a high mortality rate [1]. In the majority of cases, infective endocarditis is diagnosed by positive blood cultures. Standard blood culture technique is adequate for detecting most cultivable causes of infective endocarditis [2]. However, blood-culture-negative endocarditis, which ranges in incidence from 2.5% to 31%, presents as a diagnostic and management challenge due to difficulty in identifying microorganisms using routine culture methods [3]. Utilizing advanced molecular techniques, such as PCR, serologic testing, or valvular biopsy, the etiology of culture-negative endocarditis can be elucidated in about 60% of cases [1]. Depending on geographic and epidemiologic risk factors, causes of culture-negative endocarditis include but are not limited to Coxiella burnetii, Bartonella, Brucella, Mycoplasma, T. whipplei, and Legionella species [1]. Although rare, Whipple’s disease has been increasingly recognized as a cause of culture-negative endocarditis. In an observational cohort study, T. whipplei was detected in 6.3% of patients found to have bacterial endocarditis on explanted cardiac valves and was more common than Bartonella, Coxiella, and HACEK group organisms combined [4].

Tropheryma whipplei infection typically causes classic Whipple’s disease which involves multiple organs, with clinical manifestations including arthralgia, weight loss, abdominal pain, and diarrhea. However, it can also present as chronic localized infection, such as endocarditis [5]. Although isolated Whipple’s endocarditis without systemic involvement has been reported in the literature [6–8], this disease entity is rare. A recent literature review by McGee et al. identified 44 publications totaling 169 patients with Whipple’s endocarditis [9]. While the incidence of classic Whipple’s disease is estimated to be between 1 and 6 new cases per 10,000,000 persons per year worldwide [5], the incidence of isolated Whipple’s endocarditis is unknown.

Diagnosis of Whipple’s endocarditis is challenging due to negative blood cultures and the frequent absence of systemic signs of infection such as fever [5, 6]. Tropheryma whipplei has an estimated 18-day generation time, which makes it one of the slowest growing human pathogens. Tropheryma whipplei cultivation is extremely difficult and is limited to specialized research laboratories [10]. Therefore, routine culture as a diagnostic method is not recommended. Whipple’s disease is primarily diagnosed by histopathology and PCR testing of the involved tissue, such as the explanted valve in the case of Whipple’s endocarditis. Periodic acid-Schiff stain shows T. whipplei-infected macrophages while silver stain shows thin bacilli. Polymerase chain reaction utilizing broad-range or T. whipplei-specific primers and immunohistochemical staining with antibodies against T. whipplei increase the diagnostic yield [4, 10]. Overall, employing multimodality diagnostic testing, such as culture, histopathology, and molecular techniques, is important for the diagnosis of culture-negative and Whipple’s endocarditis.

The optimal antibiotic regimen and treatment duration for Whipple’s endocarditis are unknown. Recommended regimens consist of initial and maintenance phases, including two weeks of IV ceftriaxone or penicillin and at least 12 months of trimethoprim-sulfamethoxazole or doxycycline with hydroxychloroquine [10]. Such long-term commitment to medical treatment demands an accurate diagnosis.

CONCLUSION

The diagnosis of Whipple’s endocarditis is challenging due to the inadequacies of traditional blood culture techniques to grow the organism. Polymerase chain reaction and immunohistochemical staining require

![Image](image1.png)

Figure 2: Histopathology images of explanted aortic valve. (A) Hematoxylin and Eosin (H&E) stain, 400× magnification, shows acute inflammation and fibrin deposition. (B) Gram stain, 200× magnification, no organisms seen. (C) and (D) Gomori methenamine silver (GMS) stain, 20× magnification and 600× magnification, respectively, shows heavy, dark staining of bacteria. (E) and (F) Periodic acid-Schiff (PAS) stain, 100× magnification and 1000× magnification, respectively, shows intensely staining rod-shaped bacteria.
explanted valve tissue, but this is invasive. Having a definitive laboratory diagnosis can significantly impact medical management. This case highlights the importance of molecular testing in the diagnosis and management of Whipple’s endocarditis, a rare and diagnostically challenging cause of culture-negative endocarditis.

**Keywords:** Culture-negative endocarditis, *Tropheryma whipplei*, Whipple’s disease, Whipple’s endocarditis

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**REFERENCES**


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**Author Contributions**

Hong Loan Nguyen – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Melanie Goebel – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Nicolas Palaskas – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

David McCants – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.

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