A rare case of Whipple’s disease with endocarditis in a patient with dextrocardia

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Abstract
We report a case of an elderly Caucasian male with past medical history of dextrocardia with situs inversus totalis, polymyalgia rheumatica, history of cryptogenic stroke, and severe mitral regurgitation with mitral valve prolapse, who presented with acute heart failure symptoms, including severe dyspnea on exertion and worsening lower extremity edema in the setting of immunosuppression with steroids for a year-old diagnosis of polymyalgia rheumatica. One month prior to this presentation, the patient suffered a transient ischemic attack and during the workup, his transthoracic echocardiography showed myxomatous degeneration of posterior mitral leaflet, partially flail, with severe mitral regurgitation, which required mitral valve replacement. Genome sequencing of mitral valve anterior leaflet pathology detected *Tropheryma whipplei* as a causal agent of culture-negative endocarditis. The patient was treated with 6 weeks of ceftriaxone and ampicillin–sulbactam and further continued trimethoprim–sulfamethoxazole for 1 year. He continued antibiotic treatment with resolution of shortness of breath along with arthralgia.

Keywords
*Tropheryma whipplei*, culture-negative endocarditis, trimethoprim–sulfamethoxazole

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Introduction
Whipple’s disease is a rare (one per 1,000,000), multisystemic chronic infectious disease caused by rod-shaped bacterium *Tropheryma whipplei* (*T. whipplei*). The classical presentation of Whipple’s disease involves joint arthropathy (migratory oligoarticular or polyarticular) and digestive disorders (diarrhea, malabsorption, and weight loss). Cardiac involvement has been reported in 17%–55% of patients with classic Whipple’s disease, including pericarditis, myocarditis, heart failure, or rarely culture-negative endocarditis. This case highlights the importance of a high clinical index of suspicion *T. whipplei* culture-negative endocarditis, in the setting of arthralgia and abrupt worsening of cardiac function, without overt gastrointestinal symptoms.

Case presentation
An 81 year-old Caucasian man with past medical history of dextrocardia with situs inversus totalis, polymyalgia rheumatica (PMR), history of cryptogenic stroke and severe mitral regurgitation (MR) with mitral valve prolapse (MVP) was referred to outpatient cardiology with heart failure and a recent echocardiogram showing deteriorating function of the MV, which was now severely regurgitant.

One week prior, the patient was started on furosemide 40 mg daily due to orthopnea and lower extremity edema. In retrospect, the patient had not experienced symptoms of gastrointestinal concern, including weight loss, diarrhea, or evidence of malabsorption.

Clinical exam was consistent with volume overload status with lower extremity edema and bilateral audible crepitations on lung exam which was further supported by chest x-ray findings consistent with increased vascular markings with interstitial edema. In addition, the patient was afebrile and hemodynamically stable with the following pertinent laboratory results including brain natriuretic peptide of 384 [ref < 100] pg/mL, C-reactive protein of...
2.58 [ref < 1.0] mg/dL, sedimentation rate of 12 [ref 0–15] mm/h, and white blood cell count of 9.3 × 10^9/L.

Home medication at the time of presentation to the clinic included:

- Prednisone 7 mg daily,
- Allopurinol 100 mg daily,
- Amlodipine 5 mg daily,
- Pantoprazole 20 mg daily,
- Quinapril 20 mg daily,
- Rosuvastatin 5 mg nightly,
- Furosemide 40 mg daily

Eighteen months prior to this presentation, the patient was diagnosed with PMR and started on a prednisone taper 15 mg daily. Diagnosis was associated with C-reactive protein elevations and symmetric polyarthralgia. This prednisone course continued over the next 18 months and was unable to be weaned due to persistent polyarthralgia.

Twelve months prior to this presentation, the patient was diagnosed with cilioretinal artery occlusion. Transthoracic echocardiogram (TTE) demonstrated severe left atrial (LA) dilation, mild MVP, and mild MR. Ultimately, this cryptogenic stroke was determined to not be embolic in nature and a lumbar puncture was not performed.

One month prior to presentation, the patient was hospitalized for a transient ischemic attack (TIA). The patient presented with slurring garbled speech, drooling, ataxia, and incoordination and was evaluated for stroke workup. Transeosophageal echocardiogram was performed and revealed ejection fraction of 60%, normal diastolic function, moderately dilated LA with myxomatous degeneration of posterior MV leaflet, partially flail, resulting in severe MR (Figures 1 and 2). The patient did not have any symptoms of congestive heart failure, and a loop recorder was implanted for further embolic etiology investigation.

During this admission, a cardiac catheterization and referral to cardiology for further management of severe symptomatic MR was recommended. The subsequent angiogram did not reveal significant coronary artery disease.

Following this assessment, the patient underwent MV replacement for severe MR. At the time of surgery, the anterior leaflet of the MV was found to be studded with vegetations, rather than the posterior leaflet of the MV, and tissue was sent for culture and pathology. In addition, there was no intraoperative evidence of aortic valve pathology. Initial tissue culture did not reveal any organisms and pathology revealed degeneration with fibrin tissue and calcification. Blood cultures remained negative. The patient was initiated on vancomycin and cefepime after surgery, after which he was transitioned to ceftriaxone and ampicillin–sulbactam for culture-negative endocarditis.

The patient’s post-operative course was uncomplicated, other than slow atrial fibrillation/flutter which required cardioversion.

Bartonella quintana antibody, Bartonella henselae antibody, Coxiella burnetii antibody, Brucella antibody, and Tropheryma whipplei polymerase chain reaction (PCR) were negative. Genomic sequencing of the valve tissue was done which finally revealed T. whipplei deoxyribonucleic acid (DNA) with 16s ribosomal ribonucleic acid (rRNA) gene primer set. Periodic acid-Schiff (PAS) staining revealed characteristic foamy macrophages with inclusions consistent with T. whipplei (Figure 3).

The patient was continued on a 6-week course of intravenous ceftriaxone and ampicillin–sulbactam for culture-negative endocarditis. In 1-month follow-up visit, the patient was started on trimethoprim–sulfamethoxazole double strength (160–800 mg) twice a day for 12 scheduled months with weekly basic metabolic panel monitoring.
The patient reported significant improvement of shortness of breath and dyspnea on exertion following MV replacement. Furthermore, he was successfully tapered off from his prednisone dose for PMR without recurrent of arthralgias. This is suggestive that the patient's polyarthralgia were an early manifestation of Whipple’s disease, rather than PMR. He has been expected to complete his 12-month course of trimethoprim–sulfamethoxazole in 4 months and has had no complains in the recent follow-up visits.

**Discussion**

Whipple’s disease is a rare chronic multisystem infection with *T. whipplei*, which was first described by George Hoyt Whipple in 1907. It typically presents with arthropathy, diarrhea, and usually has systemic signs and symptoms of weight loss, intermittent fever, night sweats, and lymphadenopathy. Isolated valvular disease caused by *T. whipplei*, however, is not uncommon and can present in 20%–55% of patients with Whipple’s disease without gastrointestinal involvement. A recent study has in fact identified this pathogen as the most common cause of culture-negative endocarditis, followed by *Bartonella quintana* and *Coxiella burnetii*. A cardiovascular disease is present in up to one-third of patients with Whipple’s disease and can present with pericarditis, myocarditis, heart failure, or culture-negative endocarditis, usually affecting aortic or MV. In our case, the patient presented a *T. whipplei* endocarditis manifesting as heart failure with severe MV regurgitation. Whether the patient’s unusual condition of dextrocardia with situs inversus had any role in the development of this rare disease, entity is a difficult question to answer, as this is the first case in literature pertaining to the rarity of both diagnoses. Another aspect to consider here is that our patient carried a recent diagnosis of PMR and had been on daily steroid therapy in the last 1 year for arthralgia believed to be from PMR. In case series by Fenollar et al. of 28 patients, arthralgia was common (75%) and preceded the diagnosis by a mean of 8 years. The resolution of the patient’s arthralgia after being initiated on the antibiotic regimen for Whipple’s disease may signify the relevance of the diagnosis even prior to the cardiovascular manifestation.

Infective endocarditis (IE) with classical Whipple’s triad (arthropathy, diarrhea, and malabsorption with weight loss) due to *T. whipplei* is rare and the diagnosis is often difficult if it presents without any prior history of Whipple’s disease. Moreover, this organism does not grow under the current culture conditions, resulting in repeated negative blood cultures. As the diagnosis of *T. whipplei*-induced IE often does not meet the major criteria for IE, investigations with invasive procedures by analysis of explanted heart valve using PCR, culture, and/or immunohistology is required. According to the study done by Fenollar et al., patients with Whipple’s endocarditis have no previous heart disease, are most often afebrile with negative blood cultures, and vegetation is observed in echocardiogram in 75% of cases. These limitations have most likely resulted in underdiagnosis of this disease and inadequate treatment with antibiotics causing further complications with high morbidity.

PCR is generally useful for the diagnosis of Whipple’s endocarditis and can be directly obtained from blood or body fluid samples. However, caution should be maintained while interpreting the results as the sensitivity of PCR on blood samples may be impaired by DNA inhibitors and by the relatively low amount of circulating DNA. Screening by PCR on saliva or stool has poor sensitivity due to asymptomatic carriage in 1%–30% of population. The diagnosis of Whipple’s endocarditis is, therefore, mainly confirmed by surgical specimens of the involved cardiac valves as done in our patient. Histopathological features include fibrosis and infiltrate of foamy macrophages with inclusions staining positive by PAS stain.

Regarding the treatment of Whipple’s endocarditis, currently there is no standardized treatment, and this is based on the therapeutic protocol for classical Whipple’s disease. *T. whipplei* is susceptible in vitro to doxycycline, sulfamethoxazole, penicillin, third-generation cephalosporins, carbapenems, aminoglycosides, and chloramphenicol. Some studies have recommended 2 weeks of intravenous ceftriaxone followed by oral trimethoprim–sulfamethazine for 12 months. Some other studies have proposed 24 months of treatment and consideration for lifelong suppression. As our patient responded well to the treatment of intravenous ceftriaxone and ampicillin–sulbactam, this regimen was continued for 6 weeks followed by 12 months therapy with oral trimethoprim–sulfamethazine.
Conclusion

*T. whipplei* is thought to be a rare entity, it should be considered in culture-negative cases of endocarditis. A history of unexplained arthralgia may be a useful diagnostic clue. Gastrointestinal involvement may initially be absent and later present in cases of Whipple’s disease involving the cardiovascular system. All cases of culture-negative endocarditis should have a histological and microbiological evaluation of valvular material using standard and molecular methods to rule out *T. whipplei* infection.

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Supplemental material

Supplemental material for this article is available online.

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