Case report

Endocarditis and systemic embolization from Whipple’s disease

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A R T I C L E  I N F O

Article history:
Received 26 January 2021
Received in revised form 29 March 2021
Accepted 29 March 2021

Keywords:
Whipple’s disease
Tropheryma whippelii
Endocarditis

A B S T R A C T

Whipple’s disease (WD), caused by infection with the organism Tropheryma whippelii, is a rare disease that classically presents with diarrhea, weight loss, and polyarthralgia. Less common, Whipple’s Disease can present with endocarditis or neurologic infections. The authors report a patient with Whipple’s Disease endocarditis whose initial presentation was acute lower extremity arterial occlusion, and review current literature regarding the epidemiology, diagnosis, treatment, and prognosis of Whipple’s Disease endocarditis.

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Introduction

Whipple’s disease (WD) is a rare multiorgan disease that was first discovered by Dr. George H. Whipple in 1907 [1]. Classically presenting with diarrhea, gastrointestinal malabsorption, and polyarthralgia, a bacterial cause of WD was not postulated until 1961 with the aid of electron microscopy [2]. The causative bacterium, Tropheryma whippelii, was only more recently identified, first via sequencing of the 16S ribosomal gene in 1991 [3], and finally by culture-based techniques in 1997 [4]. Rarely, chronic WD can result in dissemination to the heart valves or central nervous system [3,6]. Here we report a case of WD endocarditis presenting as acute arterial occlusion and review relevant literature on the epidemiology, diagnosis, treatment, and prognosis of endocarditis from Whipple’s disease.

Case

A 53-year-old man with a past medical history significant for chronic obstructive pulmonary disease presented with sudden onset of right calf pain. Prior to this, he had had two months of generalized fatigue and right knee pain but was otherwise healthy. There was no fevers, chills, abdominal pain, diarrhea, weight loss, chest pain, or cough. He took no medications and his family history was unremarkable. Social history was notable in that he was a dairy farmer, had several cats, and obtained water from an artesian well.

On initial examination, vital signs included a heart rate 88 beats per minute, blood pressure 126/80 mmHg, temperature 36.8 °C, respiratory rate 16 breaths per minute, and oxygen saturation 93% on room air. Cardiac auscultation revealed no murmurs. He had normal breath sounds. Notably, the right lower extremity had diminished posterior tibial and popliteal pulses, slow capillary refill in the toes, and was cool to the touch. Doppler ultrasound did, however, detect weak distal pulses in the right leg. Initial laboratory results were significant for a white blood cell count of 12,500/μL and a creatinine of 0.6 mg/dL. He was admitted to the vascular surgery service. A transthoracic echocardiogram showed a mobile mass on the aortic valve measuring 1.3 × 0.9 cm with trace aortic valve regurgitation. Because of minimal risk factors or signs or symptoms of infection, his presentation was initially felt to be a fibroelastoma with embolic complications. Thus, antimicrobials were not initially empirically started. Heparin drip was started on admission.

Subsequently, on hospital day 6 the patient lost all doppler ultrasound signal in his right lower extremity distal pulses and underwent right popliteal/tibial-peroneal trunk/tibial thromboembolectomy. Because of concern for further embolization, on hospitalization day 12 the patient underwent an open aortic valve replacement with a bioprosthetic valve. Intraoperatively, the cardiac surgeons found a large, friable mass more consistent with an infective vegetation than a fibroelastoma. Thereafter, the infectious disease service was consulted for suspected infective endocarditis. He had been afebrile up to this point without antimicrobials.

Multiple blood cultures collected after valve replacement surgery were negative. Culture-negative endocarditis caused by fastidious organisms was considered, and work up for Bartonella quintana, Coxiella burnetii, and brucellosis was negative. Non-infectious etiologies such as antiphospholipid syndrome and

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http://dx.doi.org/10.1016/j.idcr.2021.e01105
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occult malignancy were also considered. Histologic examination of the aortic valve tissue revealed a large fibrinous vegetation with scattered clusters of distended histiocytes, and only minimal lymphocytic and neutrophilic infiltrates. Multiple special stains were initially performed, including Brown and Brenn tissue gram stain, Ziehl-Neelsen, and modified acid-fast stains, all of which were negative. Methanemine silver staining revealed smudgy, non-specific staining which was difficult to interpret. A periodic acid-schiff (PAS) stain was then ordered, revealing numerous intracellular organisms with bacillary morphology, suggestive of Whipple’s disease endocarditis (Fig. 1). Broad range polymerase chain reaction (PCR) of the patient’s aortic valve tissue was ultimately additionally positive for Tropheryma whippelii, although the serum PCR was negative. The patient was treated with ceftriaxone 2 g daily for 6 weeks followed by trimethoprim/sulfamethoxazole double-strength two tablets twice daily for an additional 18 months. In subsequent outpatient follow-up, the patient noted significant improvement in energy levels and a return in functional status back to baseline.

Discussion

Whipple’s disease (WD) is a rare chronic infection of insidious onset that typically affects multiple systems, making diagnosis a challenge. While WD is classically associated with the triad of weight loss, gastrointestinal symptoms, and polyarthralgias [7,8], there are many reports of WD presenting atypically. Beyond the triad, it has been reported that WD can involve other systems and present with a combination of the typical triad symptoms [5–9]. Because the causative bacterium Tropheryma whippelii cannot be cultured via standard techniques, diagnosis is often delayed until histopathology or molecular analysis of affected tissue is completed.

Our patient fits the typical population background of patients who acquire WD — a Caucasian male of about 50 years of age with frequent exposure to soil, animals, or sewage [10,11]. However, a recent article by Elchert et al. querying the electronic medical records of 26 major healthcare systems in the United States between 2012–2017 identified 350 WD cases [12]; they found no gender differences though WD did appear more common in Caucasian patients and those above 65 years of age.

WD has historically been considered an uncommon cause of culture-negative infective endocarditis but incidence seems to be increasing, perhaps reflecting the increased availability of molecular diagnostics. In an analysis of 348 culture-negative infective endocarditis cases from France in 2005, only two (0.5%) were found to be from WD, with C. burnetti accounting for 48% of cases and Bartonella species for 28% [13]. Two smaller case series of 18 and 15 patients respectively of culture-negative infective endocarditis from Switzerland in 1997 and Czech Republic in 2003 respectively found only one case of WD each [14,15]. A more recent study in 2010 from France by Fournier et al. of 740 cases of culture-negative endocarditis, while still predominated by Coxiella and Bartonella, revealed 12 cases (2.6% of those with an infectious etiology identified) of WD [16]. Finally, an investigation from Germany of 255 resected heart valves with detectable microorganisms in 2012 found 16 cases (6.3%) where T. whippelii was detected in the absence of other bacteria; it was the most common cause of culture negative endocarditis in that study [17]. Across case series, the initial presentation of WD endocarditis is often heart failure or systemic septic embolus, as seen in the case presented here. Richardson 2003 described a patient whose first presentation was sudden right arm arterial emboli and blurred vision from cerebral infarcts [18]. Seddon and Hettiarachchi in 2017 reported a case where a patient ultimately diagnosed with WD endocarditis presented with a painful upper extremity and a preliminary finding of ulnar artery aneurysm [19]. In cases whereby systemic embolization is the presenting complaint, patients may not have preceding fever or other overt signs of infection, as seen in our case.

Tropheryma whippelii cannot be routinely cultured, and histopathologic or molecular diagnosis is required. For our patient, WD was diagnosed via PAS staining of the aortic valve tissue and Tropheryma whippelii specific PCR of the aortic valve tissue. With the advent of PCR testing, T. whippelii was found to be ubiquitous in influxes of sewage plants [20,21] and present in a significant minority of biopsy and saliva specimens from patients without symptoms classically associated with WD. The organism has yet to be identified in specimens from domesticated or wild animals [22]. Taken together, this suggests that humans may represent the organism’s primary reservoir with asymptomatic carriage possible in the majority of cases. Given overall low rates of WD, it is suspected that various genetic risk factors may make certain individuals more susceptible to disease acquisition. When using combined PCR of

Fig. 1. Photomicrographs of cardiac vegetation. A, B Necrotic, fibrinous vegetation with numerous distended histiocytes (H&E, ×4 and x40 respectively). C Intracellular organisms positive by Periodic acid-Schiff stain (×40); D Grocott methenamine silver stain showing smudgy, non-specific staining within histiocytes (×40); E, F Intracellular organisms negative by Brown and Brenn tissue gram stain and Ziehl-Neelsen stain (×40).
saliva and stool, testing has approximately 84% sensitivity and 99% specificity for detecting classic WD [23]. However, in patients with more localized WD, the detection rate drops to 20% with combined saliva and stool PCR assays. Thus, even with negative testing of blood, saliva, or serum, high suspicion for WD should prompt obtaining tissue samples of affected areas for direct tissue PCR and histopathologic analysis.

Historically, WD was treated with tetracycline until a study of 88 patients found that 31 (35%) relapsed after an average of 4.2 years [24]. Because WD can be prone to recurrences, current treatment starts with an agent that can cross the blood-brain barrier (such as ceftriaxone) and is followed by a long-term oral antimicrobials (such as trimethoprim-sulfamethoxazole) for 1–2 years [25–27]. Others have suggested adding the combination of doxycycline and hydroxychloroquine for oral consolidation therapy; the hydroxychloroquine acts as an alkaliizing agent that counters phagosome acidification necessary in Tropheryma whippelii survival, improving the killing of doxycycline [25,28]. Indeed, in one patient with WD proesthetic valve endocarditis treated with ceftriaxone followed by trimethoprim-sulfamethoxazole, relapse occurred while on trimethoprim-sulfamethoxazole, and he was subsequently treated with prophylaxis replacement and 18 months of doxycycline and hydroxychloroquine [29]. However, direct comparative data on the ideal treatment of WD are currently not available. For our patient, he showed marked improvement with ceftriaxone and then trimethoprim-sulfamethoxazole.

Despite its rarity, WD should be included in the differential for culture-negative endocarditis, particularly if other features of WD are present. The patient presented here provides an example of the varied clinical manifestations of WD: he was without the “usual” WD symptoms until there was systemic embolization from occult cardiac involvement. This case demonstrates the difficulty of diagnosing culture-negative endocarditis and the need to maintain a high index of suspicion for fastidious organisms that require specific tests for diagnosis.

Author contributions

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Funding

None.

Declaration of Competing Interest

None of the authors report any conflicts of interest

Authorship verification

All co-authors have seen and agree with the contents of the manuscript and have contributed significantly to the work

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Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.