Whipple's endocarditis: An enigmatic cause of culture-negative bacterial endocarditis

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CASE PRESENTATION

An 80-year-old man living in Eastern Ontario was assessed at a local emergency department for a syncopal episode that occurred after awakening from sleep and ambulating to the bathroom. He had experienced malaise, anorexia and episodes of presyncope for four months. His medical history was significant for rheumatic fever in childhood without known cardiac sequelae, diverticulitis, hypertension and gastroesophageal reflux disease. A review of systems was notable for the absence of fever, weight loss, arthralgias, gastrointestinal (GI) and neurological complaints. The patient's medications were hydrochlorothiazide and rabeprazole.

A transthoracic echocardiogram revealed a mobile mass on the aortic valve. There was no history of antimicrobial exposure within the preceding 12 months, and the patient denied illicit drug use, travel or exposure to animals. A physical examination revealed a systolic ejection murmur at the left upper sternal border. No stigmata of infective endocarditis (IE) were present. The remainder of the general examination was normal.

A transesophageal echocardiogram revealed a 1.5 cm × 0.5 cm mobile mass on the right coronary cusp of the aortic valve and moderate-severe aortic insufficiency. Laboratory investigations were significant for normocytic anemia, with a hemoglobin level of 109 g/L and a serum albumin level of 39 g/L.

The patient underwent mechanical aortic valve replacement for severe aortic insufficiency. Intraoperatively, the lesion appeared to be a vegetation of infectious origin, and valve specimens were sent for Gram stain and culture. Empirical antimicrobial therapy was initiated with ceftriaxone and vancomycin for presumed IE.

Gross pathological examination revealed a thrombotic vegetation attached to the aortic valve. On high-power light microscopy, numerous small Gram-negative coccobacilli were observed along the margin of the vegetation, with no inflammatory cells present. Cultures from the valve and blood were negative after 21 days of incubation. Serologies for *Bartonella henselae* and *Coxiella burnetii* were negative. Broad-based 16S rDNA polymerase chain reaction (PCR)-based amplification and sequencing of the valvular tissue was requested through the Ontario Public Health Laboratory (Toronto, Ontario).

DIAGNOSIS

PCR molecular diagnostic testing performed on tissue from the resected valve identified *Tropheryma whippelii*. Periodic acid-Schiff (PAS) staining was subsequently performed on sections of the resected valve and demonstrated abundant PAS-positive material within macrophages (Figure 1). On identification of *T. whippelii*, vancomycin was discontinued and ceftriaxone was continued for a total of six weeks. The patient was subsequently treated with oral trimethoprim-sulfamethoxazole, which resulted in significant GI intolerance. Doxycycline combined with hydroxychloroquine was continued for a total of 12 months.

DISCUSSION

In as many as 40% of IE cases, no organism is identified (1). Causes of blood culture-negative endocarditis include recent antimicrobial use,

Figure 1 Aortic valve vegetation with numerous macrophages containing periodic acid-Schiff-positive material (original magnification ×60)

TABLE 1
Organisms and their relative frequencies identified in cases of blood culture-negative endocarditis

Microorganism	Percentage of isolates (n=740)
<i>Coxiella burnetii</i>	37.0
<i>Bartonella</i> species	12.4
<i>Streptococcus</i> species	4.4
<i>Tropheryma whippelii</i>	2.6
Fungi	1.0
Other bacteria	6.5
No etiology	36.5

Adapted from reference 1

fastidious bacterial organisms, fungi and noninfective causes of endocarditis. In the largest diagnostic series of IE reported to date, *Coxiella burnetii*, *Bartonella* species and *T. whippelii* were the most commonly isolated fastidious organisms (Table 1) (1). Of these, only serology for *C. burnetii* has been included in the modified Duke criteria (2).

T. whippelii is a ubiquitous bacterium that is classically implicated in Whipple's disease. Although the disease was first described in 1907, the bacterium was not successfully cultured until 1999 (3,4). *T. whippelii* is phylogenetically described as a Gram-positive bacillus, although it may appear as Gram-negative and gram-indeterminate. PAS staining frequently reveals PAS-positive organisms within macrophages in infected tissues (4). Whipple's disease most commonly occurs in Caucasian men of European descent, with a mean age at diagnosis of 50 years (3). The incidence is unknown, with approximately 1000 cases reported.

T. whippelii manifests as two distinct clinical presentations: classical Whipple's disease, characterized by a prodrome of polyarthritides, fever

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and weight loss followed by GI involvement with diarrhea and abdominal pain; and as isolated organ involvement without features of systemic infection. Isolated organ involvement can occur in the heart, central nervous system (CNS) and joints. Cardiac involvement is most common and occurs in 20% to 55% of cases of *T. whipplei* infection. The valvular system, myocardium or pericardium may be involved, and IE most commonly involves the aortic valve (1). Patients with isolated *T. whipplei* endocarditis generally lack symptoms of classical Whipple's disease and present with an indolent, chronic disease course, similar to that experienced by the patient highlighted in the present case (5). In a recent prospective study (6), only one case of 16 fulfilled the Duke criteria.

16S rDNA PCR diagnostic testing has been performed on EDTA-anticoagulated blood or valvular tissue since the early 1990s and demonstrates higher sensitivity and specificity than culture for detecting organisms in IE, with a reported sensitivity of 72% and specificity of 100% (7). This has led to the suggestion of including a molecular diagnostic criterion in the Duke criteria (8). However, sensitivity of PCR-based molecular diagnostic testing is lower when sampling is performed on blood compared with valvular tissue (1). PCR-based molecular diagnostic testing detects both viable and nonviable organisms and may, therefore, remain positive following effective antimicrobial therapy. Although PCR-based molecular diagnostic testing identifies pathological organisms, determination of antimicrobial susceptibility is not possible (7).

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