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Case report

Treatment refractory arthritis and stroke – A case of infective endocarditis caused by *Tropheryma whipplei*

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ABSTRACT

Whipple's disease is a rare multisystem condition affecting < 1/1.000.000 per year. The condition often presents with polyarthritis, diarrhea, and intestinal malabsorption. Endocarditis is seen in a minority of these patients, and is typically culture negative, as the causative agent *Tropheryma whipplei* does not grow in ordinary culture media. We present the case of a 78-year-old man with a history of seronegative polyarthritis that was refractory to treatment with several biological agents for a duration of 5 years prior to presentation to the emergency department with stroke. Echocardiography revealed aortic valve endocarditis with a 3.6 cm vegetation and multiple smaller vegetations. The patient underwent surgery with aortic valve replacement followed by prolonged antibiotic treatment. 16 S rDNA PCR analysis of the resected valve revealed *T. whipplei* as the causative agent. Two years after surgery and treatment with antibiotics, the patient's previously longstanding arthritis had totally disappeared and all rheumatological treatment had been discontinued.

Background

Whipple's disease is a systemic disease caused by a gram-positive bacillus, *Tropheryma whipplei.* Although the first descriptions of the disorder were that of a malabsorption syndrome with small intestine involvement, the disease also affects joints, the central nervous system, and the cardiovascular system [1,2]. In the modern era, Whipple's disease is usually diagnosed in the context of an inflammatory disease that is refractory to treatment with immunomodulatory agents, including anti-tumor necrosis factor alpha (anti-TNF-a) [3,5,7]. The disease is extremely rare worldwide; only about 1000 cases have been reported, mostly from North America and western Europe. It affects men more often than women with male-to-female ratio: approximately 8–9:1 [4].

The clinical manifestations of the disease are caused by infiltration of the various body tissues by *T. whipplei*. The patient's immune system reacts by incorporating the organisms into tissue macrophages, and an inflammatory response ensues [12].

Approximately 90% of patients with Whipple's disease present with weight loss, and 70% of patients with the disease complain of either diarrhea or arthralgias [8]. In about three quarters of patients, arthritis is followed by weight loss and diarrhea, with an average time of 6 years from onset of the joint symptoms to diagnosis of Whipple's disease [8]. Clinical symptoms of cardiac involvement have been reported to occur in around 30% of cases [4]. The central nervous system might be affected by the disease in 20% of patients with a variety of symptoms including personality changes, ataxia, dementia, and vision problems [7]. However, Whipple's disease may present with symptoms affecting the heart or the central nervous system in the absence of the typical symptoms described previously. [5,7].

No tests are specific for the diagnosis of Whipple's disease, except determining the presence of *T. whipplei* DNA through polymerase chain reaction (PCR) [6]. Moreover, endocarditis is seen in a minority of these patients and is typically culture negative, since *T. whipplei* does not grow in conventional culture media [6].

Antibiotic therapy is the mainstay of the management of Whipple's disease. A standard first line treatment is intravenous ceftriaxone 2 g once daily followed by a 12-months course of trimethoprim 160 mg/ sulfonamide 800 mg is widely used. Other agents such as doxycycline,

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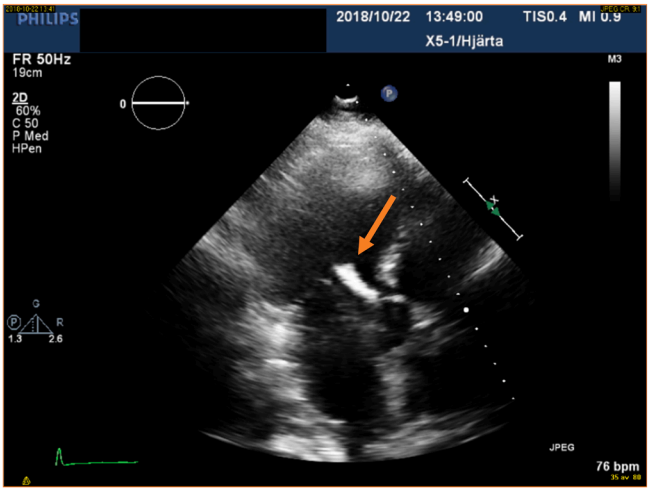

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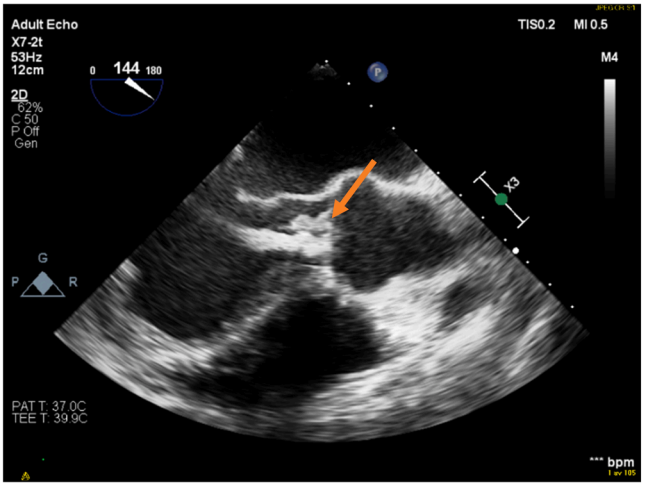

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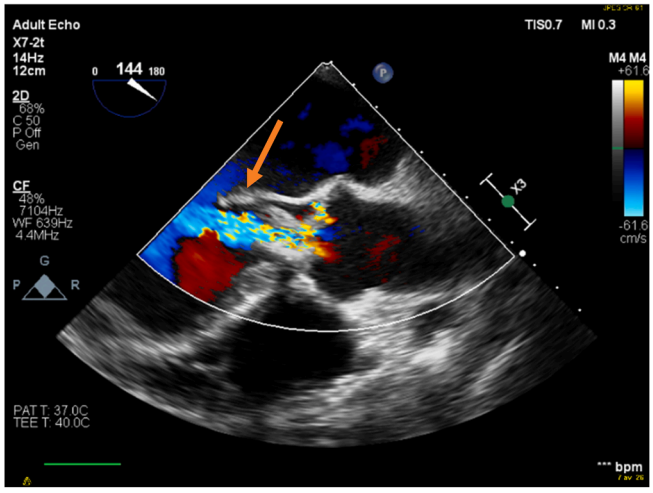

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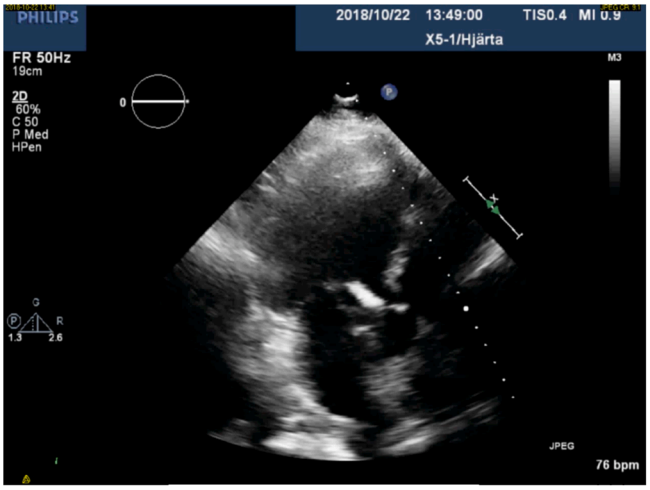
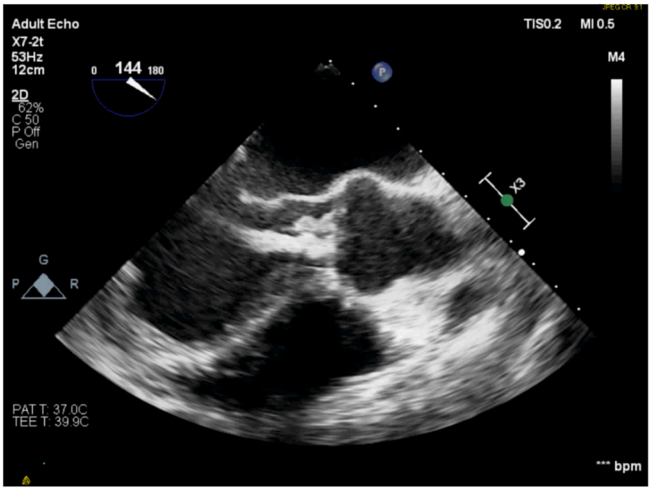
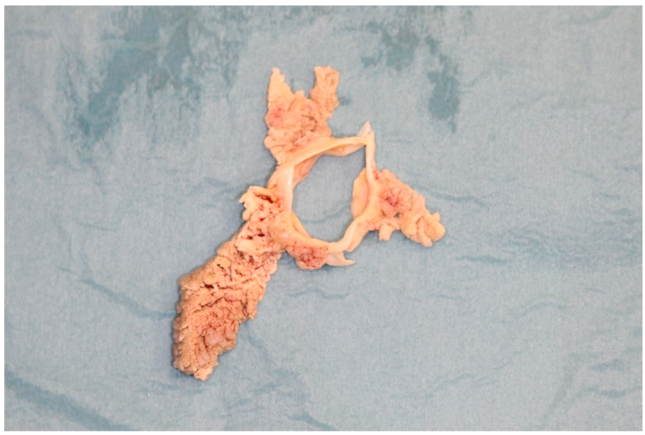


D (TTE 3 chamber view, BE)



E (TEE-144°-BE)

Fig. 1. (A-E): Echocardiography in transthoracic 3 chambers view (A) and transesophageal long axis view (B) demonstrating a 3.6 cm long vegetation protruding into the left ventricular outflow tract during diastole. TEE showed a moderate aortic regurgitation (C). Transthoracic echocardiographic clip with 3 chamber view of the infected aortic valve (D). Transesophageal echocardiographic clip presenting a long axis view of the infected aortic valve (E).



A

B

Fig. 2. A; Picture of excised valve in the operating theater with involvement of all three cusps. B; Macroscopic image of the excised aortic valve after formalin fixation showing dimensions of the largest vegetation on the right aortic cusp (scale bar in centimeters).

hydroxychloroquine and tetracycline can also be considered, but may carry a higher risk of relapse [4]. Multidisciplinary follow-up should be adopted due to multisystem involvement.

Case report

A 78-year-old man presented to the hospital with sudden left-sided weakness and loss of sensation. His past medical history was significant for seronegative arthritis for the past 5 years, joint pain and skin discoloration with multiple surgical interventions in the joints of the lower limb including bilateral ankle arthrodesis and bilateral knee replacement surgery. His arthritis had been worsening in the year before his presentation to the emergency department. He had recently been started on anakinra (IL-1Ra) for his arthritis after being unsuccessfully treated in the previous years with corticosteroids, methotrexate and with a variety of biological agents such as etanercept, tocilizumab, and tofacitinib.

On examination he was found to have left-sided hemiparesis and paresthesia. He had no fever or chills. A decrescendo diastolic murmur was heard on cardiac auscultation. Laboratory results were not indicative of ongoing infection with C-reactive protein (CRP) of only 11 mg/l on presentation and blood cultures were negative. Computed tomography scan of the brain showed a small non-hemorrhagic frontal subcortical infarct. Transthoracic and transesophageal echocardiography were performed and showed a sclerotic aortic valve with moderate aortic regurgitation, a flapping 3.6 cm vegetation on the right aortic cusp, as well as other smaller vegetations on the other cusps (Fig. 1). The patient was started on empirical antibiotic therapy with cefotaxime 2 g TID and underwent emergency surgery for infective endocarditis due to the risk of further embolization. Intraoperatively, the native aortic valve cusps showed marked destruction with vegetations of all three cusps with the largest vegetation measuring approximately 4 cm originating from the right coronary cusp (Fig. 2). The valve and vegetations were excised and a biological aortic valve prosthesis, Sorin Crown 23 mm, was implanted. The vegetations were cultured and analyzed with 16 S rDNA PCR and sequencing. The bacterial culture was negative but the 16 S rDNA PCR revealed the presence of DNA from *T. whipplei*. Histopathological examination of the infected valve showed marked destruction of the cusps consistent with an infectious process. Macro- and microscopic images are seen in Figs. 2 and 3.

Once the diagnosis of Whipple's disease was confirmed, the intravenous cefotaxime was replaced with intravenous ceftriaxone 2 g daily for 4 weeks followed by a planned 12-month treatment with oral trimethoprim 160 mg/ sulfonamide 800 mg BID. Four months into the treatment, a ^{18}F-fluorodeoxyglucose PET/CT scan showed no signs of hypermetabolism in the new aortic valve prosthesis. However, the patient showed symptoms of possible reaction to the antibiotics in the form of urticaria and elevated creatinine, which warranted the treatment regimen to be changed to a 24-month combination therapy of doxycycline 100 mg BID and hydroxychloroquine 100 mg TID (initially low dose due risk for prolonged QTc) that was later extended to 32 months of total treatment duration. Multidisciplinary follow-up was carried out throughout the treatment duration. Two years after surgery, echocardiography and laboratory testing did not show any signs of relapse of the disease. Moreover, the patient's previous arthritis improved under the postoperative period and by the end of the treatment period, it had totally resolved. Further follow-up by the rheumatology clinic was discontinued. However, the patient has residual damage in his joints after years of arthritis and orthopedic surgical interventions.

Discussion

We report the first documented case of infective endocarditis caused by *T. whipplei* in Sweden. The case demonstrates that Whipple's disease may lead to severe consequences such as worsening arthritis requiring multiple surgeries and infective endocarditis complicated by embolic stroke.

The patient presented in this case report had been diagnosed with seronegative rheumatoid arthritis several years prior to presenting with stroke and infective endoarditis. He had been treated with a variety of immunosuppressive and immunomodulatory medications, some of which were introduced a few months prior to his admission with infective endocarditis. During the course of his worsening polyarthritis, the patient underwent multiple orthopedic procedures including bilateral knee replacements and bilateral arthrodeses of the ankle joints. Many of the immunomodulatory drugs that were used to treat the patient's polyarthritis can make patients more susceptible to infections. Additionally, in case there is an ongoing chronic infection, these drugs can mask the symptoms of an infection process such as Whipple's disease while it progresses and causes tissue and organ damage. Previous case reports on Whipple's disease, have also described patients enduring extended periods of worsening polyarthritis before diagnosis of the disease [3,5]. Consequently, it is important to maintain a high clinical suspicion for Whipple's disease in patients diagnosed with chronic arthritis (with or without GI involvement) that are unsuccessfully managed with immunomodulatory agents and other immunosuppressive medications, and even more so in patients whose condition worsens after such therapy [7]. Had the patient in the current report been diagnosed with Whipple's disease at an earlier stage, some of the tissue damage that occurred and orthopedic surgeries that he underwent might have been averted.

Infective Endocarditis presentation with stroke is an unusual presenting finding in patients with Whipple's disease but has been

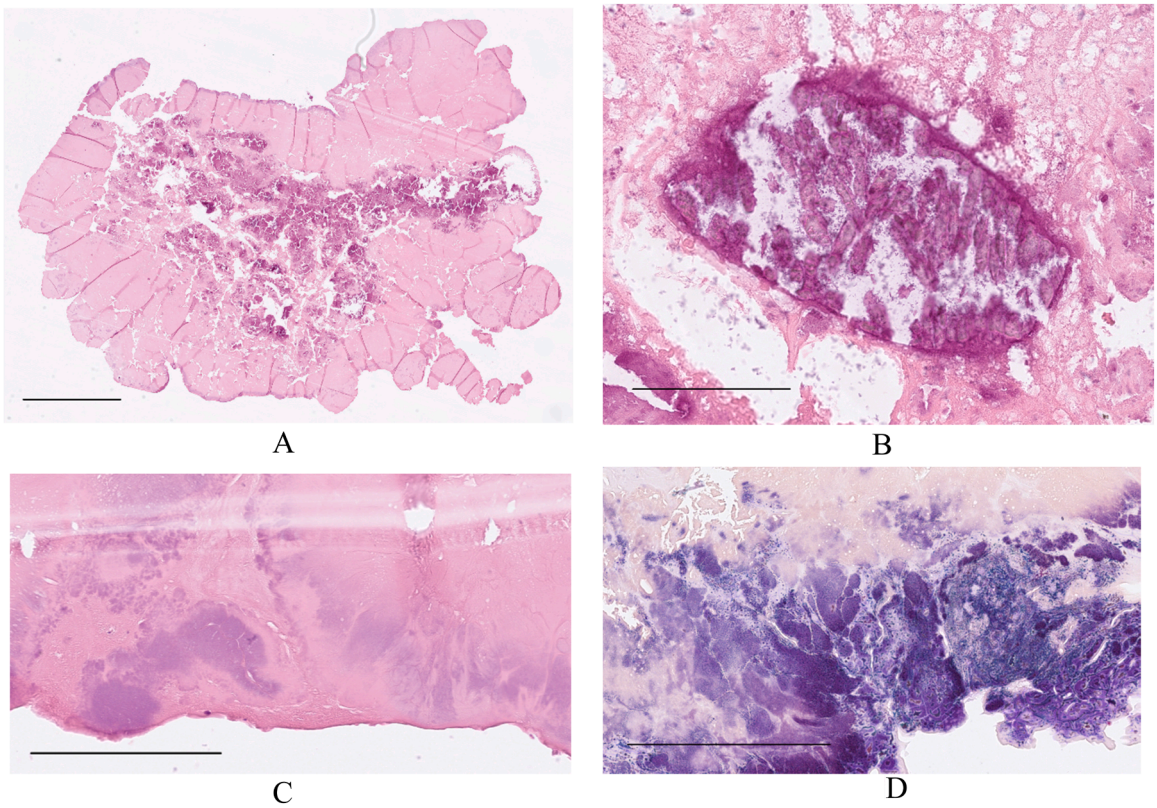


Fig. 3. Histology (A-D) shows devitalized tissue with central areas with extensive calcifications (B) and peripheral areas with appearance of bacterial colonies (C-D). Hematoxylin-eosin (A-C) or gram staining, suboptimal staining quality due to devitalized tissue (D). Scale bar is 2 mm (A) or 0.2 mm (B-D).

described in previous reports [9–11]. Considering the burden of vegetations on his valves, the patient presented in this report likely had infective endocarditis for an extended period. Although it was unfortunate that the patient suffered a stroke, it did lead to treatment of the infective endocarditis and the removal of the very large vegetation, which if it had embolized to the brain would likely have caused more severe neurological damage or even death. The aortic valve procedure served the purpose of re-establishing a functioning aortic valve, preventing further embolization, and providing the diagnosis of Whipple's disease. The procedure was uneventful, and the patient had an uncomplicated postoperative course. Two years prior to the patient being operated, there was no institutional routine on how to handle and process valve tissue in the setting of suspected endocarditis. However, when the patient was operated, an institutional routine was in place that required sending all valve tissue for both tissue culture and for PCR for 16SrDNA. The 16SrDNA PCR was crucial in this patient getting the correct treatment following surgery.

To conclude, clinicians should have a high level of suspicion for Whipple's disease in patients with therapy-resistant seronegative polyarthritis with or without cardiac symptoms prior to advancing the treatment of arthritis or introduction of immune modulatory therapies. An institutional routine of sending tissue samples for 16srDNA PCR enables the correct diagnosis of Whipple's disease. By undergoing valve surgery and receiving appropriate antibiotics, the patient made significant recovery in his joints and ultimately did not require any further treatment or follow-up by rheumatology.

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CRediT authorship contribution statement

Ziyad Ujaimi: Writing, literature review and design. **Henrik Bjursten:** Writing – review & editing. **Sanja Vucicevic:** Writing – review & editing. **Hans Brunnström:** Writing – review & editing. **Patrik Gilje:** Writing – review & editing. **Magnus Rasmussen:** Writing – review & editing. **Sigurdur Ragnarsson:** Writing – review & editing.

Ethical approval

NA.

Consent

The patient gave informed consent to the publication of this report.

Declaration of Competing Interest

The authors have no competing interests.

Acknowledgments

None.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.idcr.2023.e01800.

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