Whipple’s endocarditis: a case report of a blood culture-negative endocarditis

Miriam A. Scheurwater, Cees M. Verduin, and Jan-Melle van Dantzig

Department of Cardiology, Catharina Hospital Eindhoven, Postbus 1350, 5602 ZA Eindhoven, the Netherlands; and Department of Microbiology, Catharina Hospital Eindhoven, Postbus 1350, 5602 ZA Eindhoven, the Netherlands

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Background
Whipple’s disease is caused by Tropheryma whipplei and causes a self-limiting gastrointestinal infection. The majority of the population is an asymptomatic carrier, however, in some patients, it causes an invasive infection with for example arthritis, endocarditis, or involvement of the eyes.

Case summary
This case describes a man with long-lasting complaints of progressive dyspnoea caused by heart failure due to total destruction of the aortic and mitral valve as a result of T. whipplei endocarditis, diagnosed with serum polymerase chain reaction. The patient was treated with ceftriaxone and prolonged co-trimoxazole therapy and surgical replacement of the aortic and mitral valve. He was discharged to a rehabilitation centre.

Discussion
Tropheryma whipplei is one of the possible microorganisms classified as causing blood culture-negative endocarditis, with predominantly afebrile patients that do not fulfil the Dukes criteria, which makes it difficult to diagnose. Polymerase chain reaction is the cornerstone of the diagnosis. It requires long-term antibiotic treatment up to 12 months. It is recommended by the European Society of Cardiology to discuss treatment in an Endocarditis Team because Whipple’s endocarditis has only rarely been described in the literature previously. Whipple’s endocarditis has high mortality and relapse rates.

Keywords
Case report • Tropheryma whipplei • Whipple’s endocarditis • Endocarditis • Blood culture-negative endocarditis

Learning points
• The majority of patients are asymptomatic carriers of Tropheryma whipplei, however, clinicians must be aware of an invasive infection when migratory arthralgia, motoric and cognitive disorders, or endocarditis develops.
• Tropheryma whipplei is a frequently misdiagnosed cause of endocarditis because it is classified into the blood culture-negative endocarditis. Serum polymerase chain reaction is the cornerstone of the diagnosis.
• Whipple’s endocarditis requires long-term antibiotic treatment with meropenem, ceftriaxone, or penicillin for 14 days, followed by co-trimoxazole for up to 12 months. Despite treatment, Whipple’s endocarditis has a high mortality and relapse rate.

* Corresponding author. Tel: +31 40 402 97000, Fax: +31 40 402 96259, Email: miriam.d.jong@catharinazeichenhuis.nl
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Introduction

Whipple's disease is caused by *Tropheryma whipplei* and causes a gastrointestinal infection which is in most cases self-limiting. The majority of the population is an asymptomatic carrier, however, it is sometimes complicated by an invasive infection of the joints, eyes, or heart. Only a small number of cases with Whipple's endocarditis are reported in the literature. This is probably due to the difficulty in diagnosing Whipple's endocarditis because it is classified into the blood culture-negative infective endocarditis (BCNIE). Clinicians are therefore dependent on other diagnostic methods, for example polymerase chain reaction (PCR). Whipple's endocarditis leads to high mortality and relapse rates.

Case presentation

A 50-year-old man with a history of anxiety disorder, post-traumatic stress disorder, and depression, was admitted to the emergency room with severe progressive dyspnoea, orthopnoea, and peripheral oedema. Symptoms were present since 1 year, with progression since 8 weeks, but he delayed presentation because of anxiety. He used to work as bouncer in a beach club but was no longer able to work because of dyspnoea and anxiety.

Physical examination documented obesity (body mass index 43.6), hypertension 190/80 mmHg, respiratory rate 21 per minute, saturation 96% with 3 L O<sub>2</sub> supplementation, temperature 37.1°C, a holosystolic apical cardiac murmur grade 2/6 according to the Levine scale, bilateral basal crackles in the lungs, and pitting oedema in the extremities. There were no peripheral stigmata of endocarditis.

His resting electrocardiogram was normal. Blood results showed a normocytic anaemia 7.7 mmol/L, C-reactive protein (CRP) 33 mg/L, white blood cell count of 9.0 × 10<sup>3</sup> cells/mL, erythrocyte sedimentation rate 47 mm/h, NT-pro-BNP 1225 pg/mL, and D-dimer 1.5 (reference <0.50 mg/L). Chest X-ray showed peri-bronchial cuffing and Kerley lines. Computed tomography angiography was performed, because of the elevated D-dimer, with no sign of lung embolisms, however, mediastinal and paraseophageal lymphadenopathy was noticed. Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) revealed severe aortic valve regurgitation (pressure half-time 164 ms) due to destruction of the left and non-coronary cusps, with an abscess and large vegetation. Mild mitral valve regurgitation with a moderate size vegetation. Antibiotic therapy: intravenously penicillin.

Additional anamnesis: migratory arthralgia.

Serum polymerase chain reaction (PCR) send for *Tropheryma whipplei*.

**Timeline**

| Date          | Event                                                                 |
|---------------|-----------------------------------------------------------------------|
| 21 June 2018  | Admission day.                                                        |
| 22 June 2018  | Transthoracic echocardiography: normal left and right systolic function of the ventricle, severe aortic regurgitation. |
| 27 June 2018  | Transoesophageal echocardiography (TOE): severe aortic regurgitation due to destruction of the left and non-coronary cusps, with an abscess and large vegetation. Mild mitral valve regurgitation with a moderate size vegetation. Antibiotic therapy: intravenously penicillin. |
| 29 June 2018  | Positron emission tomography–computed tomography F-fluorodeoxyglucose (FDG): FDG positive structure in the proximal oesophagus and left ventricle. |
| 3 July 2018   | Serum: IgM *Coxiella burnetti*, IgM *Bartonella henselae*, HIV, *Treponema pallidum*, IgM *Chlamydia pneumoniae*, IgM *Mycoplasma pneumonae* negative. Faeces: *Salmonella* spp, *Shigella* spp, *Yersina* spp, *Clostridium botulinum* spp, Enterohemorrhagic E.coli, *Shiga* toxin-producing E.coli, *Cryptosporidium parvum*, *Cryptosporidium hominis*, *Entamoeba histolytica*, *Giardia lamblia* negative. |
| 4 July 2018   | Mechanic aortic valve regurgitation and mitral valve regurgitation. Perioperative TOE: slight mitral valve regurgitation. Serum PCR: *T. whipplei* positive, switch therapy to ceftriaxone. |
| 12 July 2018  | Faeces PCR *T. whipplei* negative. |
| 19 July 2018  | Heart valve PCR *T. whipplei* positive. |
| 4 August 2018 | Switch to oral co-trimoxazole. |
| 14 August 2018| Discharge to a rehabilitation centre. |
vegetations and histiocytic inflammation, without calcifications. The patient was discharged to a rehabilitation centre 8 weeks after admission. Because of the FDG-PET/CT uptake in the upper jaw, the dental surgeon extracted five diseased teeth. Because of the FDG-PET/CT uptake in the proximal oesophagus, a gastroscopy was performed which showed only a small peptic ulcer, possibly due to *Helicobacter pylori*. *H. pylori* serology was positive and eradication therapy was started. He was seen in follow-up in December 2018, March and August 2019 and is doing well. Co-trimoxazole is continued until August 2019.

**Figure 1** Transoesophageal aortic long-axis view with (A) abscess of the non-coronary cusp and large vegetation (arrowhead) and (B) severe aortic valve regurgitation with wide jet reaching the apex of the left ventricle. AO, aorta; LA, left atrium; LV, left ventricle.

**Figure 2** Transoesophageal aortic short-axis view (multiplaner review) with (A) abscess of the non-coronary cusp. (B) Transoesophageal aortic long-axis view to demonstrate the cross section.
Discussion

Whipple’s disease (lipodystrophy intestinalis) is caused by Tropheryma whipplei, a Gram-positive bacterium, which is transferred through faecal–oral transmission.1–7 The majority of the population is an asymptomatic carrier. Most carriers develop a protective immune response that prevents further spread of the bacterium or eliminates the bacterium completely.1 Only a limited number of carriers develop Whipple’s disease. Host factors, bacterial and environmental factors all contribute to the pathogenesis.6,8

Whipple’s disease occurs more often in men (80–90%) above 40 years old and starts with a gastrointestinal infection with fever, diarrhoea, steatorrhoea, abdominal pains, malabsorption, and weight loss, which is self-limiting in most patients.1–7 Migratory arthralgia or arthritis, is the most common extra-intestinal manifestation.1,2 The time between gastrointestinal and articular symptoms may be several years.2,6 Sometimes, however, patients develop an invasive infection with lymphadenopathy, pleural effusion, pulmonary infiltrates, uveitis, retinitis, motoric and cognitive disorders, headaches, epilepsy, endocarditis, and in a few cases pericarditis or myocarditis is described.2,3 A postmortem analysis by Dobbins (1988) showed central nervous system (CNS) lesions in 90% of symptomatic and asymptomatic patients.9 Clinical relapse rate is 17–35%7,10 and Whipple’s disease mortality is 5.2–15%.11–13

Culture of T. whipplei is possible, but difficult and not readily available in a routine microbiological laboratory.1,14 A periodic acid Schiff stain of duodenal or jejunal biopsy shows foamy macrophages with the included bacterium (Figure 4).1,2,5,7 Polymerase chain reaction of serum, liquor, heart valves, or synovial fluid is the cornerstone of the diagnosis.1–3,6 Meropenem, ceftriaxone, or penicillin with streptomycin is given for 14 days, with additionally cotrimoxazole treatment for 3–12 months.1–3,5,17 The coding sequence for dihydrofolate reductase, the target gene for trimethoprim, is missing which makes the treatment effect dependent of the sulfamethoxazole component.1,15,17 PCR usually becomes negative in an early treatment stage.1 Whipple’s endocarditis occurs frequently on aortic or mitral valves, in 14–40% in both, less on the tricuspid valve and more rarely, the pulmonary valve.3,5 Pathologic examination shows distorted valves with inflammatory infiltrates, without calcifications. The valves are more fibrotic compared to blood culture-positive endocarditis and less fibrotic compared to Bartonella henselae or C. burnetii endocarditis, however, pathology results only are described in a small group of patients.3,5 Meropenem, ceftriaxone, or penicillin with streptomycin is given for 14 days, with additionally co-trimoxazole treatment for 3–12 months.1–3,5,17 The coding sequence for dihydrofolate reductase, the target gene for trimethoprim, is missing which makes the treatment effect dependent of the sulfamethoxazole component.1,15,17 PCR usually becomes negative in an early treatment stage. Treatment response of an additional CNS infection is measured through liquor PCR.1 Whipple’s endocarditis has high mortality rates ranging from 31% to 57% according to two studies; however, mortality or survival is often not described and therefore more detailed information is lacking.3,4

Figure 3 Transoesophageal echocardiography dual chamber with a vegetation of the mitral valve (arrowhead). LA, left atrium; LV, left ventricle.

Figure 4 Illustrative image of PAS-positive Tropheryma whipplei bacteria in human macrophages. (Copyright Gabriele Schoedon, Department of Internal Medicine, University Hospital of Zurich).
In cases suspected of endocarditis with negative blood cultures, the ESC recommends serological testing of *C. burnetii*, *T. whipplei*, fungi (*Candida and Aspergillus* species), and Bartonella, Legionella, Brucella, and *Mycoplasma* species ([Figure 5](#)). Aramnness specifically for *T. whipplei* must include arthralgia, gastrointestinal, and neurological symptoms. Guidelines recommend to discuss treatment of Whipple’s endocarditis in an Endocarditis Team, because of the lack of clear evidence, different antibiotic strategies described in the literature and long-term treatment of patients.\textsuperscript{15}

**Conclusion**

This is another case of the only 100 known cases of Whipple’s endocarditis. Whipple’s endocarditis accounts for approximately 2.6–6.3% of BCNIE and causes only moderate inflammation. The ESC guideline infective endocarditis provides guidance for clinicians through the diagnostic process of BCNIE. Patients rarely fulfill the Dukes criteria and have a variable clinical presentation. Whipple’s endocarditis demands long antibiotic treatment and has high mortality and relapse rates. The ESC recommends to discuss treatment in an Endocarditis Team. Recommendations are based on observational studies and must be interpreted carefully.

**Lead author biography**

Drs Miriam A. Scheurwater is a resident at Catharina hospital, Eindhoven, the Netherlands. She started with her residency in Cardiology this August 2019.

**Supplementary material**

*Supplementary material* is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as *Supplementary data.*
Consent: The author(s) confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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