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CASE REPORT
Heart failure

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

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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.

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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.

Timeline

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. Additional anamnesis: migratory arthralgia. Serum polymerase chain reaction (PCR) send for *Tropheryma whipplei*.
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 pneumoniae* negative. *Faeces*: *Salmonella* spp, *Shigella* spp, *Yersina* spp, *Campylobacter* spp, Enterohemorrhagic E.coli/Shiga toxin-producing E. coli, *Cryptosporidium parvum/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.

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_2 suppletion, 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 × 10^3 cells/nL, 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 paraoesophageal 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 cusp, with an abscess of the non-coronary cusp and large vegetation (20 × 11 mm) (*Figures 1* and *2*), a mild mitral valve regurgitation and vegetation (15 × 9 mm) localized on the A2 segment (*Figure 3*). There was moderate dilatation of the left ventricle (left ventricular end-diastolic diameter 68 mm) with normal ejection fraction. Right ventricular systolic function was normal. Pulmonary artery systolic pressure was not measurable because of poor TTE quality. Treatment with intravenously administration of penicillin (12 million IU/24 h) and diuretics was started. A F-fluorodeoxyglucose positron emission tomography–computed tomography (FDG-PET/CT) was made for better understanding of the case, which revealed increased uptake in the upper jaw, proximal oesophagus, and left ventricle. Blood cultures remained negative. PCR of several viruses, parasites, bacteria (including *Bartonella henselae* and *Coxiella burnetii*) in faeces and blood, according to the European Society of Cardiology (ESC) guidelines work-up for BCNIE, remained negative. At this point, there was an impasse in the diagnostic process of the case because all cultures remained negative in a patient with a high suspicion of endocarditis. Anamnesis was taken again, which revealed a migratory arthralgia of the joints during the past year. Therefore, serum PCR for *Tropheryma whipplei* DNA was tested and found positive. Therapy was switched to ceftriaxone 2 g a day during 4 weeks, completed with co-trimoxazole 960 mg twice daily during 12 months. This was based on a brief literature study and experience of the microbiologist. Two weeks after admission, surgical valve replacement with placement of a mechanical aortic and mitral valve was performed. *T. whipplei* PCR on the heart valves was positive. PCR on faeces remained negative. Macroscopy and microscopy of the heart valves showed degeneration with fibrinous

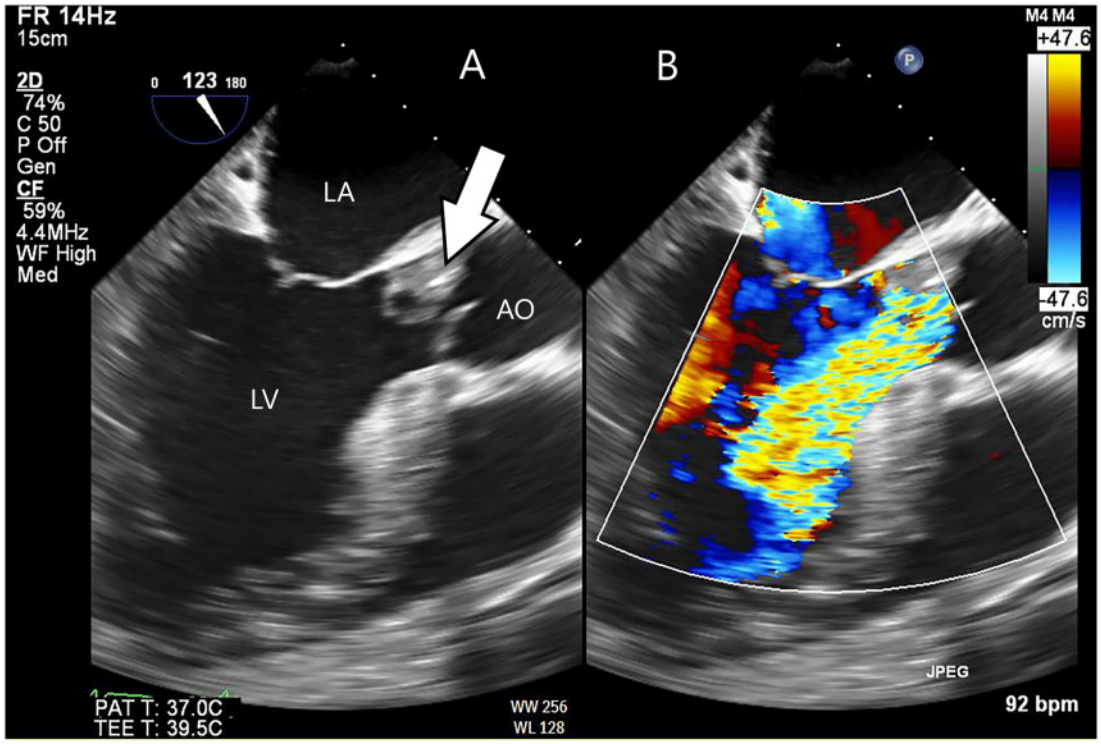

Figure 1 Transoesophageal aortic long-axis view with (*A*) abscess of the non-coronary cusp and large vegetation (arrowhead) and (*B*) severe aortic valve regurgitation with wide jet reaching the apex of the left ventricle. AO, aorta; LA, left atrium; LV, left ventricle.

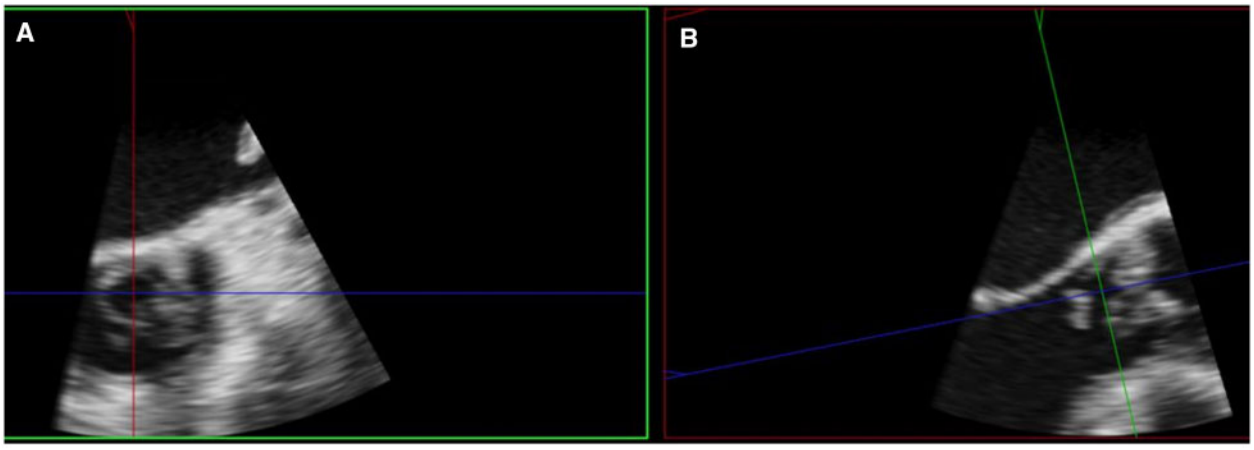

Figure 2 Transoesophageal aortic short-axis view (multiplanner review) with (*A*) abscess of the non-coronary cusp. (*B*) Transoesophageal aortic long-axis view to demonstrate the cross section.

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.

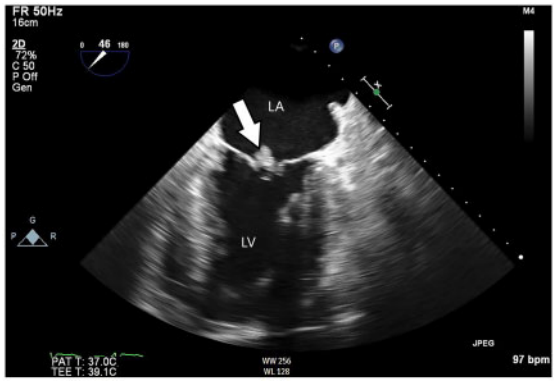

Figure 3 Transoesophageal echocardiography dual chamber with a vegetation of the mitral valve (arrowhead). LA, left atrium; LV, left ventricle.

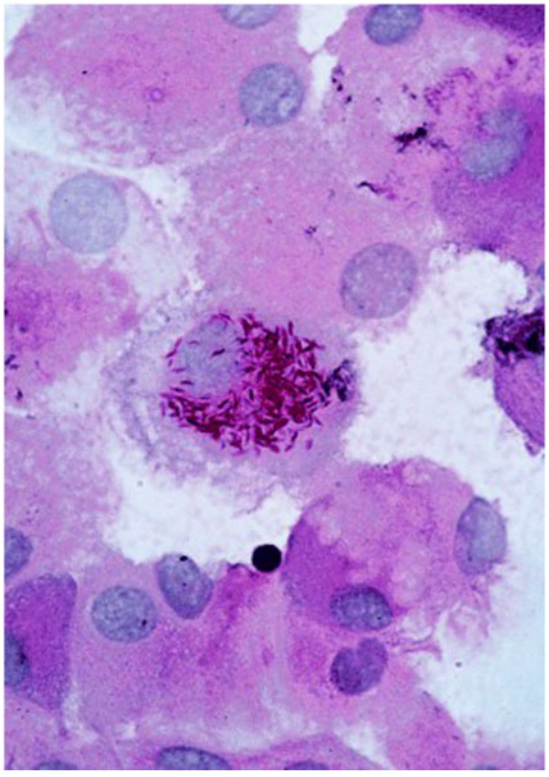

Figure 4 Illustrative image of PAS-positive *Tropheryma whipplei* bacteria in human macrophages. (Copyright Gabriele Schoedon, Department of Internal Medicine, University Hospital of Zurich).

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.[1,2,6] 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.[2,3,6] 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.[1–3,6,15]

Whipple's endocarditis is only described in approximately 100 patients. It can be accompanied by Whipple's disease, but 20% has an isolated endocarditis. Incidence rates are between 2.6% and 6.3% in patients with BCNIE, according to two studies.[4,16] Fenollar *et al.*[3] reported 35 patients with Whipple's endocarditis, of which 89% male, 26% had fever and 66% arthralgia. Patients with Whipple's endocarditis are predominantly afebrile, blood cultures remain negative and they generally do not fulfil the Dukes criteria.[1,3–5,15] Patients usually have a normal leucocytes count, mildly elevated CRP, and elevated sedimentation rate. Arthralgia and intestinal symptoms should raise suspicion in endocarditis patients. Seventy-five percent of the patients have vegetations on TTE or TOE with 88% on native heart valves.[1,3] 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.[1–3,5–7,17] 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]

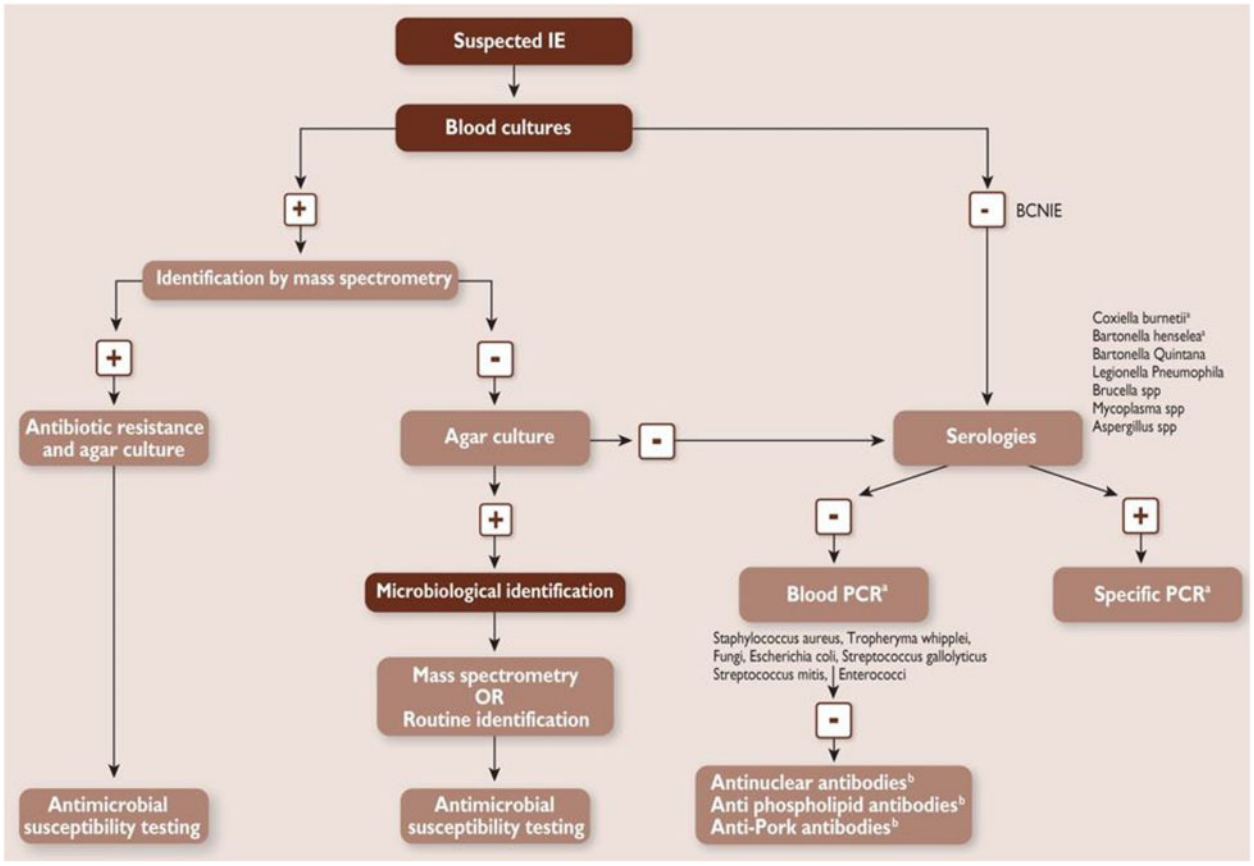

Figure 5 Flow chart of suspected infectious endocarditis with the recommended diagnostics of blood culture-negative infectious endocarditis. (Copyright 2015 ESC guidelines for the management of infective endocarditis).

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*). Anamnesis 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.[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 fulfil 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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