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Abstract
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Case Report

Relapse of *Tropheryma whippelii* endocarditis treated by trimethoprim/sulfamethoxazole, cured by hydroxychloroquine plus doxycycline

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SUMMARY

The best treatment for *Tropheryma whippelii* infections is controversial. We report a patient who suffered from *T. whippelii* aortic native valve endocarditis that relapsed despite surgery and four weeks of intravenous ceftriaxone followed by several months of oral trimethoprim/sulfamethoxazole. Cure was achieved after replacement of the prosthesis with a homograft and 18 months of oral doxycycline-hydroxychloroquine. We discuss the need for a change in treatment guidelines for *T. whippelii* infections.

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1. Case Description

A 60 year old man with Child B cirrhosis secondary to chronic alcohol abuse presented to our hospital with cardiac insufficiency. Transthoracic and transesophageal echocardiography revealed severe leaking of the aortic valve with a large vegetation (>1 cm).

The patient had lost weight during the last six months and was asthenic, but did not complain of fever or arthralgia. White blood cell count and C-reactive protein were normal. The aortic valve was replaced by a TriFecta pericardial aortic bioprosthesis (St. Jude Medical, Minnetonka, MN, USA) along with administration of intravenous (iv) ceftriaxone, vancomycin and gentamycin.

Blood cultures performed before valvular replacement remained negative after three weeks of incubation. *Brucella, Coxella, Bartonella, Mycoplasma and Legionella* serologic tests were negative. Gram staining of the explanted native aortic valve was negative, but acridine orange staining revealed small rods (*Figure 1*). The diagnosis of *Tropheryma whippelii* aortic endocarditis was established by positive 16S rDNA broad range PCR performed on valvular tissue. Specific *T. whippelii* immunohistochemistry was retrospectively positive (*Figure 2*). Vancomycin and gentamycin were discontinued and ceftriaxone was continued for one month, followed by oral double-strength trimethoprim/sulfamethoxazole (TMP-SMX) three times daily.

Five weeks after valvular replacement, while still receiving TMP-SMX, the patient was admitted again with symptomatic pericardial effusion. Transcutaneous drainage was followed by clinical relapse with hemodynamic instability and fever. A mediastinal collection was removed surgically, and a pericardio-pleural fenestration of the pericardial membrane was performed. All blood and mediastinal fluid cultures were positive for *Enterococcus faecalis*, suggesting prosthetic valve *E. faecalis* endocarditis and mediastinitis. The bacterium was highly resistant to gentamycin, but susceptible to penicillin. Conservative treatment was attempted with iv amoxicillin two grams six times daily and iv ceftriaxone two grams twice daily for eight weeks as
reported by Fernandez-Hidalgo. The patient was discharged on double strength TMP-SMX, which had been used since the first hospitalization. One month later, the patient was admitted again with hematemesis. A gastroscopy revealed gastric hypertension due to cirrhosis and mycotic esophageitis, without signs of intestinal Whipple’s disease. Two weeks after admission, while still taking TMP-SMX, the patient developed dyspnea with peripheral edema and weight gain. A transesophageal echocardiography showed partial de-insertion of the aortic prosthetic valve associated with pseudo-aneurysm and vegetation on the posterior aortic ring. Blood cultures as well as specific real-time PCR for T. whipplei on peripheral blood were negative. The St-Jude bioprosthesis was replaced by a homograft, and TMP-SMX was replaced with iv amoxicillin-ceftriaxone and oral doxycycline. Direct examination, cultures and 16S broad-range PCR of the explanted bioprosthesis remained negative. The operative material (explanted valve and cardiac tissue) was sent to a reference center in Marseille, France. The specific PCR for E. faecalis was negative, but T. whipplei DNA could be recovered from para-valvular tissue 5 months after the initial diagnosis, confirming relapsing Whipple’s endocarditis. The folP sequence was obtained but did not show mutations associated with resistance to TMP-SMX. Amoxicillin and ceftriaxone were discontinued, and hydroxychloroquine by mouth was added to doxycycline during rehabilitation. The patient was treated for 18 months after the last aortic replacement surgery without relapse five months after the end of treatment.

2. Discussion

Tropheryma whipplei is a rare cause of endocarditis and was first reported in 1997 as an agent of blood culture-negative endocarditis. The incidence of T. whipplei among blood culture-negative agents ranges from 2.6 to 6.3% in France and Germany. Whipple’s endocarditis is mostly seen in men (>80%). It has been linked with genetic predisposition suggested by the association with HLA B27 and HLA DRB*13 et DQB1*06. This association was not found in our patient. His immunity was, however, compromised by alcohol abuse and cirrhosis.

The diagnosis of T. whipplei endocarditis remains challenging because clinical signs of infection are subtle and absent and microbiological identification is difficult. The diagnosis frequently relies on 16S rRNA amplification and sequencing (or specific immunohistochemistry) on explanted cardiac valve tissue, but not on blood, where it performs poorly. Our initial diagnosis, performed using 16S rDNA broad range PCR, was confirmed by specific PCR as well as immunohistochemistry. The relapse was diagnosed by specific PCR performed on para-valvular tissue in a reference center. This case highlights the higher sensitivity of specific T. whipplei PCR than 16S rDNA amplification and sequencing as previously reported.

The management of patients with T. whipplei infections remains difficult, and the use of TMP-SMX is controversial in classic Whipple’s disease, characterized by a histological small-bowel involvement. This drug was suggested empirically for a prolonged suppressive treatment in classic Whipple’s disease, after an initial therapy with either penicillin or ceftriaxone, in order to reach high concentrations in CSF, which are crucial in case of CNS involvement. Since then, the cultivation of the causative intracellular bacteria allowed building in vitro knowledge regarding antibiotic susceptibility. Genomic analysis and biological tests suggest that trimethoprim is not active against T. whipplei, because its target is lacking, and acquired resistance to sulfamethoxazole has been commonly reported. To date, 34 cases of relapse have been reported after treatment of classic Whipple’s disease with TMP-SMX. Among them, two cases of endocarditis in relapse of classic Whipple’s disease have been published. Tetracyclines were abandoned long ago due to a high failure rate, especially when there was CNS involvement. Quinolones, usually active against intra-cellular pathogens, are not a good option in Whipple’s disease because of frequent mutation of the gyrA and parC genes. The combination of doxycycline with hydroxychloroquine has proven to be the only bactericidal treatment in vitro. T. whipplei survives inside the phagosome by inhibiting phago-lysosome fusion. It requires the acidic environment of the vacuole to survive. Hydroxychloroquine favors the killing of T. whipplei by augmenting the pH inside the phagosome. Clinicians should be aware of the side effects of long antimicrobial therapy, such as alteration of the microbiota accompanied by weight gain with doxycycline, and the risk of irreversible retinopathy with hydroxychloroquine.

Classically, the outcome of patients suffering localized T. whipplei endocarditis is better than those with classic Whipple’s disease. The present case clearly documents for the first time a relapse of T. whipplei endocarditis treated by TMP-SMX. The latter may not be adequate to treat T. whipplei infections, as predicted by the in vitro tests and highlighted by the treatment failure described in this case and many others. Treatment guidelines should probably be modified accordingly.

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