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Endocarditis following ocrelizumab in relapsing-remitting MS

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Ocrelizumab is a monoclonal anti-CD20 antibody targeting B cells, which is authorized for relapsing-remitting MS (RRMS) and active primary progressive MS. Here, we report, to the best of our knowledge, the first case of infective endocarditis in a patient treated with ocrelizumab.

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Case report

A 43-year-old man was admitted due to clinical deterioration within the last 4 weeks. He complained about worsening of gait and progressive weakness, aggravated double vision, and night sweats. The patient had a history of highly active RRMS with a disease course of 3 years and an Expanded Disability Status Scale (EDSS) score of 4.5. He had been treated with glatiramer acetate and was switched to ocrelizumab 17 months before the current admission due to progressive paraparesis of the legs (EDSS score 3.0). Despite treatment with 3 cycles of ocrelizumab (CD19/CD20 cells were fully depleted 7 weeks before the onset of symptoms), there was further clinical progression (EDSS score 4.5). In addition, he was treated with intrathecal triamcinolone 9 months prior this presentation. Apart from arterial hypertension, the patient had no other underlying condition.

On admission, he presented with a predominant left-sided spastic tetraparesis with spastic-ataxic gait. Routine diagnostic workup revealed an increased body temperature of 38°C, elevated leukocytes of 10,060/μL (normal 4,600–9,500), and a C-reactive protein (CRP) of 50.3 mg/L (<5.0). Clinically, there was no evident focus of the presumed infection. He was therefore treated with an empiric antibiotic regime using ceftriaxone. Chest x-ray and sonography of the abdomen were unremarkable. Blood cultures revealed an infection with *Enterococcus faecalis*. Hence, infective endocarditis was assumed, and antibiotic therapy was switched to gentamicin along with ampicillin. However, because transesophageal echocardiography revealed no signs of endocarditis, the antibiotic therapy was de-escalated to piperacillin/tazobactam for 7 days, resulting in gradual clinical improvement and regression of CRP values. On discharge, the body temperature was normal. Fifteen days later, he presented again due to elevated body temperature (38.5°C). Blood testing revealed re-elevation of leukocytes (10,680 leukocytes/μL) and CRP (84.7 mg/L). Now, transesophageal echocardiography exhibited aortic valve vegetations (5 × 5 mm) with moderate regurgitation and mitral valve vegetations (4 × 10 mm) with perforation of the posterior leaflet and moderate regurgitation (figure and Video 1). The patient was immediately re-treated with gentamicin and ampicillin, leading to gradual improvement over the following weeks.

Discussion

Here, we present the first case of infective endocarditis following ocrelizumab therapy. Ocrelizumab was investigated in 2 pivotal phase 3 clinical trials in RRMS and in 1 trial in primary progressive MS. In the OPERA I and II clinical trials, therapy with ocrelizumab reduced the

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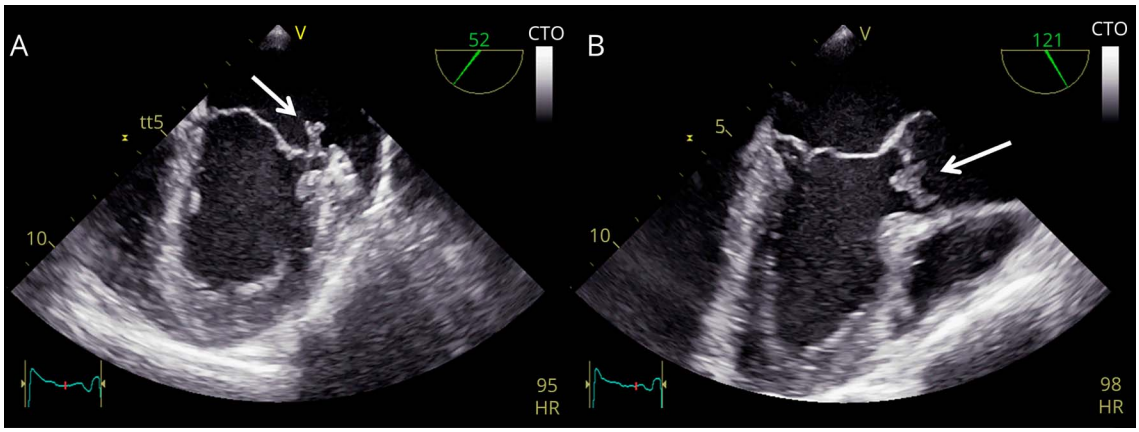
Figure Transesophageal echocardiography



(A) The view of the mitral valve revealed an endocarditic lesion of the posterior mitral valve leaflet (white arrow). In addition, a perforation of the leaflet was seen. (B) On the aortic valve, an endocarditic lesion appeared (white arrow), which was also associated with a regurgitation jet. CTO = Continuous Tissue Optimization; HR = heart rate; LA = left atrium; LAA = left atrial appendage; LV = left ventricle.

relapse rate by 46% compared with interferon beta-1a and disability progression (hazard ratio 0.6, 95% CI, 0.43–0.84; p = 0.003) in patients with RRMS[1] and disability progression after 12 weeks in the ORATORIO trial in patients with primary progressive MS by 24%.[2] Side effects, reported in the trials, include infusion-related reactions in about 30% of the patients and infections[1] such as nasopharyngitis (22.6% ocrelizumab and 27.2% placebo), urinary tract infection (19.8% vs 22.6%), influenza (11.5% vs 8.8%), and upper respiratory tract infections.[2] In the phase 3 trials conducted in rheumatoid arthritis, ocrelizumab combined with methotrexate (MTX) induced more serious infections than placebo (ocrelizumab 500 mg + MTX 6.1% vs 3.1% MTX + placebo group) with a higher risk for patients recruited in Asia.[3] Until now, infective endocarditis has not been reported in association with ocrelizumab therapy.

However, endocarditis has occurred in B cell–depleted patients following rituximab treatment, another B cell–depleting antibody. For example, 1 patient with damaged valves due to Libman-Sacks endocarditis more than 20 years before treatment with rituximab developed endocarditis with Streptococcus intermedius.[4] By contrast, there was no previous history of underlying heart disease, which could have facilitated the development of endocarditis in our patient. Pathomechanistically, it could be speculated that a depletion of innate-like B cells such as B1 cells, critical for the primary immune response[5] and involved in local reaction during infection,[6] might have facilitated the infection with *E faecalis* in this patient. Although not investigated in this patient, low immunoglobulin levels could have contributed to the infection.

In summary, we present the first case of infective endocarditis in a patient treated with ocrelizumab. Although infective endocarditis seems to be a rare complication following ocrelizumab therapy, treating physicians should be aware of this rare and previously unreported side effect of ocrelizumab in patients with otherwise unexplained recurrent episodes of fever and laboratory signs of systemic inflammation under treatment with ocrelizumab.

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Appendix Authors

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Carolin Schwake, MD	Ruhr-University Bochum, Germany	Author	Acquisition of data, analysis and interpretation of data, and revision of the manuscript
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Ralf Gold, MD	Ruhr-University Bochum, Germany	Author	Acquisition of data, analysis and interpretation of data, revision of the manuscript, and study supervision

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