Coronavirus disease 2019 in a patient treated with rituximab.

Mild course of Coronavirus disease 2019 and spontaneous severe acute respiratory syndrome coronavirus 2 clearance in a patient with depleted peripheral blood B-cells due to treatment with rituximab.

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Competing Interests None to declare.

Funding The authors do not declare any specific grant for this research.

Acknowledgments The authors thank their patient for the permission to report on her case.

Contribution All authors contributed substantially to conception, drafting and revising the article.
Over 4 million cases of Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been confirmed worldwide. Up to 20% of cases develop severe disease and the fatality rate are high.[1] Little is known however on the course of the infection in immunosuppressed patients. We therefore report the case of a patient with COVID-19 under immunosuppression with rituximab. This 77-year-old woman was admitted to the hospital with a 5-week history of unclear fever (up to 38.5°C), hypotension (80 mmHg systolic on self-measurement), occasional mild shortness of breath and intermittent dry cough. Two years before she was diagnosed with granulomatosis and polyangiitis (GPA) presenting with otitis media, sinusitis and arthritis, for which she had received repeat courses of rituximab. She was on daily treatment with 5 mg of prednisone and 20 mg of weekly methotrexate. Further medication consisted of folic acid, calcium and vitamin D3, pantoprazole, rosuvastatin and zolendronate. Her main comorbidities were a Sjögren’s syndrome, osteoporosis and hypercholesterolemia. Two weeks prior to admission, she had commenced a seven day course of amoxicillin-clavulanic acid for presumptive sinusitis which however had no effect on her fever. On admission, the clinical examination revealed no signs of active GPA. Her body temperature was 37.7°C, the respiratory rate 16/min, the peripheral oxygen saturation 100%, the blood pressure 110/70 mmHg and the chest auscultation was normal. Eye, ear, nose and throat examinations were unremarkable, previously elevated proteinase-3 autoantibody titers had normalized. The B-cell compartment in the peripheral blood was completely depleted.

During her subsequent hospitalization, the patient continued to complain of fatigue and hypotension. The fever and cough had settled. A chest computed tomography (CT) scan displayed new discrete bilateral ground glass opacifications in comparison to a CT carried out 2 years before, but no other remarkable lung pathology. Nasal swab testing by two independent real-time reverse-transcriptase-polymerase-chain-reactions (rRT-PCR) was positive for SARS-CoV-2 (viral load 149'000 copies/ml). There was no SARS-CoV-2 viremia in the peripheral blood by rRT-PCR. The woman continued not to require any oxygen supply and stayed afebrile. On days 5 and 6 after admission, two consecutive nasopharyngeal swabs were negative for SARS-CoV-2 and the patient was discharged. SARS-CoV-2 serological testing detected no antiviral IgG (EDI™ Novel Coronavirus COVID-19 IgG ELISA, Epitope Diagnostics) up to 1 day after virus-clearance. Figure 1 summarizes the clinical course of this elderly COVID-19 patient who successfully cleared her coronavirus infection despite a depleted peripheral B-cell compartment. This immunosuppressed person commonly considered ‘at risk’ of developing severe COVID-19 had only a mild illness despite proven alveolitis. Murine models point towards an important role of T-cells in mediating organ injury,[2, 3] but antiviral immunoglobulins G (IgG) also induced severe lung inflammation in a primate model.[4] Moreover, serum antiviral antibodies correlated with disease severity in SARS patients.[4, 5] Although the magnitude and speed of antiviral antibody response was not associated with COVID-19 severity,[6] the complete lack of antiviral antibodies might have prevented severe disease in our patient. We can also not exclude that the additional treatment with methotrexate participated in mitigating immune-driven organ damage. Interestingly, the patient successfully cleared the SARS-CoV-2 infection independent of specific antibody production. Although murine models point towards a critical role of antibodies, cellular
immunity also plays an important role in virus elimination and T-cell responses to some viral antigens have been shown to remain intact under rituximab exposure.\cite{3, 6, 7} SARS-CoV-2 was confirmed in two independent PCRs, making a false positive result unlikely. An elevated body temperature was measured more than one month before SARS-CoV-2 detection. It remains unclear if the fever was due to COVID-19 during the entire period. The GPA showed no signs of activity and is therefore an unlikely cause of the fever. It is also unlikely that the alveolitis seen on CT represents rituximab-induced lung edema, given the 4-week time-lapse between rituximab infusion and imaging. Further studies are needed to determine the role of antiviral antibodies and immunosuppression in organ injury and viral clearance of COVID-19.

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**Figure 1:** Graphic representation of symptoms presentation, progression of fever and CRP, diagnostic workup and treatments.
