













## Fatal Enterovirus-related Myocarditis in a Patient with Devic's Syndrome Treated with Rituximab

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### Abstract

Enteroviruses are a frequent source of infection and among the most common central nervous system viral pathogens. Enteroviruses – in particular, the Coxsackie B viruses – are a known cause of myocarditis. Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody. Many reports in the literature suggest a higher risk of infection following repeated rituximab therapy, including viral infection. However, observations of enterovirus-related myocarditis in the context of rituximab treatment are scarce. The authors describe the case of a patient with neuromyelitis optica spectrum disorder who developed severe and fatal enterovirus-related myocarditis after rituximab therapy with a difficult differential diagnosis of autoimmune or giant-cell myocarditis. This case highlights the importance of complete diagnostic workup in difficult cases of myocarditis, including endomyocardial biopsies.

### Keywords

Devic's syndrome, enterovirus, myocarditis, rituximab

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Devic's syndrome (or neuromyelitis optica spectrum disorder; NMOSD) is a rare autoimmune disorder involving the central nervous system. The disease spectrum includes longitudinally extensive transverse myelitis and optic neuritis. Treatment relies on high-dose steroids and maintenance immunosuppressant therapy, such as rituximab.<sup>1</sup> Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody. It causes depletion of CD20<sup>+</sup> B cells and decreased immunoglobulin production.

Many reports in the literature suggest a higher risk of infection – including viral infection – following repeated rituximab therapy.<sup>2</sup> Human enteroviruses are a group of viruses related to the picornavirus family. They are a known cause of myocarditis – in particular Coxsackie B viruses.<sup>3</sup> Reports of enterovirus-related myocarditis due to rituximab are scarce.<sup>4,5</sup> Cases of acute fatal viral myocarditis are mostly described among neonatal and young patients, in contrast to chronic forms of heart failure and dilated cardiomyopathy, which are more common in the adult population.<sup>6</sup>

Here, we describe the case of a patient with NMOSD who developed a severe and fatal enterovirus-related myocarditis after rituximab therapy.

The differential diagnosis included autoimmune or giant-cell myocarditis. This case highlights the importance of the complete diagnosis workup in difficult cases of myocarditis, including endomyocardial biopsies.

In accordance with French legislation, written information was provided and consent was obtained from the patient. French legislation does not require that written consent is obtained for this type of study.

### Case Report

We report a 29-year-old patient with NMOSD associated with anti-aquaporin-4-antibodies. She experienced multiple retrobulbar optic neuritis despite corticosteroid therapy. Since 2012, she received prednisone pulses and plasma exchange for the management of these optical attacks. Since the introduction of rituximab in 2012, prednisone and plasma exchange were not repeated. A 1 g dose of rituximab was administered on day 1, repeated on day 15, then followed by rituximab maintenance therapy of 1 g every 6 months for 7 years. The eleventh and final rituximab infusion was performed in September 2019, thus a total dose of 11 g had been administered with three missed administrations over the years of treatment due to pregnancies.

Prior to rituximab initiation, the patient's immunoglobulin level was normal (gamma globulin 9.6 g/l; normal range 8.0–13.5 g/l) along with CD4 cell count (755/mm<sup>3</sup>; normal range 400–1,300/mm<sup>3</sup>). After rituximab treatment, CD19 depletion was complete. Immunoglobulin G (IgG) level in the remission phase of the disease was low, reaching 6.2 g/l.

In November 2019, 2 months after the last rituximab infusion, the patient suddenly developed cyanotic acute respiratory failure and loss of consciousness while resting. When the rescue team found the patient, she was in cardiac arrest. Transthoracic echocardiogram revealed a left ventricle ejection fraction of 35% (compared with a normal value of 65% during a previous assessment in 2012). Cardiac MRI revealed global hypokinesia with concentric left ventricle hypertrophy and significant increase of T2 mapping values, suggesting a diffuse myocardial oedema. CT coronary angiography revealed no significant stenosis.

A subcutaneous defibrillator was implanted on day 22 post cardiac arrest. The patient was eventually discharged without a clear final diagnosis. On day 47, 10 days after discharge, she was re-admitted to the intensive cardiac care unit with recurrent ventricular tachycardia, despite treatment with amiodarone and lidocaine, resulting in severe cardiogenic shock. With the working hypothesis of giant cell myocarditis, she received prednisone pulses before further results.

Myocardial biopsy was performed on day 51. It revealed acute inflammatory myocardial lymphocytic infiltrate with no signs of giant cells or eosinophilic infiltration. We completed the diagnostic workup, including exhaustive serology and molecular testing. This revealed a positive enterovirus reverse-transcriptase polymerase chain reaction (RT-PCR) on blood, identified as Coxsackie type B4. The first positive enterovirus RT-PCR on blood was reported on day 47. Retrospectively, the analysis of blood sample and pectoral biopsies dating from days 12 and 22 were also positive for enterovirus. Enterovirus RT-PCR was also strongly positive on myocardial tissue. Stool and throat samples were negative, suggesting a long-term enteroviral infection.

Based on these results, the final diagnosis was acute enterovirus-related myocarditis in an immunocompromised patient receiving rituximab. In the absence of specific antiviral treatment, she received IV immunoglobulin 0.4 g/kg/day over 5 days from day 53 to day 57 along with blood PCR monitoring. Enterovirus viral load dramatically decreased from the initiation of IV immunoglobulin therapy. Heart transplantation would have been the best therapeutic option in this situation. However, our patient had high panel reactive alloantibodies and no desensitisation strategies allowing access to heart transplantation in safe conditions. She was finally implanted with a biventricular extracorporeal total artificial heart (Berlin Heart) as a bridge to transplant.

Nonetheless, after 6 weeks of intensive resuscitation the patient deteriorated despite maximum therapy and ultimately died on day 91.

### Discussion

We describe the case of a patient with NMOSD who developed a severe and fatal enterovirus-related myocarditis after rituximab therapy.

Because of the multiple possible causes of myocarditis in this context, we considered the following hypotheses. First, we explored the possibility of a cardiac manifestation of the underlying autoimmune condition. To our knowledge, no cardiac symptoms have been described so far with NMOSD. Second, in light of the severe presentation and

rhythmic disorders, we considered giant cell myocarditis. This particular myocarditis affects younger patients with an autoimmune disorder in 20% of cases, causing rapidly progressive and heart failure that is frequently fatal.<sup>7</sup> Because of the patient's severe presentation, we decided to start immediate corticosteroids and consider rapid immunosuppression. However, we were concerned by the immunocompromised status of the patient. Moreover, although guidelines are scarce, official guidelines of the European Society of Cardiology advocates the role of endomyocardial biopsies in the management of patients with viral PCR both on blood and myocardium.<sup>8</sup> Thus, before starting immunosuppression, we performed a thorough diagnostic workup including myocardial biopsies.

In our patient, RT-PCR for enterovirus was positive both in blood and in myocardium, establishing the diagnosis of enterovirus-related myocarditis. Interestingly, the PCR was positive for samples taken during her first admission, allowing us to consider retrospectively that the patient had this diagnosis since the first event.

Severe enterovirus infections, including meningoencephalitis and myocarditis, are usually described among neonates. Among adults, patients with primary humoral immune deficiencies such as Bruton's X-linked agammaglobulinaemia are more likely to develop chronic enterovirus meningoencephalitis. Low immunoglobulin count increases sensitivity toward enteroviral infections. Our patient was clearly immunocompromised as a result of the rituximab treatment, having low levels of IgG, immunoglobulin (IgM) and CD19.


Rituximab induces B-cell depletion via different mechanisms, including complement- and antibody-dependent cellular cytotoxicity along with induced apoptosis. CD20-expressing cells remain undetectable for approximately 6 months post first administration.<sup>9</sup> Repeated cycles of rituximab are associated with low IgM and, to a lesser degree, low IgG, especially in patients with an underlying B-cell maturation defect. However, data concerning the risk of infection associated with rituximab are contradictory, varying according to the population studied and the accompanying treatments.

Some studies do not find significant increase in the risk of infection under rituximab therapy, despite decreased immunoglobulin levels, whereas multiple reports have identified a link between rituximab regimen therapy and the occurrence of severe infection.<sup>9</sup> Moreover, in a recent study, our team showed that the 1- and 2-year incidences of serious infections were 17.3 (12.0–22.5) and 11.3 (8.1–14.5) per 100 person-years, respectively. Identified risk factors of severe infections were age, history of diabetes, history of cancer, concomitant steroid treatment and low CD4 lymphocyte count at rituximab initiation. Immunoglobulin replacement therapy was started in 22 rituximab courses (8%).<sup>10</sup>

Acute and chronic enterovirus meningoencephalitis have been described among patients under rituximab therapy for B-cell malignancies or autoimmune disorders. Chronic enteroviral myocarditis is more frequent among adults, resulting in dilated cardiomyopathy.<sup>11–13</sup> However, rituximab-related enterovirus myocarditis observations are very scarce. Only one report of a child receiving rituximab treatment for nephrotic syndrome and one report of an adult treated for lymphoma were found in the literature.<sup>4,5</sup>

In terms of treatment, by the time the diagnosis of enterovirus had been made, the patient's clinical status was already severely compromised.

Therapeutic options are scarce. Pleconaril, pirodavir, and vapendavir are capsid-binding agents that are theoretically active on enteroviruses with modest antiviral activity, unapproved in the therapeutic arsenal of enterovirus infections. Interferon beta has been tested in phase 2 trials for cases of persistent left ventricle dysfunction linked to chronic enteroviral infection, but without success. In the absence of availability of specific treatments, we started IV immunoglobulin therapy, based on protocols used in paediatric and immunocompromised populations. Of note, following IV immunoglobulin therapy, the enteroviral RNA load rapidly dropped to zero, yet without any obvious effect on clinical status and myocardium recovery.

Our case is a red flag for physicians about the possible association between rituximab and life-threatening enteroviral myocarditis in other immunocompromised patients. It also highlights the importance of a correct diagnostic workup including endomyocardial biopsies and viral PCR. Without them, we could have wrongly concluded on autoimmune myocarditis or giant cell myocarditis. In our case, despite a fatal course of evolution, the administration of IV immunoglobulin was highly effective on enterovirus RNA viral load, yet without leading to clinical improvement in an already severe patient. Earlier administration – when the patient was first admitted – may have changed the course and the patient's outcome. 

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