ACN
ANNALS OF CLINICAL NEUROPHYSIOLOGY

CASE REPORT
Ann Clin Neurophysiol 2024;26(2):54-56
https://doi.org/10.14253/acn.24001

Early relapse after rituximab treatment in a patient with seronegative neuromyelitis optica spectrum disorder: a case report

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Received: January 26, 2024
Revised: March 22, 2024
Accepted: May 9, 2024

Rituximab (RTX) is a monoclonal antibody that targets CD20 on B cells and is used to reduce the relapse risk in neuromyelitis optica spectrum disorder (NMOSD). Some patients experience relapse or exacerbation shortly after RTX treatment. We report a 54-year-old female with seronegative NMOSD who relapsed soon after RTX treatment.

Key words: Neuromyelitis optica spectrum disorder; Rituximab; Recurrence

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Neuromyelitis optica spectrum disorder (NMOSD) is a demyelinating inflammatory autoimmune disease of the central nervous system (CNS) that primarily affects the optic nerve and spinal cord.[1] Rituximab (RTX) is a monoclonal antibody that has been found to reduce the relapse risk in NMOSD.[2] However, some patients experience relapse or exacerbation shortly after RTX treatment,[3-6] the mechanism of which is currently unclear. Here we report a case of the RTX-induced rebound phenomenon in seronegative NMOSD.

CASE

A 54-year-old female was admitted to with acute bilateral visual disturbances. These disturbances were attributed to inflammatory lesions that involved the optic chiasm (Fig. 1A). The patient had two previous inflammatory episodes in the CNS. She had presented with double vision and decreased visual acuity in the right eye 4 years previously. She experienced longitudinal extensive transverse myelitis (LETM) at the C2-C6 level 2 years later, and presented with right arm numbness, weakness, and gait disturbance. Both episodes

http://www.e-acn.org
pISSN 2508-691X
eISSN 2508-6960

exhibited a favorable response to steroid pulse therapy.

On admission, the visual acuity had decreased from 1.0 to 0.6 in the right eye but remained unchanged in the left eye. Visual field testing revealed hemianopia accompanied by a relative afferent pupillary defect in both eyes. No additional neurological deficits were observed. Laboratory analysis revealed an antinuclear antibody level of less than 1:40, with negative results for all autoantibodies including antineutrophil cytoplasmic antibody and rheumatoid factor. She consistently tested negative for both myelin oligodendrocyte glycoprotein (MOG) and aquaporin 4-immunoglobulin G (AQP4-IgG) antibodies throughout the disease course. Serum analysis was performed to detect AQP4-IgG and MOG-IgG using a flow cytometry-based live cell assay with AQP4- and MOG-transfected cells. She met the diagnostic criteria for seronegative NMOSD with two key clinical features: optic neuritis and LETM.[7]

Following intravenous methylprednisolone pulse therapy, she was maintained on oral prednisolone. Mycophenolate mofetil (MMF) was initiated at 2 g/day as a steroid-sparing agent, allowing for the gradual tapering of the oral steroid. She developed leukopenia 1 year after MMF treatment was initiated, which persisted despite adjusting the dose of MMF to 1 g/day. MMF therefore had to be discontinued.

She experienced a relapse of optic neuritis that involved the optic chiasm 3 months after MMF was discontinued, and presented with bilateral visual disturbance (Fig. 1A). She immediately started steroid pulse therapy at the time of hospitalization, followed shortly by RTX (protocol: 375 mg/m^2/week intravenous for 4 weeks). At 7 days after the first RTX infusion, she reported symptom deterioration with almost total blindness in the right eye and only finger counting in the left eye. Subsequent brain magnetic resonance imaging (MRI) revealed increased intensity of the T2-weighted/fluid attenuated inversion recovery hyperintensity lesion in the optic chiasm (Fig. 1B) accompanied by mild gadolinium enhancement (Fig. 1C, D), relative to MRI conducted approximately 2 weeks earlier. Plasma exchange was performed to address this acute exacerbation, which improved the visual impairment.

DISCUSSION

The exact mechanisms that underlie the acute exacerbation or relapse shortly after RTX treatment are not understood. One hypothesis is that RTX-induced rapid B-cell depletion inadvertently elevate the levels of proinflammatory cytokines, such as interleukin 6, B-cell activating factor, and tumor necrosis factor alpha, which can all be accompanied by increased T cell activity.[8] Gong et al.[9] also found that germinal-center B cells exhibit resistance to RTX-induced apoptosis. This resistance could lead to the clonal expansion of memory B cells in germinal centers, which would be further fueled by the aforementioned proinflammatory cytokines. These persistent cytokines have been postulated to contribute to the rebound phenomenon, and could explain why acute exacerbation or relapse can occur during this period.

Sixteen cases of RTX-induced exacerbation or relapse have been reported in the literature, primarily in patients who

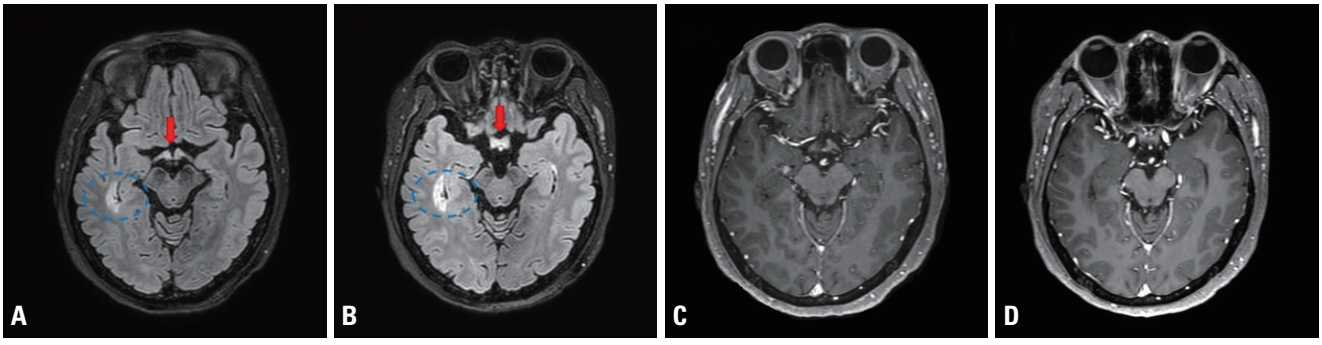

Fig. 1. Serial brain MRI revealed the disease exacerbation shortly following RTX treatment. FLAIR MRI revealed hyperintense lesions at the optic chiasm (red arrow) and right temporal horn of the lateral ventricle (blue dot circle) at 1 month prior to the initial RTX infusion (A) and at 2 weeks posttreatment (B). (C, D) Post-enhancement images corresponding to (A) and (B), respectively, revealing mild gadolinium enhancement with no significant changes. MRI, magnetic resonance imaging; RTX, rituximab; FLAIR, fluid attenuated inversion recovery.

were seropositive for antiaquaporin-4 antibodies. It is particularly notable that more than half of these cases occurred after the active or acute phase of the disease, had a previous episode within 3 months, and where the location of the relapse overlapped with that of the pre-RTX relapse.[3] The decision to treat using RTX should therefore be informed by the possibility of RTX-induced rebound phenomenon and its typical period. Close monitoring during initial RTX therapy may be necessary in patients with active disease due to the increased risk of exacerbation or relapse, even for those who are seronegative. Initiating RTX treatment during a stable phase of the disease, where feasible, may help to mitigate this risk.

Conflicts of Interest

Yoon-Ho Hong serves as the Editor-in-Chief of ACN and was not involved in the review process of this article. No other potential conflicts of interest relevant to this article were reported.

Funding

None.

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