

Recurrence of COVID-19 in a Patient With NMO Spectrum Disorder While Treating With Rituximab

A Case Report and Review of the Literature

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Introduction: In the context of coronavirus disease 2019 (COVID-19) pandemic, patients with neuromyelitis optica spectrum disorder (NMOSD) are vulnerable to develop COVID-19 due to the immunosuppressive therapy. The objective of this study is to describe a known case of NMOSD on rituximab who experienced 2 episodes of COVID-19.

Case Report: A 25-year-old woman, a known case of NMOSD on rituximab was diagnosed with asymptomatic COVID-19. Eight months later, following her last infusion of rituximab, she developed moderate COVID-19. After a partial recovery, she exhibited exacerbation of respiratory symptoms leading to readmission and invasive oxygenation. She was eventually discharged home after 31 days. Her monthly neurological evaluation did not reveal evidence of disease activity. She later received intravenous immunoglobulin and the decision was made to start rituximab again.

Conclusions: Our case raises the possibility of persistent virus shedding and reactivation of severe acute respiratory syndrome coronavirus-2 in a patient with NMOSD and rituximab therapy. We aimed to emphasize a precise consideration of management of patients with NMOSD during the COVID-19 pandemic.

Key Words: NMOSD, rituximab, COVID-19, reinfection

(The Neurologist 2021;26:281–283)

The current coronavirus disease 2019 (COVID-19) pandemic continues to affect populations worldwide. Numerous questions have been raised about immunomodulatory and immunosuppressive therapy in patients with demyelinating disorders as neuromyelitis optica (NMO) spectrum disorder in the COVID-19 pandemic.¹ Neuromyelitis optica spectrum disorder (NMOSD) is a chronic inflammatory disorder of central nervous system that particularly involves the optic nerve and spinal cord. Unlike multiple sclerosis, a progressive clinical course is unusual and the accrual of disability is related to relapses. Long term immunosuppression is the mainstay of treatment in patients with NMOSD which might theoretically increase the risk of infections as COVID-19.² On the other hand, protective long-lasting immunity following COVID-19 is uncertain which makes the current crisis even more challenging.³ Herein, we

aimed to report a young female, a known case of NMOSD who was complicated with 2 distinct episodes of COVID-19 while treatment with rituximab.

CASE PRESENTATION

In April 2020, a 25-year-old woman referred for COVID-19 screening test due to close contact to a patient with COVID-19. Her past medical history was remarkable for NMOSD since 7 years ago. Tracing back her medical history, it was found that she had an episode of severe left optic neuritis with a sequela of some degree of persistent visual impairment since 7 years ago. Two years later, she developed another episode of right optic neuritis in a same fashion leading to complementary assessments. The brain magnetic resonance imaging was roughly normal and cervical magnetic resonance imaging showed an elongated hyper-signal lesion over C4-C6 on T2-weighted images. More over, the results of cerebrospinal fluid analysis were unremarkable, with no oligoclonal bands. For confirmation of NMO syndrome, NMO-immunoglobulin G (IgG) was assessed and the result was positive. On the basis of the International consensus diagnostic criteria (2015), the patient was diagnosed with NMOSD and treatment started with rituximab (1 g intravenous every 6 month) without a clinical relapse within the next years. The last infusion was instituted 5 months prior referral.

At the time of referral for COVID-19 screening, she had no complaints of upper respiratory tract irritation and was asymptomatic. The neurological examination was notable for Expanded Disability Status Scale of 2. Due to COVID-19 phobia and the near time to the next infusion of rituximab, the patient underwent serologic testing which revealed positive severe acute respiratory syndrome coronavirus (SARS-CoV) IgM and IgG. Serum anti-SARS-CoV-2 IgG was measured by enzyme-linked immunosorbent assay-based chemiluminescent immunoassay using the commercially available kit (with a sensitivity of 97% and false positive rate of 3%) manufactured by Pishtaz Teb Company (Tehran, Iran).

Given the Iranian guideline to continue disease modifying treatment during COVID-19 pandemic and low levels of B cell counts, the time to receive her scheduled rituximab was extended to September 2020. Twenty-five days later, in November 2020, the patient presented with a 5-day history of severe chills, fever and shortness of breath. Her chest computed tomography (CT) showed bilateral ground glass infiltrates in keeping with COVID-19. The patient was admitted and underwent standard treatment for COVID-19 and noninvasive O₂ supplementation. The diagnosis was later confirmed by a nasopharyngeal polymerase chain reaction (PCR) assay. The patient gradually improved and was discharged 2 weeks later given the lack of progression of the disease. However, the patient's symptoms did not resolve completely. Unfortunately, the patient exhibited an exacerbation of her respiratory symptoms 3 weeks later leading to readmission. The initial vital signs revealed temperature of 38.0°C, respiratory rate of 22, heart rate of 110, blood pressure of 120/75, and saturating 86% at room air. She was also found to have an Expanded Disability Status Scale score of 3.5. The chest CT was in favor of diffuse bilateral lung involvement. Moreover, COVID-19 PCR was still positive.

The patient was admitted in the intensive care unit and underwent ventilation support due to respiratory distress. Based on

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Patient consent for publication was obtained.

The authors declare no conflict of interest.

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ISSN: 2331-2637/21/2606-0281

DOI: 10.1097/NRL.0000000000000371

pulmonary disease service consultation, treatment started with therapeutic plasma exchange (TPE) due to severity of respiratory involvement related to COVID-19. We did a total of 5 sessions of TPE (alternate days). One standard TPE session was 1.5 plasma volume exchange using 5% albumin as a replacement fluid. The patient experienced gradual resolution of the symptoms and was extubated on day 10. Five days later, she was transferred to the ward. She was hemodynamically stable and her chest CT revealed a significant resolution of the lung infiltration. She was eventually discharged home on day 31. Her monthly neurological evaluation did not reveal evidence of clinical activity of the disease and her neuroimaging was similar to previous ones demonstrating a nonenhancing longitudinally extensive cervical plaque.

In March 2021, the patient was evaluated to continue the immunomodulatory treatment. Based on the current communitarian Iranian MS guideline, the serum IgG levels were checked and due to low IgG levels, the patient received intravenous immunoglobulin (20 g intravenously daily for 5 d) and the decision was made to start rituximab again.

DISCUSSION

Given the ongoing COVID-19 pandemic, there are poorly answered questions about the postinfection immunity elicited by COVID-19 raising the possibility of recurrence versus persistent viral shedding. Although neutralizing antibody develops rapidly after acute infection, its titers start to drop as early as 1 to 2 months after the infection which is considered as the main possible mechanism of COVID-19 reactivation.^{4,5} The first reports of reactivation of SARS-CoV-2 were brought to public attention in April 2020.⁶ Later, Ye and colleagues reported a 9% chance of COVID-19 recurrence. Based on their results, host status as age, sex, and the underlying disease required for treatment with immunosuppressive, virologic factors as high baseline SARS-CoV-2 load and variable genotype, and degree of immunosuppression were estimated as the main contributing factors to develop reinfection.⁷ Similarly, Gousseff and colleagues reported a case series of 11 patients with recurrence of COVID-19. Their results revealed a similar clinical manifestation in both episodes with a shorter duration in the second episode.⁸ However, other reports did not conclude a convinced rate of recurrence as a combination of virologic and epidemiologic factors may together contribute to viral reactivation. It is proposed that a SARS-CoV-2 variant with Spike G614 is associated with lower reverse transcription polymerase chain reaction cycle thresholds, suggestive of higher upper respiratory tract viral loads, but not with increased disease severity.⁹ Another study of 98 individuals with a full recovery with 2 negative reverse transcription polymerase chain reaction tests revealed that, while 17 patients (17.3%) were re-positive, only 1 patient returned to clinically symptomatic disease.¹⁰

The case we described points to both persistent viral shedding (the second scenario of readmission) and a real reactivation of the infection (the first scenario of admission) as there was a long interval between the 2 episodes accompanied by laboratory and epidemiologic evidence of COVID-19 which fulfill twice the case definition of COVID-19 proposed by the World Health Organization. In contrast to previous reports, our patient was asymptomatic in the first episode and the second episode was complicated with respiratory distress associated with persistent viral shedding.

In contrast, there is no evidence supporting the patients on immunosuppressant therapy are more vulnerable to higher risk of COVID-19 complications.¹¹ Moreover, to best of our knowledge, there are no reports of the accurate recurrence rate of COVID-19 in immunosuppressed patients or of the

significant role of immunosuppressant therapy in COVID-19 recurrence.

With this in mind and a possibility of the overwhelming sequels associated with NMOSD relapses, patients with NMOSD ought to continue their routine treatment. Although theoretically, rituximab appears to increase the potential risk for severe SARS-CoV-2 infection, a muted vaccination response, and viral reactivation, observational studies on multiple sclerosis and COVID-19 have not established a role for rituximab in COVID-19 incidence.^{12,13} However, in the context of anti-CD20, reactivation of SARS-CoV-2 has been reported 21 days after rituximab infusion in a patient with multiple sclerosis which was similar to our case.¹⁴

Taking all considerations into account, our case highlights the importance of particular consideration to the vulnerable populations as patients with NMOSD in the COVID-19 pandemic, especially in circumstances with recurrence of COVID-19.

CONCLUSIONS

The COVID-19 pandemic is a global concern with an unforeseeable course. Patients with NMOSD are a group of interest in this context as they need to continue immunosuppressive treatment. The case we described is unique as we highlighted the occurrence of both reactivation and persistent viral shedding in a patient with NMOSD while on rituximab.

ACKNOWLEDGMENT

The authors thank the Department of Intensive Care Unit of Beheshti Hospital for their kind help to manage the patient.

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