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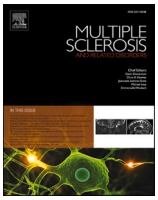

Reactivation of SARS-CoV-2 after Rituximab in a Patient with Multiple Sclerosis

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ABSTRACT

A 32-year-old woman with highly active MS was infected with SARS-CoV-2 while on treatment with rituximab. She recovered and was symptom-free for 21 days before receiving rituximab and IVIg for comorbid hypogammaglobulinemia. Three days after the infusion she redeveloped respiratory symptoms and required admission. Three SARS-CoV-2 nasopharyngeal swabs and antibody testing was negative; however, bronchial alveolar lavage detected SARS-CoV-2. Reactivation of SARS-CoV-2 after rituximab for MS has not been reported but is a known risk in other conditions. The timing of anti-CD20 treatment after SARS-CoV-2 infection requires further investigation and individual consideration to reduce the risk of reactivation.

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the Coronavirus Disease 2019 (COVID-19) pandemic, has infected over 120 million people around the world, causing over 2.5 million deaths as of March 2021. Risk factors for more severe COVID-19 include older age, body-mass index over 30 km/m^2, smoking or lung diseases, diabetes or heart conditions, as well as those in an immunocompromised state.(SeyedAlinaghi et al., 2020) Patients with highly active multiple sclerosis (MS), who have continued disease activity despite first-line treatments, are often treated with higher efficacy treatments, such as anti-CD20 therapies, which result in a more immunocompromised state. Guideline recommendation on continued treatment with anti-CD20 therapies during the COVID-19 pandemic are mixed, given that these treatments may lead to more severe SARS-CoV-2 infection, potentially a muted vaccination response, or potentially viral reactivation.(Korsukewitz et al., 2020) However, in certain patients anti-CD20 therapy is very effective in reducing MS disease activity, thus are continued. Here we present a patient who developed reactivation of SARS-CoV-2 shortly after anti-CD20 treatment.

2. CASE PRESENTATION

A 32-year-old woman with highly active MS was treated with rituximab. The onset of MS was 12 years prior with optic neuritis. In the first 6 years she sustained 7 clinical attacks, including a severe brainstem attack, each requiring intravenous (IV) steroids. These occurred despite transition to four different disease-modifying treatments. In the 7th year of her disease, she developed difficulty walking and an enhancing spinal cord lesion, thus was escalated to anti-CD20 therapy with rituximab, 1000mg IV every 6 months. After this, she had no further clinical or radiographic disease activity, nor clinical worsening on the Expanded Disability Status Scale (EDSS).

Subsequently, she developed recurrent sinus infections that were managed by otolaryngology with nasal irrigation, inhaled fluticasone, azelastine and loratadine, as well as multiple courses of antimicrobials including amoxicillin clavulanate, azithromycin, and levofloxacin. She also had reduced immune globulin (Ig) G levels over this period, ranging from 380 mg/dL to 510 mg/dL (normal 700-1600 mg/dL), but maintained an EDSS score of 1.5, mild disability, on rituximab.

At the start of the COVID-19 pandemic, given her aggressive history, she received her scheduled rituximab and subsequently developed an exacerbation of her chronic sinusitis. MRI showed high T2 lesion burden, however no new or expanding T2 lesions, nor gadolinium enhancing lesions were found, shown in Figure 1. She tested negative for SARS-CoV-2 polymerase chain reaction (PCR) by nasopharyngeal (NP) swab. Over the year she developed 3 further sinusitis exacerbations, treated with different antibiotics, thus her next rituximab dose was delayed with the plan to initiate IVIg to prevent further infections. Prior to this starting, the patient was exposed to SARS-CoV-2 and developed respiratory symptoms.

The timeline since exposure to SARS-CoV-2 is shown in Figure 2. Seven days after exposure she developed symptoms of fever, anosmia, and cough, and her SARS-CoV-2 PCR by NP swab returned positive 2 days later (day +0). Her symptoms lasted 7 days total and she fully recovered. She had been symptom-free for 21 days without any further exposure, so she was scheduled for her IVIg and rituximab infusions (day +26), which was 9 months after her prior rituximab course. At this point her B cell counts were still suppressed and her IgG levels were still reduced at 502 mg/dL. Within three days of the infusion, she developed myalgias, fever, and recurrent maxillary sinus pain with purulent discharge, but tested negative for SARS-CoV-2 PCR by NP swab (day +29). She was admitted to hospital after worsening despite acetaminophen, hydration, and amoxicillin clavulanate, with repeat testing again negative for SARS-CoV-2 PCR by NP swab (day +33). She continued to worsen symptomatically and required supplemental oxygen, had computed tomography (CT) of the chest which showed bilateral multifocal infiltrates in keeping with COVID-19, yet had a third negative SARS-CoV-2 PCR by NP, as well as non-reactive antibodies to SARS-CoV-2 nucleocapsid(N)antigen (day +41). She had persistent oxygen requirements and ultimately underwent bronchial alveolar lavage (BAL) which did detect SARS-CoV-2 PCR. She was treated with

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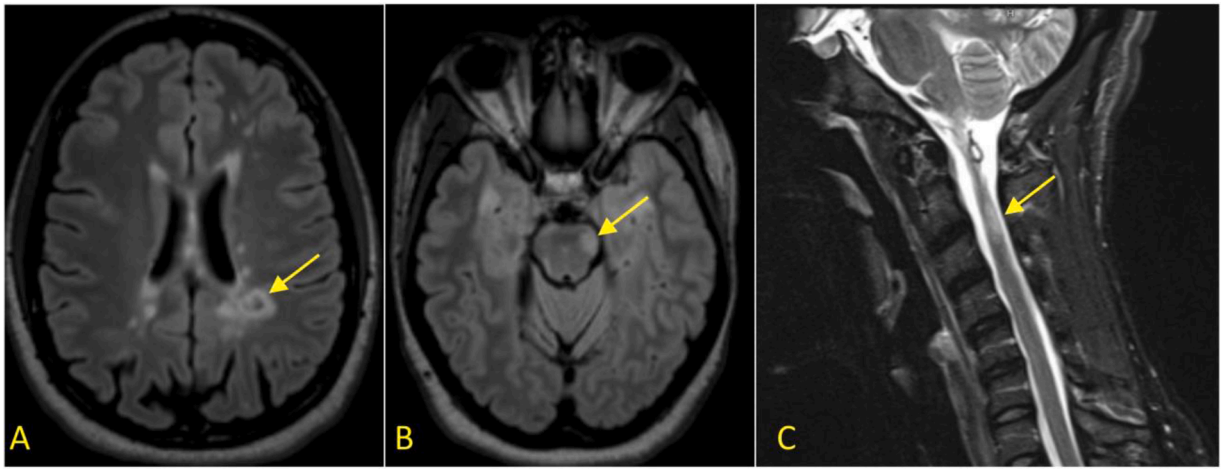

Figure 1. Representative MRI sequences demonstrating this 32-year-old female patient's lesion burden. A. Axial T2 fluid-attenuation inversion recovery (FLAIR) sequence showing diffuse periventricular lesion burden, left parietal white matter lesion with central hypointensity (arrow), and diffuse atrophy. B. Axial T2 FLAIR sequence demonstrating hyperintense foci within the left pons (arrow). C. Sagittal T2 short tau inversion recovery (STIR) sequence demonstrating a hyperintense foci at the left C2-C3 hemicord (arrow).

dexamethasone, remdesivir, and the REGN-COV2 antibody cocktail of casirivimab/imdevimab, and eventually was discharged to rehabilitation.

3. DISCUSSION

This case demonstrates a patient who developed reactivation of SARS-CoV-2 after treatment with rituximab despite being initially symptom-free from COVID-19 for 21 days. The fact that the patient had no new exposure to SARS-CoV-2, maintained negative SARS-CoV-2 PCR on three separate NP swabs in the 12 days after symptom recurrence, but had detected SARS-CoV-2 PCR from BAL fluid on the 15th day of ongoing clinical symptoms, potentially suggests reactivation of SARS-CoV-2. (SeyedAlinaghi et al., 2020) SARS-CoV-2 PCR from BAL fluid has been shown to be positive despite false-negative NP testing and the World Health Organization recommends lower respiratory tract sampling when there is high index of suspicion for COVID-19 and negative upper respiratory tract testing.(Gualano et al., 2020; World Health Organization, 2020)

Recurrence of SARS-CoV-2 infection has been reported in the literature. One systematic review of 1350 patients found recurrence to occur a mean 34.5 days from first positive sample, similar to our case.(Gidari et al., 2021) Risk factors for recurrence include immune suppression, as this may reduce clearance of SARS-CoV-2 and reduced development of SARS-CoV-2 antibodies, as seen in our patient.(Gousseff et al., 2020) In the context of anti-CD20 therapy, reactivation of hepatitis B viral infection is a known risk, and viral reactivation of SARS-CoV-2 has been reported in a patient with B-cell leukemia.(Lancman et al., 2020) The

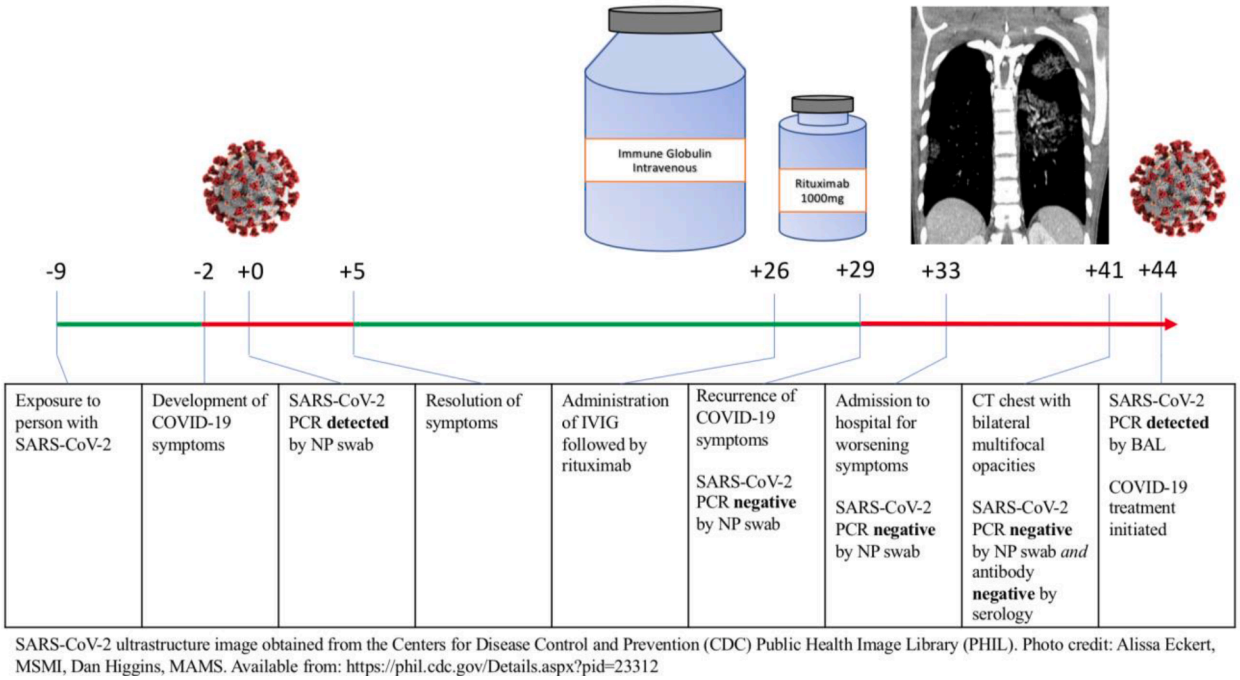

Figure 2. Timeline from first exposure to SARS-CoV-2. The green timeline indicates period when patient was asymptomatic, while the red timeline indicates periods when patient had symptoms of COVID-19. BAL = Bronchial alveolar lavage; IVIG = intravenous immunoglobulin; NP = nasopharyngeal; PCR = Polymerase chain reaction

American College of Rheumatology has published guidelines suggesting regardless of COVID-19 severity, biologics (including anti-CD20 therapies) ought to be held until 7 to 14 days after symptom resolution, which is shorter than the duration without symptoms in our patient.(Mikuls et al., 2021)

The rate and overall risk of COVID-19 in patients with MS compared with the general population is not definitively known. Reports out of France and Italy suggest that subgroups of patients with MS who are older age, male sex, have increased disability, recently received methylprednisolone, or are treated with anti-CD20 medications may be at higher risk of developing more severe COVID-19.(Louapre et al., 2020; Sormani et al., 2021). Despite this, there are mixed recommendations for continuation or delay of anti-CD20 therapies during the COVID-19 pandemic.(Brownlee et al., 2020; Giovannoni et al., 2020; Korsukewitz et al., 2020) At the MSVirtual2020: 8th Joint ACTRIMS-ECTRIMS Meeting, a large aggregate dataset of 1540 MS patients across 21 countries showed that developing COVID-19 while being treated with anti-CD20 therapies was associated with higher rates of hospitalization, ICU admission, and ventilator use.(Simpson-Yap et al., 2020) Further complicating our case is that our patient had developed hypogammaglobulinemia, which has been correlated with protracted COVID-19. (Hueso et al., 2020)

Ultimately, the prevalence of COVID-19 may remain high for the foreseeable future and the efficacy of SARS-CoV-2 vaccination in the context of anti-CD20 therapy is unknown.(Khayat-Khoei et al., 2021; Vishnevetsky et al., 2021) The disease course of COVID-19 is unpredictable, and even in the same patient viral reactivation may have differing severity. The use of anti-CD20 therapy during the COVID-19 pandemic likely requires careful consideration of continuing or delaying therapy, especially in circumstances with recent SARS-CoV-2 infection or comorbidities that increase infection risk, such as hypogammaglobulinemia.

Conflict of Interest / Role of Funding Source

Disclosures

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