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Case Report

Successful use of casirivimab/imdevimab anti-spike monoclonal antibodies to enhance neutralizing antibodies in a woman on anti-CD20 treatment with refractory COVID-19

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ABSTRACT

Management of COVID-19 patients with humoral immunodeficiency is challenging. We describe a woman with COVID-19 with multiple relapses due to anti-CD20 monoclonal antibody treatment. She was successfully treated with casirivimab/imdevimab and confirmed to have neutralizing antibodies. This case suggests that monoclonal antibodies have therapeutic and prophylactic value in patients with humoral immunodeficiency.

1. Introduction

Humoral immunity plays a major role in the elimination of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals with coronavirus disease (COVID-19). Humoral immunity contributes to the production of neutralizing antibodies by B-lymphocytes, which are considered to be important for viral clearance during acute infection or controlling disease progression during the chronic phase [1,2]. Patients treated with anti-CD20 monoclonal antibodies (mAbs) have a poor prognosis and are prone to relapses if they develop COVID-19 because the production of these antibodies is suppressed [3,4]. Casirivimab/imdevimab is a cocktail of monoclonal antibodies with neutralizing activity against SARS-CoV-2 [5]. It has been shown to prevent disease progression in COVID-19 patients at risk of severe disease [6,7]. The drug is thought to provide passive immunity due to its neutralizing antibody activity [8], so it may be an effective treatment for COVID-19 patients on anti-CD20 mAbs treatment, which suppresses antibody production. Here, we describe a patient who developed refractory COVID-19 while receiving maintenance treatment with anti-CD20 mAbs and was successfully treated with casirivimab/imdevimab.

2. Case presentation

A 58-year-old woman who had been treated for follicular lymphoma presented to another hospital with cough and sore throat. After remission, she had been given rituximab every 2 months for 6 months to prevent recurrence of the follicular lymphoma. Two days after the administration of rituximab, she developed cough and sore throat and sought medical care. Four days after the onset of symptoms, her SARS-CoV-2 quantitative reverse transcription polymerase chain reaction (qRT-PCR) test result was positive. Although she was admitted to the

Abbreviations: COVID-19, coronavirus disease; CT, computed tomography; mAbs, monoclonal antibodies; NT_{50}, 50% neutralizing titer; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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same hospital, she had mild symptoms and did not require oxygen administration during the course of her hospitalization. Six days after admission, her symptoms improved spontaneously without any treatment including casirivimab/imdevimab and she was discharged. However, her cough and fever recurred 8 days after discharge. She was readmitted to the hospital and treated with remdesivir for 5 days and dexamethasone 6 mg daily. Her fever rapidly resolved, but flared up when dexamethasone was tapered to prednisolone 10 mg daily on day 16 of readmission. As she developed hypoxemia and lung infiltrates were visible on a chest computed tomography (CT) scan (Fig. 1A), baricitinib 4 mg daily was initiated; the corticosteroid was switched from prednisolone to dexamethasone 6 mg daily; and she was treated with another 5-day course of remdesivir. Her hypoxemia and fever temporarily improved and the corticosteroid was gradually tapered, but on day 35 after admission, the fever recurred when dexamethasone was switched to prednisolone 10 mg daily. Dexamethasone 6 mg daily was reinitiated and oral levofloxacin 500mg daily was started because her unresolving pneumonia was considered to be a concomitant bacterial pneumonia with COVID-19. She continued to have fever and dyspnea after tapering of corticosteroids and her SARS-CoV-2 antigen test results were positive with a high titer. In addition, chest CT revealed new lung infiltrates (Fig. 1B). She was transferred to our hospital on day 55 after admission due to a lack of response to COVID-19 treatment.

On admission to our hospital, she was afebrile, had a blood pressure of 111/54 mmHg, heart rate of 89 beats/min, and respiratory rate of 18 breaths/min with oxygen saturation of 98% on 1 L/min of oxygen, and had bilateral fine crackles on chest auscultation. Laboratory test results showed leukocytes, 4640 cells/μL, 95% neutrophils; hemoglobin, 10.7 g/dL; platelets, 312,000/μL; albumin, 3.1 g/dL; lactate dehydrogenase, 443 U/L; C-reactive protein, 4.92 mg/dL; IgG, 273 mg/dL (normal range: 861–1747 mg/dL); beta-D-glucan, 16.0 pg/mL (normal range: < 20.0 pg/mL). A nasopharyngeal swab sample tested positive for SARS-CoV-2 on qRT-PCR testing, and genomic sequencing (see Appendix) revealed an N501Y mutation. No pathogens were detected by a FilmArray respiratory panel test of a nasopharyngeal swab sample and there was no evidence of coinfection with another respiratory pathogen, such as *Pneumocystis jirovecii*.

We continued treatment with oral dexamethasone 6 mg daily. We attributed the persistence of COVID-19 to humoral immunodeficiency induced by anti-CD20 mAbs and suppression of neutralizing antibody production, and administered remdesivir for 5 days and neutralizing monoclonal antibody casirivimab/imdevimab on day 6 of hospitalization. The patient's hypoxemia improved on day 8 and she was discharged on day 16 after confirming negative for SARS-CoV-2 on nasopharyngeal qRT-PCR testing on days 12 and 13. The corticosteroids were tapered over the course of a month, with no recurrence of fever or dyspnea. Chest CT findings on day 37 (after the discharge) showed that the infiltrates had almost disappeared (Fig. 1C). The virus isolated from

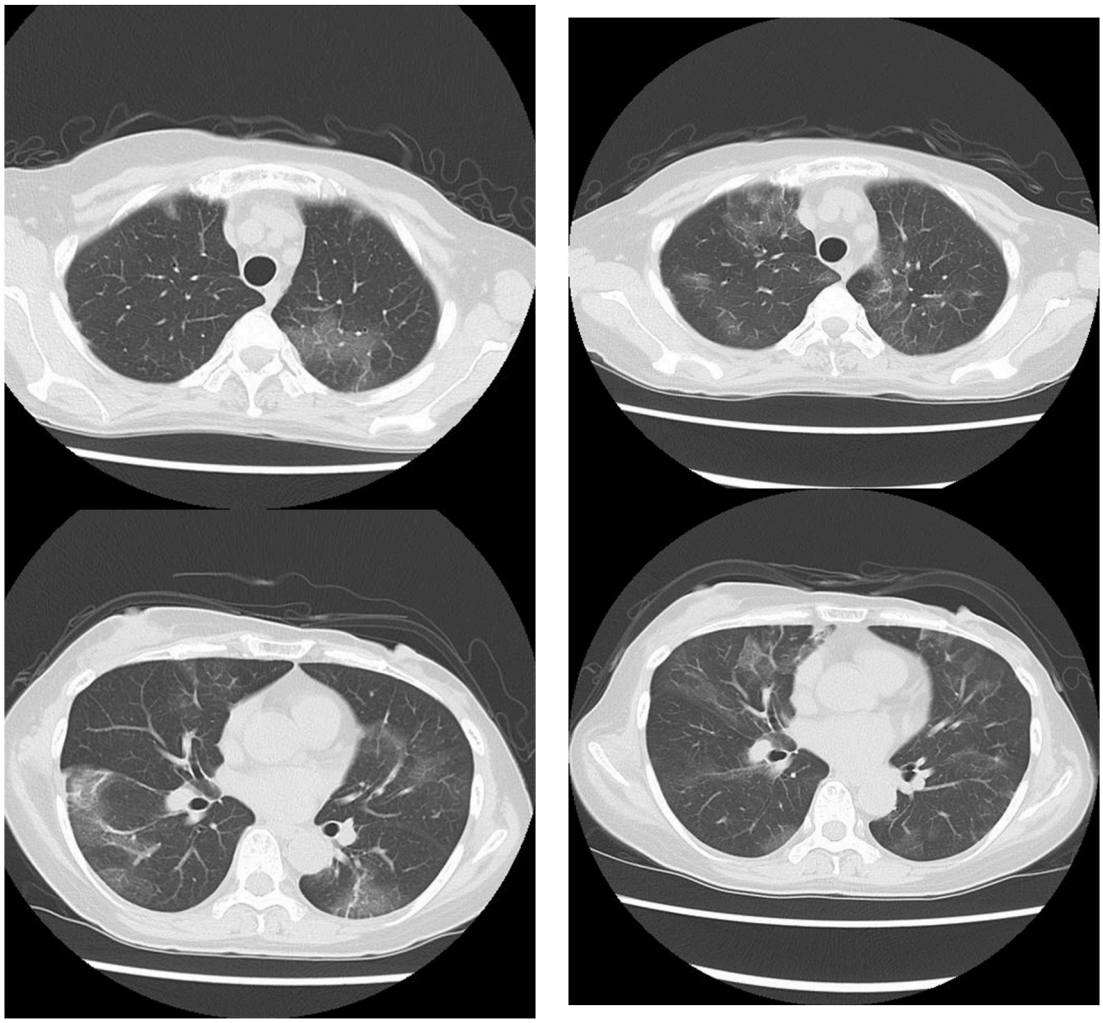

Fig. 1. Chest computed tomography (CT) showing COVID-19-related lung lesions. (A) Chest CT performed on day 21 of readmission showing bilateral lung infiltrates; (B) follow-up chest CT performed on day 47 of readmission showing new lung infiltrates; (C) follow-up chest CT performed on 50 days after admission to our hospital (after discharge). The lung infiltrates have almost disappeared.

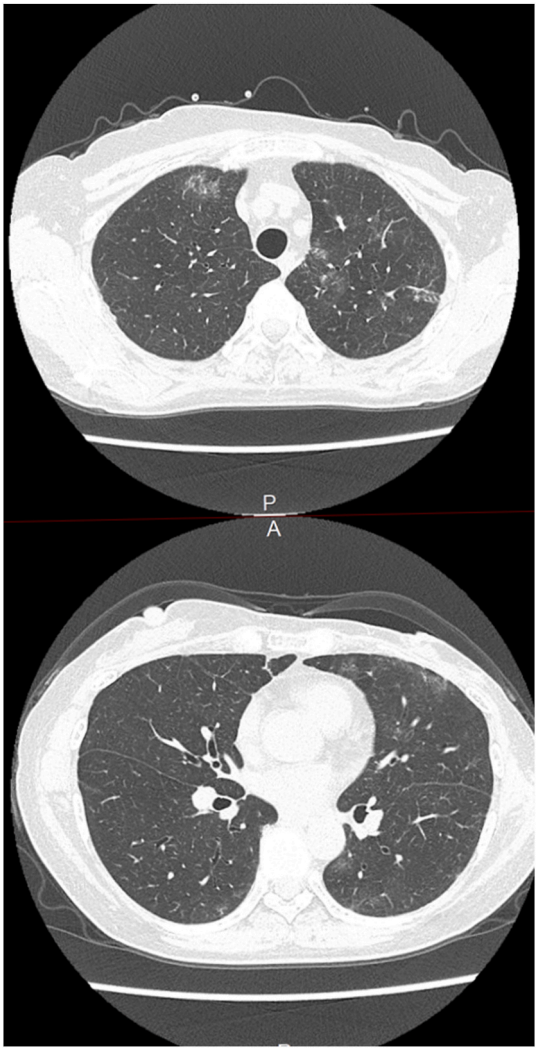

Fig. 1. (*continued*).

the nasopharyngeal swab sample collected on hospital admission had no remdesivir-related drug resistant amino acid mutations in the RNA-dependent RNA polymerase (RdRp) region. The serum 50% neutralizing titer (NT_{50}) on hospitalization (prior to casirivimab/imdevimab administration) was below the limit of detection (<40-fold), but increased to 55,700-fold on day 8 (2 days after casirivimab/imdevimab administration), and then gradually decreased to 41,730-, 44,360-, and 26,380-fold on days 12, 15, and 37 (after discharge), respectively (Fig. 2).

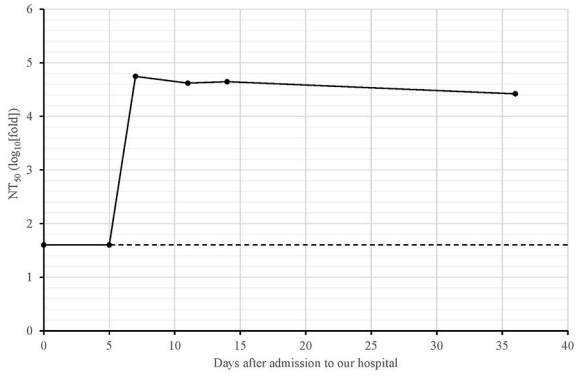

Fig. 2. Changes in neutralizing activity levels against SARS-CoV-2 over the course of hospitalization. The patient was treated with casirivimab/imdevimab monoclonal antibodies on day 6 of hospitalization, leading to a sharp increase in her neutralizing antibody levels. The neutralizing antibody levels gradually declined over the following month, but remained high. The assay detection limit (40-fold dilution) is indicated as a dashed line. NT_{50}, 50% neutralizing titer.

3. Discussion

The clinical course of this patient raises two important clinical issues. First, monoclonal antibody therapy with casirivimab/imdevimab may be effective for treating COVID-19 patients on anti-CD20 mAbs treatment. Second, the administration of casirivimab/imdevimab to patients on anti-CD20 mAbs treatment may also prevent SARS-CoV-2 reinfection.

Recurrence of SARS-CoV-2 infection in patients on anti-CD20 mAbs treatment is common, and these patients are often difficult to treat [4], possibly because low levels of neutralizing antibodies are associated with prolonged viral shedding [9]. In this patient, SARS-CoV-2 was isolated from nasopharyngeal swabs collected after transfer to our hospital, suggesting the presence of live virus capable of replication for more than 2 months after the onset. Although her symptoms had repeatedly improved and worsened, we suspected a relapse rather than a reinfection based on the information about the SARS-CoV-2 variant in this patient identified by genomic sequence, the prevalence of SARS-CoV-2 variant at the time in Japan, and the lack of her history of

contact with other COVID-19 patients. This is consistent with the finding that relapses are common in COVID-19 patients on anti-CD20 mAbs treatment [4].

COVID-19 convalescent plasma, remdesivir, and corticosteroids are sometimes used to treat refractory cases [4]; however, there is no established treatment for refractory COVID-19. One case report demonstrated the effectiveness of casirivimab/imdevimab in patients with COVID-19 with B-cell depletion [10], but to the best of our knowledge, this is the first case in which viral culture confirmed persistent infection and in which an increase in neutralizing antibody titer was documented after the administration of casirivimab/imdevimab. Considering the pharmacological mechanism of the drug, monoclonal antibody therapy of casirivimab/imdevimab is likely to be effective in situations where the viral load is high and antibody production is low, and may be less effective in patients with strong inflammatory responses. In patients with COVID-19 on anti-CD20 mAbs treatment, antibody production is often suppressed, making viral clearance difficult, so theoretically, casirivimab/imdevimab are likely to be beneficial.

In addition, the administration of casirivimab/imdevimab to patients on anti-CD20 mAbs treatment may also prevent SARS-CoV-2 reinfection. Some reports suggest that the effectiveness of COVID-19 vaccines may be reduced in patients on anti-CD20 mAbs treatment due to diminished humoral immune responsiveness [11,12]. However, this patient's serum neutralizing antibodies remained remarkably high for at least one month after administration of casirivimab/imdevimab, considering the results of a study of the neutralizing antibody titer after COVID-19 mRNA vaccination (BNT162b2) in healthy individuals [13]. Although it is unclear how long neutralizing antibodies persist, monoclonal antibody therapy with casirivimab/imdevimab may be useful for COVID-19 prophylaxis in patients with humoral immunodeficiency, in whom vaccine efficacy is low. According to the manufacturer, COVID-19 prophylaxis with casirivimab/imdevimab lasts for 2–8 months [14].

In summary, casirivimab/imdevimab may be effective for both treatment of COVID-19 and prevention of SARS-CoV-2 infection in patients on anti-CD20 mAbs treatment. Currently, the number of patients receiving anti-CD20 mAbs treatment is increasing. The use of casirivimab/imdevimab should be considered in refractory cases of COVID-19 that occur in such patients. Moreover, future studies are needed to confirm the effectiveness of the monoclonal antibodies, not only in mild cases, but also in cases of refractory and relapsed COVID-19.

Authorship statement

All authors meet the ICMJE authorship criteria.

YM and KY wrote the manuscript, YM, KY, YN, SM, and MY collected the clinical data, JST, MK, and WS provided data of genome sequence and contributed methodological inputs, YT, KM, and HM provided data of serum neutralizing activity and viral culture, and contributed methodological inputs, All authors reviewed the manuscript critically.

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Declaration of competing interest

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Appendix. Methods used for SARS-CoV-2 genome sequencing

The SARS-CoV-2 genome sequence was determined using the Illumina COVIDseq test ARTIC V3 (Illumina, Inc. USA), performed according to the manufacturer's instructions. Briefly, viral RNA was extracted from nasopharyngeal swab sample, followed by cDNA synthesis, target amplification, and library preparation. The libraries were pooled, normalized, and sequenced on Illumina iSeq 100 System. Raw reads were analyzed through the Illumina BaseSpace DRAGEN COVID Lineage v3.5.4. The genome sequence determined in this study was submitted to the GISAID database (GISAID ID: EPI_ISL_8623342). The sequenced SARS-CoV-2 genome was classified into the nextstrain 20I clade (Alpha V1). No mutations were found in either the RNA-dependent RNA polymerase (RdRp) or the spike regions, except for key mutations of the Alpha variant.

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