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Short Communication

Casirivimab/Imdevimab for Active COVID-19 Pneumonia Which Persisted for Nine Months in a Patient with Follicular Lymphoma during Anti-CD20 Therapy

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ABSTRACT: Immunocompromised patients are more likely to develop severe COVID-19, and exhibit high mortality. It is also hypothesized that chronic infection in these patients can be a risk factor for developing new variants. We describe a patient with prolonged active infection of COVID-19 who became infected during treatment with an anti-CD20 antibody (obinutuzumab) for follicular lymphoma. This patient had persistent RT-PCR positivity and live virus isolation for nine months despite treatment with remdesivir and other potential antiviral therapies. The computed tomography image of the chest showed that the viral pneumonia repeatedly appeared and disappeared in different lobes, as if a new infection had occurred continuously. The patient's SARS-CoV-2 antibody titer was negative throughout the illness, even after two doses of the BNT162b2 mRNA vaccine were administered in the seventh month of infection. A combination of monoclonal antibody therapy against COVID-19 (casirivimab and imdevimab) and antivirals resulted in negative RT-PCR results, and the virus was no longer isolated. The patient was clinically cured. During the 9-month active infection period, no fixed mutations in the spike (S) protein were detected, and the in vitro susceptibility to remdesivir was retained. Therapeutic administration of anti-SARS-CoV-2 monoclonal antibodies is essential in immunocompromised patients. Therefore, measures to prevent resistance against these key drugs are urgently needed.

The mortality of individuals infected with coronavirus disease 2019 (COVID-19) is reported to be 1–3% (1). This disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is infectious for approximately 8–10 days after its onset (1). However, in immunocompromised patients, mortality is generally higher, and in patients asymptomatic or post-recovery, prolonged RT-PCR positivity and virus isolation have been reported (2,3). These risks appear to be higher in patients receiving anti-CD20 therapy (4). In this report, we describe a patient with symptomatic COVID-19 which persisted for nine months, and with which he had been infected during anti-CD20 therapy for follicular lymphoma. On the ethical approval for the present study, the patient provided written informed consent for the publication of the study. Off-label use of favipiravir, hydroxychloroquine, ciclesonide, ivermectin, and camostat was granted by the IMSUT off-label drug use board, with the consent of the patient. Laboratory work was conducted with ethical approval granted by the ethics board of the Institute of Medical Science, University of Tokyo (2019-71-0201).

A 68-year-old man with follicular lymphoma (grade 2) presented with chills and a fever. Two days prior, he had received an eighth course of maintenance therapy with bimonthly obinutuzumab. The patient's lymphoma was diagnosed two years ago and showed complete

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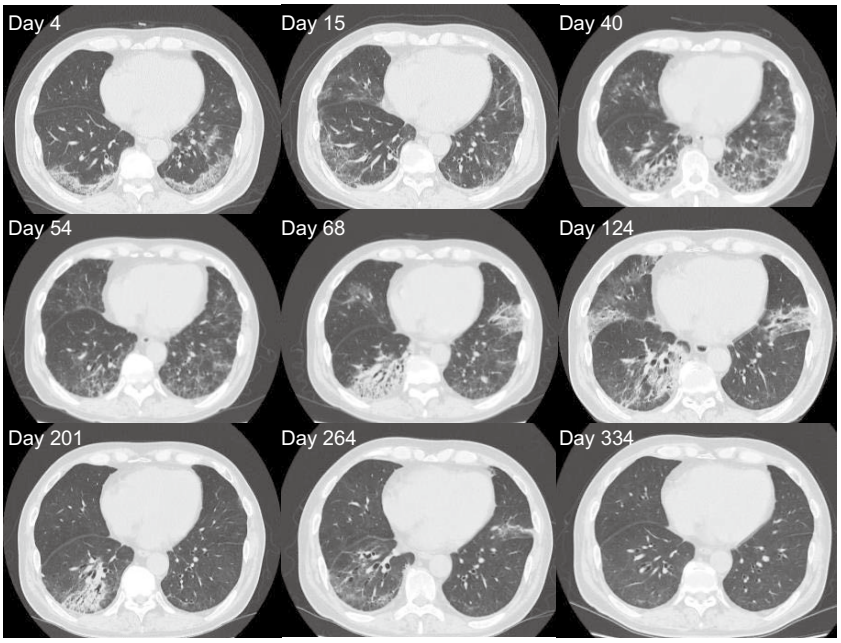

Fig. 1. Chest computed tomography images of persistent active COVID-19 pneumonia over nine months.

remission 15 months ago, after receiving six courses of obinutuzumab with bendamustine.

On the sixth day after the onset of symptoms, COVID-19 was confirmed by RT-PCR using BD SARS-CoV-2 N1 and N2 reagents with the BD-MAX system. The patient was then admitted to our hospital. Chest computed tomography (CT) revealed bilateral ground-glass opacity (GGO); however, oxygen therapy was not required during the first hospitalization. Vital signs were as follows: body temperature, 37.1°C; blood pressure, 158/96 mmHg; pulse rate, 77 beats/min; respiratory rate, 18 breaths/min; and saturation of percutaneous oxygen (SpO_2), 96% (ambient air). Blood samples showed a white blood cell count of 1,910 cells/μL (lymphocyte count, 315 cells/μL), lactate dehydrogenase level of 406 U/L, ferritin level of 867 ng/mL, and C-reactive protein level of 5.72 mg/dL. Only symptomatic treatments were administered. The patient remained afebrile after day 9 and was discharged on day 12. After discharge, the patient exhibited a low-grade fever of approximately 37.0°C, and on day 14, experienced shortness of breath on exertion. On day 15, he was hospitalized again because of hypoxemia, exhibiting SpO_2 levels of 90–94% while breathing ambient air. The patient's body temperature was 37.2°C on admission. Initially, the patient's symptoms and vital signs were carefully monitored and symptomatic treatment was administered. However, on day 20, the patient exhibited a high fever of 39°C, and oral dexamethasone (6 mg) treatment was started. Treatment was stopped shortly after the patient became afebrile, and his fever and hypoxemia subsequently deteriorated again. Corticosteroid treatment with prednisolone was restarted; however, no clear improvement was observed. As the patient's symptoms persisted and the RT-PCR cycle threshold (Ct) remained low (between 20–25 cycles) after one month, virus isolation was attempted, and infectious virus was detected in the sample taken on day 33. Remdesivir was administered, and the hypoxemia and lung images improved. However, after stopping remdesivir treatment, the fever and hypoxemia relapsed with radiographic deterioration in pneumonia.

Seven courses of 14–28 days of remdesivir was administered without any apparent adverse events but did not lead to virological eradication and clinical cure. While remdesivir was administered, the fever and inflammatory biomarkers improved, and the Ct value increased temporarily by approximately 5. However, RT-PCR did not yield negative results, and the virus was persistently isolated, suggesting that the virus could not be eliminated. The patient's symptoms flared up every time approximately a week after remdesivir treatment was discontinued. In the CT image of the chest, GGO repeatedly appeared and disappeared in different locations, rather than exacerbating the original region (Fig. 1). Any available drugs which may be effective against SARS-CoV-2 in vitro, namely favipiravir, hydroxychloroquine, ciclesonide, ivermectin, and camostat were also tried (with or without remdesivir), but monotherapy with these oral antivirals did not prevent recurrence of fever and pneumonia (Fig. 2). Additionally, two doses of the BNT162b2 mRNA vaccine (days 216 and 237 after onset) were administered, but no antibody production was observed within three weeks of the second dose. The patient was severely immunosuppressed with obinutuzumab chemotherapy and follicular lymphoma. The patient's lymphocyte count was approximately 100–400, and his CD4 count was approximately 50 during the infection.

The infectivity of the virus was monitored weekly and was consistently confirmed in vitro until day 258. As the patient was isolated in a single room, no variant viruses prevalent in Japan were detected. Amino acid changes in the spike (S) protein were sporadically and temporarily detected between days 49 and 258. The susceptibility of the isolates to remdesivir was confirmed on days 91 and 196.

On day 258, casirivimab and imdevimab (anti-

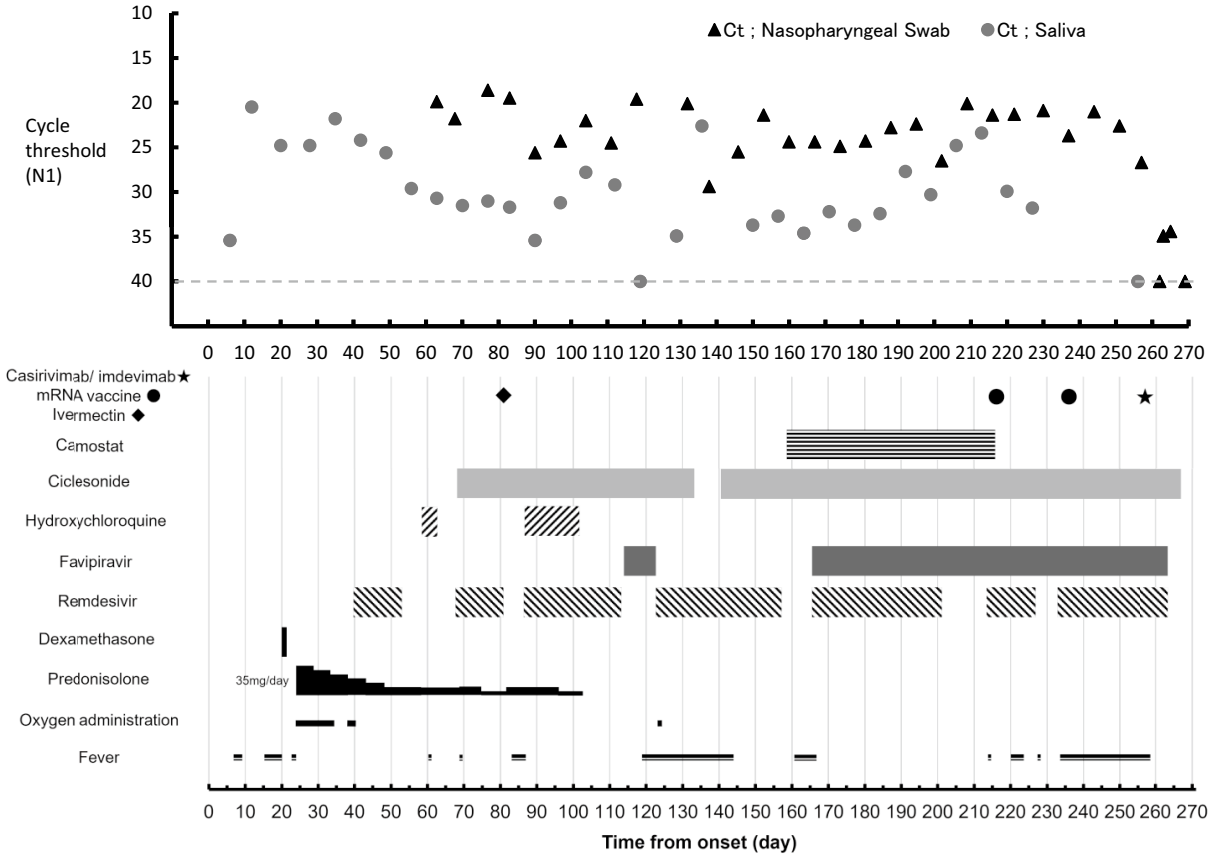

Fig. 2. Nine months of persistent active COVID-19 infection in a patient receiving anti-CD20 therapy for follicular lymphoma. Fever is defined as body temperature ≥37.5°C. Only cycle threshold (Ct) values for N1 were plotted with a dashed line indicating the negative cut-off value of 40.

SARS-CoV-2 monoclonal antibody) treatment was started, as it became available in Japan around that time. After a fever spike of 38°C in the evening, the patient became afebrile from day 259, and fever had not been recorded since then. On day 263, RT-PCR results became negative, and the virus was no longer isolated. The patient was discharged on day 271 since the initial onset of COVID-19 symptoms. Abnormal blood test results, including inflammatory markers and lymphocyte counts, improved after the administration of casirivimab and imdevimab. The IgG levels for SARS-CoV-2 S protein (Abbott Laboratories Inc. US) were 63,925 AU/mL 35 days after the administration of the monoclonal antibody therapy. No antibodies against the nucleocapsid protein were detected. Up to 232 days after monoclonal antibody therapy, the patient remained free from COVID-19 both clinically and virologically, and his IgG titer was 2,878 AU/mL.

Failure to acquire immunity against SARS-CoV-2, which can lead to a higher risk of severe disease, higher mortality, and prolonged infection, was reported in immunocompromised patients, including those living with HIV, solid-organ transplant recipients, and particularly those who were receiving anti-CD20 therapy (2–5). Seroconversion after two doses of the mRNA vaccine was reported to be achieved in only 20–40% of patients with hematological malignancies, and the response was noticeably weaker among those who had received anti-CD20 therapy (6). In the present case, this was likely due to the combination of obinutuzumab chemotherapy and follicular lymphoma. Considering that the administration of monoclonal antibodies achieved clinical and virological cure, we conclude that both humoral and cell-mediated immunity are needed for the clearance of SARS-CoV-2.

Chemotherapy with anti-CD20 antibodies (e.g. rituximab and obinutuzumab) was originally developed as a treatment for B-cell hematological malignancies; however, it is also used for a variety of autoimmune diseases. Anti-CD20 antibodies bind to the CD20 antigen of B cells and induce complement- or antibody-dependent cytotoxicity, resulting in an anti-tumor effect. This depletion of B cells persists after anti-CD20 therapy. In patients with chronic lymphocytic leukemia, some showed recovery of CD19+ B-cells approximately nine months after the last dose, while others did not even 18 months after the last dose (7,8). In patients who received anti-CD20 therapy, although CD4+ and CD8+ T-cell responses against SARS-CoV-2 were observed after infection and mRNA vaccination, antibody production was impaired (2,9).

The current case was successfully treated with casirivimab and imdevimab, achieving both clinical and virological cure. Casirivimab and imdevimab recognize different sites on the S protein of SARS-CoV-2 and inhibit its entry into host cells via the angiotensin-converting enzyme 2 receptor (10).

Patients with COVID-19 and an underlying immune deficiency will benefit the most from anti-SARS-CoV-2 monoclonal antibody therapy.

However, several case reports have indicated that SARS-CoV-2 variants could arise during persistent SARS-CoV-2 infection, particularly in immunocompromised patients (11). This is a major public health concern. Partial immunity in immunocompromised patients may contribute to the emergence of these variants in at least two ways. First, a prolonged period of infection can provide more opportunities for the virus to develop and accumulate random mutations. Second, because of the lower host immunity, the chances of survival of the infected virus under selective pressure caused by therapeutics is higher. This may lead to escaping mutants, virus variants that have developed drug resistance. Most reports of these escaping mutants were in immunocompromised patients after convalescent plasma use, with a few reports of escaping mutants in immunocompromised patients with severe COVID-19 after monoclonal antibody use. The antibody titer is known to be much lower in convalescent plasma than in monoclonal antibody products, and the risk of escaping mutants is higher with the use of single monoclonal antibody therapy than with combination (cocktail) monoclonal antibody therapy (12). Resistance to remdesivir seems to be rare; only recently has the development of remdesivir resistance in immunocompromised patients been reported (13).

A possible reason for the absence of new fixed mutations and retained susceptibility to remdesivir in this case could be that the combination therapy of remdesivir, favipiravir, and monoclonal antibody was curative, even in this immunocompromised patient, leaving no room for developing escaping mutants. A combination of remdesivir and favipiravir has been reported to work synergistically against SARS-CoV-2 in the hamster model (14). Combination therapies consisting of drugs with different mechanisms of action are regarded as the most reliable way to prevent the development of resistance, particularly in pathogens which human immunity alone cannot eliminate, including viruses (e.g. HIV), bacteria (e.g. tuberculosis) and parasites (e.g. malaria).

In early 2022, after the patient recovered, the Omicron variant became dominant in Japan, impacting the use of available monoclonal antibody therapies. It has been reported that the neutralizing antibody binding ability of monoclonal antibodies against Omicron variants decreased, while antivirals retained their efficacy (15). Based on these findings, casirivimab and imdevimab are no longer used for Omicron BA.1. Sotrovimab, which was effective against BA.1, was shown to be less effective against Omicron BA.2; therefore, it is no longer recommended.

The short- and long-term effects of COVID-19 on immunocompromised patients are of considerable importance. Therapeutic administration of anti-SARS-CoV-2 monoclonal antibodies can be considered for immunocompromised patients with reduced antibody-producing capacity, as these are the only curative treatments for immunocompromised patients. Currently available antivirals alone do not appear to cure COVID-19 in severely immunocompromised patients. The emergence of escaping mutants is of great concern for society, and is critical and life-threatening for immunocompromised patients. The development of new monoclonal antibody products, strategic use of these products to prevent the development of resistance, including combination therapies with antivirals, and continuous monitoring of the efficacy of these available drugs against circulating variants are needed.

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Conflict of interest None to declare.

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