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Case Report

Prolonged SARS-CoV-2 infection associated with long-term corticosteroid use in a patient with impaired B-cell immunity

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ABSTRACT

Corticosteroids are widely used to treat severe COVID-19, but in immunocompromised individuals, who are susceptible to persistent infection, long term corticosteroid use may delay viral clearance. We present a case of prolonged SARS-CoV-2 infection in a man with significantly impaired B-cell immunity due to non-Hodgkin lymphoma which had been treated with rituximab. SARS-CoV-2 shedding persisted, despite treatment with remdesivir. Viral sequencing confirmed the persistence of the same viral strain, ruling out the possibility of reinfection. Although SARS-CoV-2 IgG, IgA and IgM remained negative throughout the treatment period, after reduction of the corticosteroid dose, PCR became negative. Long-term corticosteroid treatment, especially in immunocompromised individuals, may result in suppression of cell-mediated immunity and prolonged SARS-CoV-2 infection.

1. Introduction

Corticosteroids are widely used to treat severe COVID-19, but in immunocompromised individuals, who are susceptible to persistent infection, long term corticosteroid use may delay viral clearance.

B-cell depletion caused by rituximab impairs the adaptive immune response and the ability to produce neutralizing antibodies, and long-term use of corticosteroids may weaken the cell-mediated immune response, resulting in persistent infection.

We present a case of prolonged SARS-CoV-2 infection in a patient with significantly impaired B-cell immunity due to non-Hodgkin lymphoma, which had been treated with rituximab, who recovered after the dose of corticosteroids was decreased.

2. Case report

On September 7, 2020, a 51-year-old man with a history of non-Hodgkin lymphoma presented to his doctor with fever and was hospitalized. He had been treated with rituximab, which had last been administered in June 2020 (Fig. 1). SARS-CoV-2 polymerase chain reaction (PCR) performed on a nasopharyngeal swab was positive, confirming the diagnosis of COVID-19. Twelve days after admission, he developed a high fever and hypoxia. More than 10 days had passed since the onset, so the symptoms were thought to be organizing pneumonia, and dexamethasone 6 mg/day was started. Temporarily, he needed 8 L of oxygen, but after starting steroid therapy his fever and respiratory status improved. After 10 days of dexamethasone administration, there was still a demand for oxygen, so 40mg prednisone was restarted as an organized pneumoniae after COVID-19 infection. The prednisone dose was reduced to 30 mg, and he was discharged from hospital on October 24, 2020.

However, 5 days after discharge, he was readmitted due to a recurrence of fever. When the dose of prednisone was increased to more than 35 mg per day his fever declined, but with lower doses, the fever re-emerged. This pattern occurred repeatedly. Additionally, during the 3 months of treatment, SARS-CoV-2 PCR tests of nasopharyngeal swabs

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remained positive. For further treatment, he was transferred to our hospital on November 30, 2020.

He had no fever on admission to our hospital on a dose of 35 mg of prednisone per day. We thought that the long-term use of corticosteroids may be delaying clearance of SARS-CoV-2 virus, so we reduced prednisone to 20 mg, and he was discharged on December 9, 2020, with no symptoms. In order to determine the amount of active virus, we submitted a sputum sample and nasopharyngeal swab for viral testing.

However, the day after discharge, he developed fever again and was readmitted to our hospital on December 16, 2020. Viral isolation testing revealed viable virus (with a cytopathic effect on Vero E6/TMPRSS2 cells) in both the nasopharyngeal swab and sputum samples from the previous admission. Therefore, to reduce the amount of virus, remdesivir was administered for 10 days. PCR testing of a nasopharyngeal swab was negative on December 24, 2020, and the patient was discharged again on December 28.

On January 19, 2021, the patient returned to the hospital with anosmia and a SARS-CoV-2 PCR test of a nasopharyngeal swab and viral culture were positive. We conducted SARS-CoV-2 whole-genome viral sequencing of virus isolated from sputum specimens collected on December 3, 2020 (during the first admission to our hospital) and on January 19, 2021. Both viral isolates had the same mutation in common, indicating persistent infection with the same viral strain rather than reinfection (Fig. 2A).

At this time, the patient had no fever or hypoxia so we did not provide any treatment. A PCR test was negative a week later. The last administration of rituximab had been in June 2020. The effect of rituximab is thought to last about 6 months, so we assumed that the effect of rituximab had worn off and that his humoral immunity had recovered and cleared the virus. However, anti-SARS-CoV-2 IgG, IgA and IgM were all negative throughout his treatment, even after his SARS-CoV-2 PCR results became negative (Fig. 2B). We tapered the dose of prednisone and discontinued steroids on February 23, 2021. During the following 7 months of follow-up, the patient did not experience any subsequent relapses and did not require steroids.

3. Discussion

We encountered a case of prolonged SARS-CoV-2 infection in a patient with significantly impaired B-cell immunity due to non-Hodgkin lymphoma treated with rituximab. SARS-CoV-2 PCR and virus culture remained positive 133 days after the first PCR test. The ability to produce neutralizing antibodies was evaluated repeatedly, but no IgG, IgA or IgM production was observed, indicating probable rituximab-induced B cell dysfunction. Moreover, phylogenetic analysis indicated that viruses in the specimens collected on December 3, 2020 and January 19, 2021 were identical and consistent with persistent infection. In some cases, SARS-CoV-2 PCR positivity is known to persist longer than a few weeks, but "positive" PCR results does not necessarily mean presence of viable virus [1,2]. Therefore, we at first thought this theory was also true to our case, meaning that there was no longer viable virus at the first discharge. Then we permitted him to discharge, but we could not confirm the PCR test negative, so we asked him to refrain from going to work. However, it revealed that virus culture was also positive. Thus, we tried to reduce the amount of viable virus with remdesivir and decrease of corticosteroids, and moreover, the next time of discharge, we confirmed PCR negative twice.

As to transmission of the virus, throughout our treatment and follow-up period, there was no episode of infection of the people around the patient. He lived with his wife, who transmitted the virus to the patient, and she never got reinfection.

Considering the theory above, there was some risk of transmission at the first discharge. Presence of symptoms such as cough is also known to affect transmission risk [3], and in this case the only symptom was fever, which might be one of the factors that prevented the transmission.

A literature review revealed other 21 cases of persistent SARS-CoV-2 infection in immunocompromised hosts [4–10] (Table 1). In the 14 cases in which the treatment prior to developing SARS-CoV-2 infection was specified, nine patients had been treated with anti-CD20 monoclonal antibody (seven used rituximab, one used obinutuzumab and one used mosunetuzumab). Thus, it appears that anti-CD20 treatment is a risk factor for prolonged SARS-CoV-2 infection.

In the nine cases in which treatment after developing SARS-CoV-2 infection was reported, six patients were treated with remdesivir. In all six cases, the patient's symptoms recovered, but the infection subsequently relapsed. Therefore, remdesivir may play a role in decreasing viral load, but is insufficient to clear infection, especially in immunocompromised patients. Four of the six patients transfused with convalescent plasma were reported to have recovered, so insertion of SARS-CoV-2 antibody from outside such as convalescent plasma or monoclonal antibodies may be an option for treating immunocompromised patients with persistent infection.

In our patient, as in previous reports, symptoms decreased after administration of remdesivir, but he relapsed and his SARS-CoV-2 PCR result became positive again. Our patient differs from the patients described in previous case reports in that he recovered without any antibody treatment.

In this case, it could be concluded that cell-mediated immunity

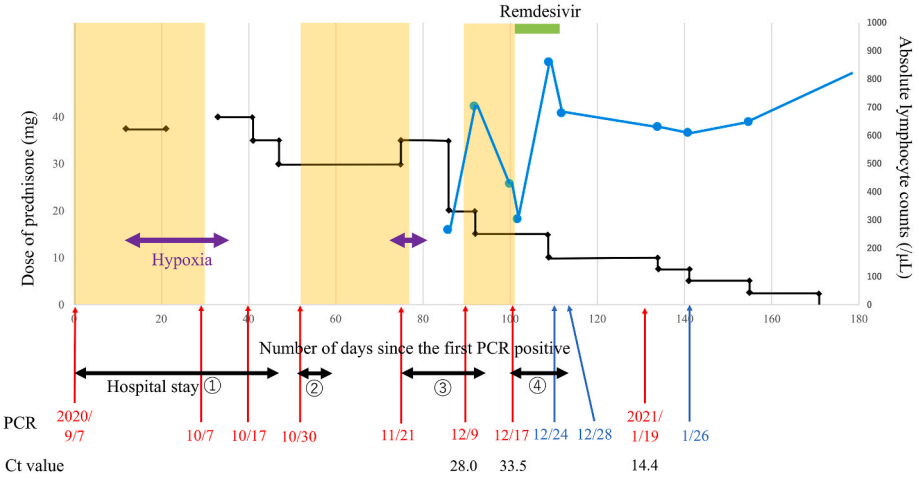
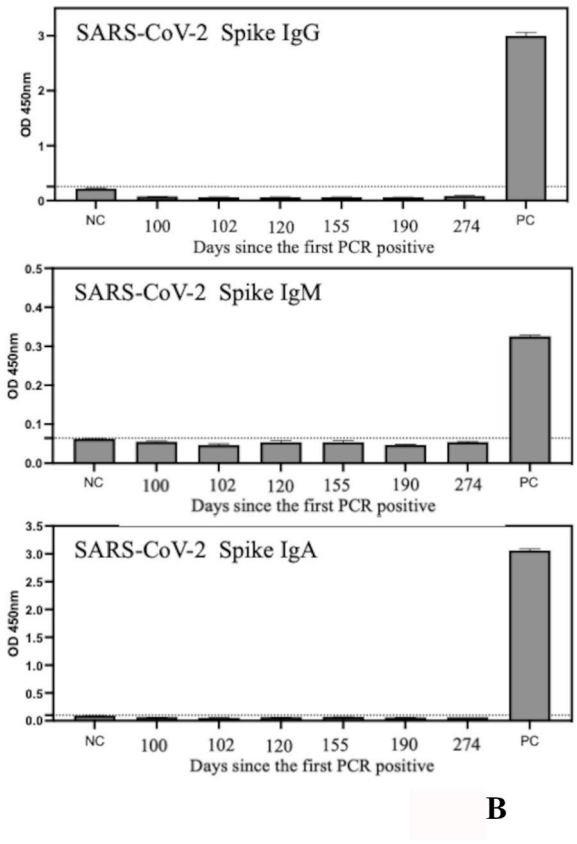


Fig. 1. Timeline of the patient. The dose of prednisone is shown in black and lymphocyte count is shown in light blue on the graph. A dexamethasone dose of 4 mg is counted as equivalent to prednisone 25 mg. The SARS-CoV-2 PCR results shown in red were positive, and those shown in blue were negative. Ct value shows cycle threshold value in PCR tests. The four hospital admissions are shown as thick black lines. The orange area represents the period of fever of 38 °C or higher.

position	Reference (Wuhan-Hu-1:MN908947.3)	2020/12/3	2021/1/19
241	C	T	T
313	C	T	T
3037	C	T	T
4058	C	T(55.35%) C(44.65%)	C
4105	G	G(53.93%) T(46.01%)	T
6021-6118	omission	No mutation	No mutation
6734	G	G	A
8917	C	T	T
10202	C	C(55.89%) T(44.05%)	T
11083	G	G(58.75%) T(31.52%) -(9.7%)	T(78.73%) -(21.11%)
11219	A	A	G
14408	C	T	T
14514	T	T(83.13%) C(16.87%)	T
14621	C	T	T
17363	T	T(84.47%) C(15.53%)	T
18167	C	T	T
21518	G	T	T
21575	C	C	C(69.88%) T(29.65%)
23403	A	G	G
25513	C	C(56.15%) T(43.85%)	T
26681	C	C(58.75%) T(41.25%)	T
27761-28254	omission	No mutaion	deletion
28881-28883	GGG	AAC	AAC
28975	G	T	T
29081	G	G(61.09%) T(38.86%)	T
29085	C	T(61.19%) C(38.77%)	C
29940	G	G(79.27%) T(20.73%)	G

A

Fig. 2A. Whole-genome viral sequencing from sputum specimens of December 3, 2020 and January 19, 2021. Both specimens have the same mutations, which indicates persistent infection, rather than reinfection.



B

Fig. 2B. The repeated tests for SARS-CoV-2 IgG (top), IgM (middle), and IgA (bottom) remained negative throughout the treatment period. The bars on the left (NC) and right (PC) of each graph show the optical density values for the negative and positive control, respectively.
Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ig, Immunoglobulin; PC, Positive control.

cleared virus in the absence of anti-SARS-CoV-2 antibodies. Coordinated immune responses of humoral and cell-mediated immunity are important for SARS-CoV 2 recovery [11], and CD8 T-cell responses are thought to be an important determinant of persistence [12].

In this case, use of rituximab is likely to have been the main cause of persistent infection, but decreasing the dose of corticosteroids might have helped to stimulate cell-mediated immunity. Actually, as the dose of corticosteroids was decreased, a slight upward trend in absolute lymphocyte counts was observed. T cells are affected more than B cells by corticosteroids [13], so in this case, we could assume that the decrease in lymphocyte counts reflected the decrease in T cells, and as the T cell counts recovered, cell-mediated immunity also recovered. Recently, the RECOVERY trial showed the effectiveness of corticosteroids in severe cases [14] and corticosteroids are now widely used. However, corticosteroids might be associated with a risk of prolonging SARS-CoV 2 shedding, especially in immunocompromised patients. Tang et al. [15] suggested that the early use of corticosteroids is a risk factor for prolonged virus shedding. This case supports this theory.

In conclusion, immunocompromised individuals are at risk of prolonged SARS-CoV-2 infection, and long-term use of corticosteroids, may aggravate this risk. Therefore, as the prolonged use of corticosteroids not only provides anti-inflammatory effects, but is also associated with delayed viral clearance due to cellular immunosuppression, it is important to consider early reduction of corticosteroid use in patients with SARS-CoV-2 infection, especially in immunocompromised patients.

Author statement

All authors meet the ICMJE authorship criteria;

Momoko Morishita and Manabu Suzuki managed the patient. Manabu Suzuki was responsible for the conception of the work and Morishita Momoko was responsible for the interpretation of data and draft of the work. Yoshie Tsujimoto, Akane Ishida, Masao Hashimoto, Satoru Ishii,

Table 1
21 cases of persistent SARS-CoV-2 infection in immunocompromised individuals.

	Age	Sex	Baseline	Baseline-Treatment	Treatment for COVID19
Taramasso et al.	70	M	Mantle cell lymphoma	Rituximab, Bendamustine, Cytarabine	NA
	50	F	Neuromyelitis Optica	Rituximab	NA
	47	F	MM	Dexamethasone, Cisplatin, Doxorubicin, Cyclophosphamide	NA
Baang et al.	70	M	Mantle cell lymphoma	Mosunetuzumab	Remdesivir, convalescent plasma
Aydillo et al.	NA	NA	haematopoietic stem cell transplantation	NA	NA
	NA	NA	haematopoietic stem cell transplantation	NA	NA
	NA	NA	haematopoietic stem cell transplantation	NA	NA
	NA	NA	Haematological malignany	NA	NA
Nakajima et al.	47	M	Follicular lymphoma	Obinutuzumab	Favipiravir
Avanzato et al.	71	F	CLL, hypogammaglobulinaemia	IVIG	convalescent plasma
Decker et al.	62	M	Heart transplantation	MMF, steroid, Cyclophosphamide	NA
Guetl et al.	NA	NA	X-linked agammaglobulinaemia	NA	lopinavir, ritonavir and hydroxychloroquine sulfate, convalescent plasma
Choi et al.	45	M	Antiphospholipid syndrome	Rituximab, steroid	Remdesivir
Daniel et al.	37	F	Follicular Lymphoma	Rituximab, Etoposide, Cisplatin, steroid, Cytarabine	Remdesivir, convalescent plasma
Phillip et al.	56	F	Follicular Lymphoma	Rituximab	Remdesivir, convalescent plasma
Marie et al.	50s	M	CLL	Cyclophosphamide, Rituximab, Fludarabine Phosphate	Remdesivir, convalescent plasma
Jennifer et al.	70s	M	B cell Lymphoma	NA	NA
Matthew et al.	73	M	MM	CAR-T cell therapy	Remdesivir
Hassan et al.	66	M	HIV	NA	NA
	71	M	Cardiac transplantation	steroid, Mycophenolic acid, Belatacept	NA
	35	M	RA	Rituximab	NA

Abbreviations: NA; Not; Available, MM; Multiple Myeloma, CLL; Chronic Lymphocytic Leukemia, HIV; Human Immunodeficiency Virus, RA; rheumatoid arthritis, IVIG; intravenous immunoglobulin, MMF; mycophenolate mofetil, CAR; chimeric antigen receptor, COVID-19; coronavirus disease 2019.

Jin Takasaki, Go Naka, Motoyasu Iikura, Shinyu Izumi were participated in the discussion for the treatment and gave the important suggestion. Masayuki Hojo and Haruhito Sugiyama reviewed and supervised the manuscript. Akihiro Matsunaga and Yukihito Ishizaka performed the immunological analysis. Keishi Ishizhima, Tsukasa Yamamoto, Yudai Kuroda, Takayuki Kanno, Tadaki Suzuki, and Ken Maeda performed the bacteriological, molecular, and genomic analyses. All authors have contributed significantly to the work and approved the final version of the manuscript.

Declaration of competing interest

There are no conflicts of interest in this study.

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