CASE REPORT

A case of COVID-19 reinfection in a hemodialysis patient: the role of antibody in SARS-CoV-2 infection

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Abstract

Hemodialysis patients are vulnerable to severe and lethal COVID-19, and their protective immunity against COVID-19 is not yet fully understood. Therefore, we report a case of COVID-19 reinfection in a hemodialysis patient 81 days after the first episode and discuss the role of antibodies in SARS-CoV-2 infection. A hemodialysis patient developed asymptomatic COVID-19 due to an outbreak in a hospital on October 29th, 2020. As he was hospitalized and did not develop any symptoms, he was discharged on November 9th. On January 18th, he presented with symptomatic COVID-19 due to close household contact. Then, he developed respiratory failure and was transferred to National Center for Global Health and Medicine if he would need intensive care. He recovered with oxygen inhalation, favipiravir, and steroid treatment, and was discharged on February 12th. To evaluate anti-SARS-CoV-2 antibodies during two hospital stays, we measured immunoglobulin (Ig) G specific for S1 subunit of Spike (S) protein of SARS-CoV-2 (IgG-S1) , IgG specific for the full-length S protein (anti-Spike IgG) and neutralizing antibodies. No seroconversion occurred 5 days after initial infection, the seroconversion of IgG-S1 was observed 10 days after the second infection. Similar to IgG-S1 antibody titer results, anti-Spike IgG and neutralizing antibodies increased from 12 days after the second infection. In conclusion, we experienced a case of COVID-19 reinfection in a hemodialysis patient 81 days after the first episode and showed the kinetics and role of antibodies in SARS-CoV-2 infection. Further studies are needed to understand SARS-CoV-2 reinfection risk in hemodialysis patients and its clinical significance.

Keywords COVID-19 · Reinfection · End-stage renal disease · Severe acute respiratory syndrome coronavirus 2 antibodies · Hemodialysis

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Introduction

At the end of 2019, coronavirus disease 2019 (COVID-19) has rapidly spread all over the world and resulted in a global pandemic [1, 2]. One of the main concerns is the duration of protective immunity to severe COVID-19 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) in recovered patients, and its protectivity against SARS-CoV-2 reinfection [3]. Recent studies reported that a previous infection offers some protection for at least 4–5 months in immunocompetent hosts, and seropositive recovered patients have been estimated to have 89% protection from reinfection [4–6].

Regarding hemodialysis (HD) patients, they are considered a highly vulnerable population to COVID-19 because of a higher probability of having comorbidities, such as diabetes and cardiovascular disease. Indeed, recent studies reported that patients on HD are at high risk for adverse outcomes of COVID-19, and the mortality rates from COVID-19 can reach as high as 20% [7, 8]. However, the duration and strength of protective immunity in HD patients with COVID-19 are not yet fully understood. Therefore, reports of SARS-CoV-2 reinfection in HD patients and their immune responses are very important to understand the protective immunity against reinfection. Here, we report a case of COVID-19 reinfection in an HD patient, which occurred 81 days after the first episode, and the role of antibodies in SARS-CoV-2 infection.

Case report

A 62-year-old man who was on maintenance HD for 5 years due to end-stage renal disease with type 2 diabetes presented with asymptomatic COVID-19 on October 29th, 2020. He had a medical history of hepatitis C and T2N0M0 stage II hepatocellular carcinoma (HCC), and he was in another hospital for the treatment of HCC when he was accidentally exposed to a confirmed COVID-19 patient due to outbreaks at the hospital. He was screened for a COVID-19 with reverse transcription polymerase chain reaction (RT-PCR) test using FilmArray RP v2.1 (Bio-Mérieux, Marcy-l'Etoile, France) using a nasopharyngeal swab sample, and tested positive (cycle threshold values are unavailable). Then, he was transferred to Okubo hospital, Tokyo, Japan, on October 30th, 2020. On admission, he had no symptoms, such as fever, cough, or abnormal smell and taste. His vital signs were normal, and a physical examination was unremarkable. We did not perform PCR retesting at our hospital. The laboratory data revealed a white blood cell count of $4.74 \times 10^3/\mu L$, hemoglobin level

of 10.6 g/dL, platelet count of $205 \times 10^3/\mu L$, lymphocytopenia as indicated by a lymphocyte count of $0.39 \times 10^3/\mu L$, C-reactive protein (CRP) level of 3.05 mg/dL, ferritin level of 430.85 ng/mL, aspartate transaminase level of 47 IU/L, alanine transaminase level of 85 IU/L, and D-dimer level of 0.97 µg/mL. High-resolution thorax computed tomography (CT) did not reveal any abnormalities suggesting COVID-19 (Fig. 1a). He did not develop any symptoms during hospitalization, and after confirming improvements in the CRP and lymphocytopenia levels, which were 0.83 mg/dL and $0.50 \times 10^3/\mu L$, respectively; he was discharged on November 9th.

On January 8th, 2021, his wife developed a fever and tested positive for COVID-19 with an RT-PCR test. He was then screened with COVID-19 RT-PCR on the next day due to close household contact and was negative. On January 18th, he presented with fever, wet cough, sore throat, and fatigue. He took the antigen test at the maintenance HD facility, which was positive. It had been 81 days, since he was initially diagnosed with COVID-19. Then, he was admitted to Okubo hospital again on January 25th. Upon
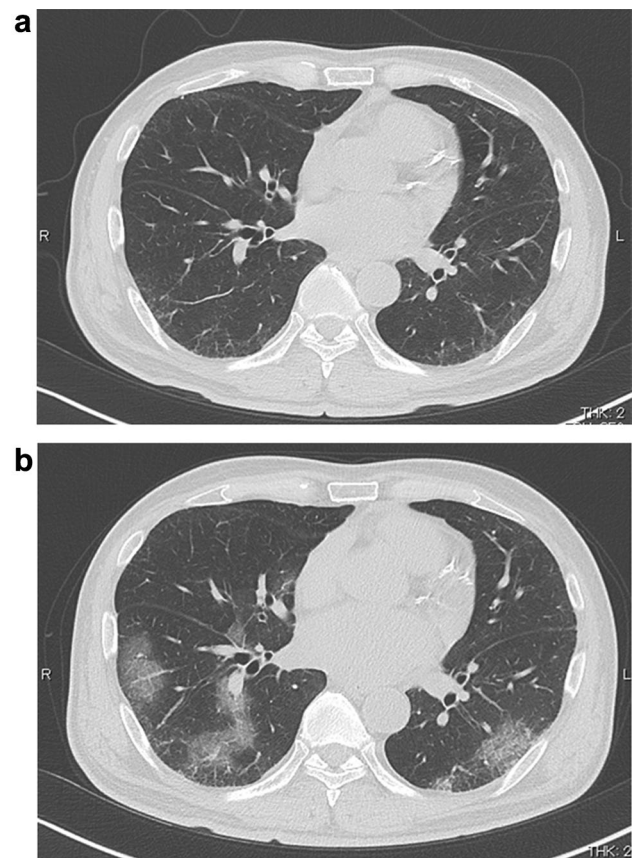

Fig. 1 a Initial axial chest computed tomography images did not show any abnormalities suggesting COVID-19. **b** Axial chest computed tomography images in the second episode showed moderate ground-glass opacities in bilateral lungs

examination, his temperature was 37.9 °C, pulse was 82 beats per minute, blood pressure was 131/79 mm Hg, respiratory rate was 20 breaths per minute, and oxygen saturation was 97% on room air. The physical examination was unremarkable. On this presentation, the patient's chest CT showed moderate ground-glass opacities in the lungs bilaterally (Fig. 1b). Laboratory data showed white blood cell count of 2.28×10^3 /μL, hemoglobin level of 11.8 g/dL, platelet count of 122×10^3, lymphocytopenia as indicated by lymphocyte count of 0.21×10^3 /μL, C-reactive protein level of 5.05 mg/dL, ferritin level of 333.33 ng/mL, aspartate transaminase level of 14 IU/L, alanine transaminase level of 14 IU/L, and D-dimer level of 1.10 μg/mL. The COVID-19 PCR test from a nasopharyngeal swab was conducted to assure the diagnosis and the result was positive (Cycle threshold values of *E* gene and *N* gene were 23.7 and 29.39, respectively). Favipiravir was started on the first day of admission to treat mild COVID-19. On January 27th, he developed respiratory failure and started receiving constant oxygen (3 L canula), after which we added dexamethasone 6 mg/day and heparin as prophylactic anticoagulation treatment. Okubo Hospital falls within the Tokyo Metropolitan public hospital network and is designated to provide inpatient care for COVID-19 patients who do not require high-flow oxygen or intensive care. Since he was at high risk of COVID-19, he was transferred on January 29th to National Center for Global Health and Medicine (NCGM), Tokyo, Japan in case he would develop severe illness and need intensive care. At NCGM, dexamethasone treatment was continued and oxygen requirement did not increase beyond 3 L. On January 30th, the constant oxygen requirement tapered to zero, and the fever was alleviated on the next day. The dexamethasone and heparin treatments were ended on the same day. However, he developed fever again on February 3rd and required continued isolation. Then, he was retransferred to Okubo hospital for observation and quarantine on February 4th. After confirming fever alleviation for more than 72 h, he was discharged on February 12th. To summarize, Fig. 2 shows the clinical course from the day; he was initially diagnosed with COVID-19 to the second infection episode.

To investigate the kinetics of antibody production against SARS-CoV-2, we measured the levels of immunoglobulin G (IgG) specific for the S1 subunit of S protein (IgG-S1) using iFlash 3000 chemiluminescence immunoassay analyzer (Shenzhen YHLO Biotech, China;) [9] and IgG specific for full-length S protein (anti-Spike IgG) using conventional ELISA [3]. According to the instructions, results with values ≥ 10 arbitrary units (AU)/mL for IgG-S1 and with values ≥ 0.087 OD 450 nm for anti-Spike IgG were considered positive. In addition, we evaluated the levels of neutralizing antibodies [3]. As shown in Table 1, the seroconversion of antibodies was not observed from days 0 to 5 after the onset of symptoms during the first episode of infection, while the seroconversion of IgG-S1 was observed at day 10 after the onset of symptoms during the second infection. Similar to

Fig. 2 Clinical time course
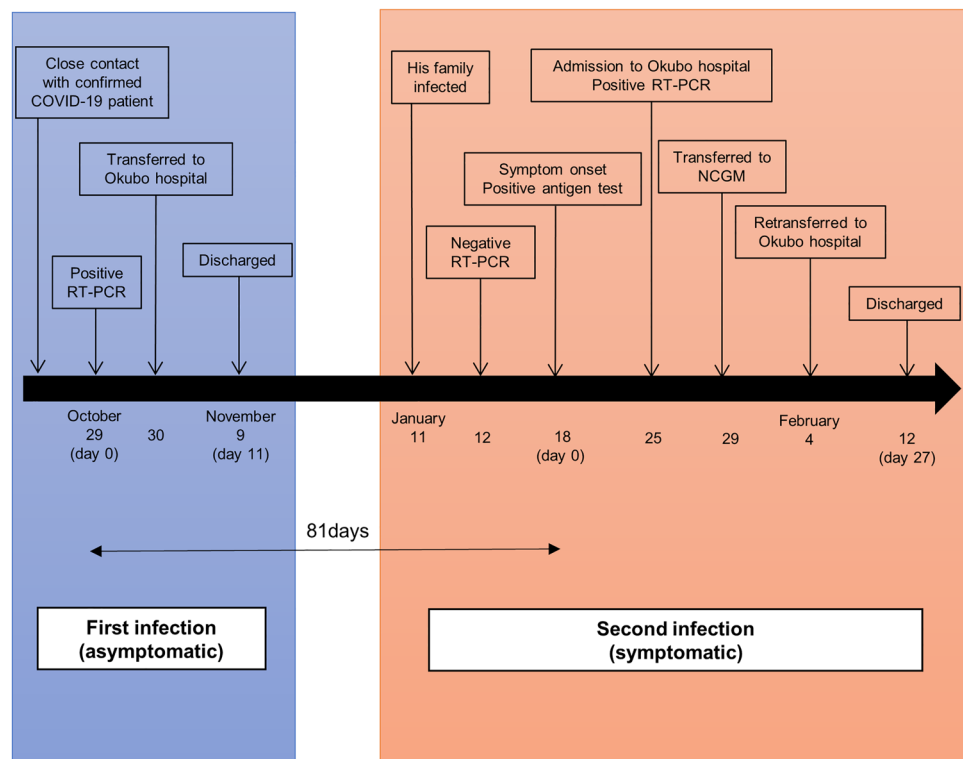
Table 1 Quantitative measurements of IgG-S1, anti-Spike IgG, and neutralizing antibodies in SARS-CoV-2 infection

Episode	Days after onset	IgG-S1[a]	Anti-Spike IgG[b]	Neutralizing antibodies[c]
First	1	0.36	0.073	< 20
	5	0.33	0.074	< 20
Second	8	1.5	0.078	< 20
	10	**11.44**	NA	NA
	11	**22.31**	NA	NA
	12	NA	**0.177**	**220**
	14	NA	**0.357**	**680**
	17	**617.76**	NA	NA
	21	**854.23**	NA	NA
	23	**760.74**	NA	NA

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, *NA* not available

[a]Results with values ≥ 10 arbitrary units (AU)/mL for IgG-S1 were considered positive

[b]Results with values ≥ 0.087 OD 450 nm for anti-Spike IgG were considered positive

[c]Neutralization titers are expressed as the dilution at which cytopathic effects were observed in 50% of the wells

Bolded areas indicate positive results

the trend in the IgG-S1 antibody titer results, the results of anti-Spike IgG and neutralizing antibody showed an increase starting 12 days after the onset of the second infection.

Discussion

We presented a case of COVID-19 reinfection in an HD patient. The patient was diagnosed with reinfection for the following reasons. First, we confirmed the negative test result between the first and second episodes. Second, the interval between the two episodes was 81 days. Although some patients have prolonged SARS-CoV-2 RNA virus shedding, the current consensus is that most patients are not infectious 20 days after the onset of symptoms [10–14]. Third, the patient came in close contact with infected people in both episodes. Although the possibility that the initial asymptomatic infection was a false-positive PCR test cannot be completely ruled out, the probability of false-positive tests is reported to be very low [15], and the improvement in CRP elevation and lymphopenia can be explained as a course of recovery from the disease, which suggests that the patient had a true coronavirus infection.

In this case, we evaluated the kinetics and role of antibodies in SARS-CoV-2 infection. We could not detect IgG seroconversion during the entire hospital stay for the first episode and up to 6 days after the onset of the second episode.

Possibly, the patient did not have an antibody response after the first infection, but this cannot be confirmed, because the first infection only had stored serum collected on days 1 and 5 after the onset of symptoms, while IgG seroconversion in HD patients usually occurs in the first to second week after the onset of symptoms, similar to non-HD patients [13, 16–18]. Another possibility is that there was indeed an antibody response after the first infection, but the antibody titer dropped below the detection limit of the assay. Previous studies have shown that patients with asymptomatic or mild symptoms have a limited initial humoral response to the virus, developing IgG antibodies with a half-life of about 36 days and that these low antibody titers may not provide adequate immunity [19]. HD patients who survive SARS-CoV-2 infection are reported to generate an antibody response that is well maintained and associated with a reduced frequency of reinfection, although fewer than 3% of patients show no evidence of humoral immunity at 6 months after the infection [20] and patients with lower responses may be at increased risk of reinfection [21]. The present case supports these studies and suggests that asymptomatic infections may not confer long-term protective immunity to all patients, thus, making them susceptible to reinfection. Inadequate protective antibody titer response after SARS-CoV-2 infection may be the cause of reinfection.

This report has some limitations. First, whole genome sequencing data among two episodes were not available. Nevertheless, considering the fact that the B.1.1.7 strain (alpha variant) was first identified in December 2020 in Japan and was responsible for more than 80% of community infections in May 2021 [22], the first and second episodes were thought to be caused by the native strain, B.1.1.7 strain (alpha variant). Studies in the general population have reported that reinfection by SARS-CoV-2 could occur with a low frequency of < 1% [23, 24]. Interestingly, a recent study demonstrated the possibility that previous infection by a native strain remains highly protective against reinfection by the alpha variant [25], presumably suggesting that the first infection contributes to the fact that this patient did not have a critical outcome. Second, there were limited samples for antibody evaluation. During the first episode, we only had samples on days 1 and 5 after the onset of symptoms, and the samples from the second episode did not match all the samples evaluated for IgG-S1 antibody, anti-Spike IgG, and neutralizing antibodies. Despite these limitations, to our best knowledge, this case is the first SARS-CoV-2 reinfection case in HD patients in Japan, and it showed the kinetics and role of antibodies in SARS-CoV-2 infection.

In conclusion, we experienced a case of COVID-19 reinfection in an HD patient, which occurred 81 days after the first episode, and showed the kinetics and role of antibodies in SARS-CoV-2 infection. Since hemodialysis patients are a vulnerable population with multiple risk factors for severe

COVID-19, further studies are needed to improve our knowledge on SARS-CoV-2 reinfection risk in HD patients and its clinical significance.

Declarations

Conflict of interest All the authors have declared no competing interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

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