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CASE REPORT

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Hospital-at-home care for immunodeficient patients with COVID-19: Approach to persistent COVID-19 infection

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Key Clinical Message: Patients with COVID-19 who have undergone B-cell depletion therapy could have prolonged SARS-CoV-2 infection; therefore, even in the hospital-at-home setting, primary care physicians should carefully consider the treatment regimen and the timing of ending isolations in such cases, and should not hesitate to consult with infectious disease specialists if necessary.

Abstract: We presented the first reported case of hospital-at-home care for a patient with persistent COVID-19 who had undergone B-cell depletion therapy. He received hospital-at-home care, including two courses of remdesivir; however, he ultimately failed to recover and was transferred to the hospital.

KEYWORDS

COVID-19, home care medicine, hospital-at-home, immunodeficiency, primary care

1 | INTRODUCTION

The increased patient surge during the coronavirus disease-2019 (COVID-19) pandemic put tremendous pressure on the healthcare systems. In Japan and other countries, many patients with COVID-19 were forced to stay in their homes due to lack of in-hospital beds, despite these patients requiring therapeutic fluid or oxygen administration.[1-3] To counter this problem, the Hospital at Home (HaH) system for patients with COVID-19 has become widespread in some countries.[4-6] In the HaH setting, physicians, nurses, and paramedics can provide medical treatment, including administration of intravenous fluid, oxygen, antibiotics, oral/intravenous antiviral drugs, and COVID-19 antibody drugs at patients' homes.[4-6] For example, in the United States, a hospital provides the HaH care system as a private service.[4] In Japan, some general practitioners provide HaH care at the request of local public health centers or local government admission control centers for COVID-19.[5] Specifically, local public health centers collect patients' information in the area, including basic characteristics, clinical information, and other necessary information, and appropriately allocate healthcare resources, including hospital beds and general practitioner visits. For the latter, the local public health centers request local general practitioners who are available to visit patients' houses and provide HaH care.[5]

Although the HaH system has become widespread during the pandemic, little is known about triaging patients who can be treated at home and those who require hospitalization. For example, a previous study showed that HaH for elderly patients with COVID-19 could be safe and effective[5]; however, there has been little evidence to confirm the safety of the HaH system for those with immunodeficiency, such as those undergoing B-cell depletion therapy. Most patients do not display severe

symptoms during the early stage; the condition of patients with COVID-19 often worsens around the seventh day from their symptom onset. Identifying patients who require hospitalization during the early stages of the disease could benefit both patients and medical providers.

In this paper, we present the report of a patient with COVID-19 with malignant lymphoma who had been treated with obinutuzumab and received HaH care. However, he did not respond to the HaH treatment and was admitted to the hospital. Here, we aim to discuss whether HaH care for B-cell-depleted patients with COVID-19 is reasonable and acceptable.

1.1 | Case history

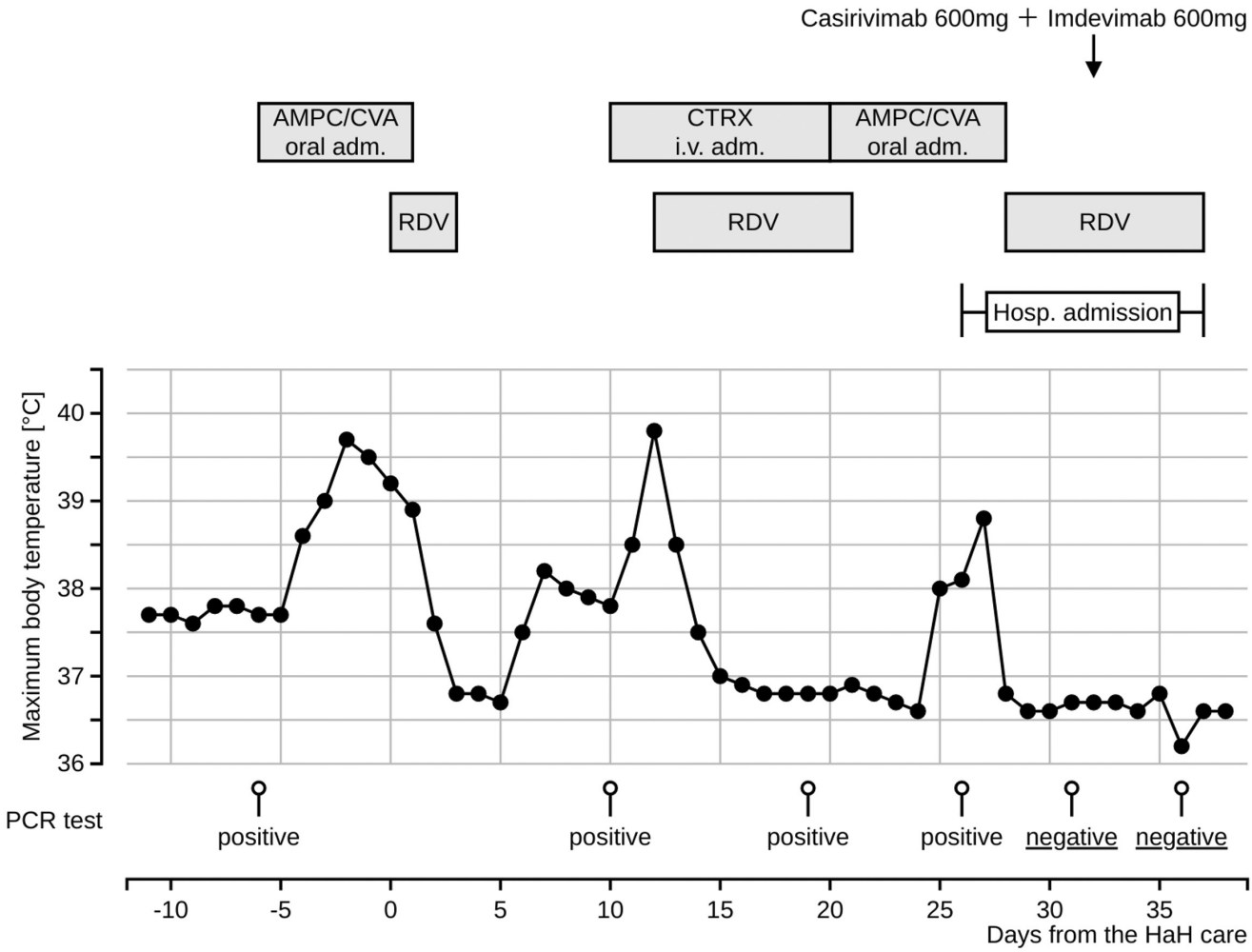
The patient was a man in his 60s who had been treated for follicular lymphoma at the hematology department in a hospital. Six months previously, he had demonstrated complete response to treatment with obinutuzumab plus bendamustine, after which he was treated with obinutuzumab every 2 months as remission maintenance therapy. Prior to the presentation, he had received three doses of the COVID-19 vaccine at 3, 11, and 12 months, respectively. Twenty-seven days before the HaH intervention, he developed a fever and was diagnosed with COVID-19. His illness resolved without administering any antiviral or monoclonal SARS-CoV-2 antibody drugs, and he maintained isolation for 10 days. However, 12 days before the HaH intervention, he developed a fever again, along with a persistent cough (Figure 1). Six days before the intervention, he went to the hospital and was diagnosed with COVID-19 reinfection through nicking enzyme amplification reaction (NEAR) testing. He was prescribed antipyretics and observed only via telemedicine from a local public health center. However, the local public health center asked our clinic to provide face-to-face HaH care intervention because his fever did not resolve.

1.2 | Treatment

On the first day of HaH care, his oxygen saturation level was 97%, and he was diagnosed with a mild case of COVID-19, for which we started remdesivir. We stopped his antibiotics (amoxicillin and clavulanate) that the former hospital had prescribed. On the third day of HaH care, his fever had resolved. Because the cycle threshold (Ct) value of the polymerase chain reaction (PCR) testing and virus culture testing were unavailable in our clinic then, we performed a nasopharyngeal COVID-19 antigen test for reference purposes, which was negative. Based on the information, we decided to halt the administration of remdesivir. On the sixth day of HaH care, he developed a fever over 38°C (Figure 1). Results of a blood test on the seventh day showed no significant change, and we considered that his fever might have been due to a rebound of COVID-19 and that no special treatment was required. However, the fever persisted even on the 11th day of HaH care. We considered the possibility of a bacterial coinfection; therefore, we collected blood and urine culture samples and started the patient on 2 g/day of ceftriaxone sodium. On the 13th day of HaH care, even though the antibiotics had been started more than 48 h previously, the fever was exacerbated, and the patient was exhausted. The blood test showed no significant change in white blood cell and C-reactive protein levels; however, his liver enzyme and ferritin levels were elevated. His oxygen saturation level was around 94%. We diagnosed the patient with relapse COVID-19-associated pneumonia, for which treatment was needed, and we resumed the administration of remdesivir. Although we recommended that the patient be administered oxygen therapy, he refused it because he did not feel short of breath at that time. On the 16th day of HaH care, 72 h after remdesivir administration, the fever decreased to ~37°C, and we switched his antibiotics to amoxicillin and clavulanate. On the 22nd day of HaH care, following remdesivir administration for 10 days, although the reverse transcription-polymerase chain reaction (RT-PCR) test result was still positive, his body temperature remained under 37°C for more than 120 h, and we finally decided to halt the administration of remdesivir. However, on the 26th day of HaH care, 4 days after stopping remdesivir administration, the fever increased to 38°C again, and the cough and fatigue symptoms were also exacerbated. We determined that he should be admitted to the hospital for treatment by infectious disease specialists. He was admitted to the hospital on the 27th day of HaH care.

1.3 | Outcome and follow-up

Following hospitalization, the patient underwent an RT-PCR test using the specimen taken from his nasopharynx. Using the GeneXpert system, the Ct value of the E gene was 27.3, and that of the N2 gene was 28.4. A chest computed tomography scan showed bilateral, patchy, mixed-pattern opacities of reticular patterns and consolidations. An abdominal computed tomography scan showed no significant evidence of infection other than pneumonia (Figure 2). The infectious disease specialists clinically diagnosed persistent COVID-19 infection; thus,



	Upper	Lower	Unit	Day 1	Day 7	Day 14	Day 21	Day 27	Day 33
WBC	3500	8500	/μL	2700	3700	2700	4600	5160	4490
CRP	0	0.3	mg/dl	1.32	1.25	2.74	0.18	0.90	0.11
AST	0	35	U/L	47	67	49	47	49	87
ALT	0	30	U/L	70	77	65	74	55	100
Ferritin	21.8	274	ng/ml	738	798	1615	551	887	1067

FIGURE 1 The patient's maximum body temperature, treatment, polymerase chain reaction test results over time, and laboratory data from 11 days prior to 38 days after the date of the HaH intervention. Adm, administration; AMPC/CVA, amoxicillin and clavulanate; CRP, C-reactive protein; CTRX, ceftriaxone sodium; HaH, hospital at home; hosp, hospital; PCR, polymerase chain reaction; RDV, remdesivir; WBC, white blood cell.

they resumed the administration of remdesivir from the day of admission and administered 600 mg of casirivimab and 600 mg of imdevimab on the fifth day of admission (32nd day of HaH care). The specimen on the day of admission was transferred to the university hospital, and additional tests were performed. The genome sequencing test showed that 91.4% of the complete genome length was analyzed, and the variant belonged to the BA.2 lineage. A subgenomic ribonucleic acid-specific RT-PCR test was also performed, wherein six of nine canonical transcripts were discovered.[7] The RT-PCR test taken on the fifth day and ninth day of admission demonstrated negative results. Based on these test results, remdesivir administration was halted on the 10th day of admission, and the patient was discharged from the hospital on the 11th day. Two months after his discharge, we sought an update on his health via a telephone call, and he reported no symptoms suggesting COVID-19 infection.

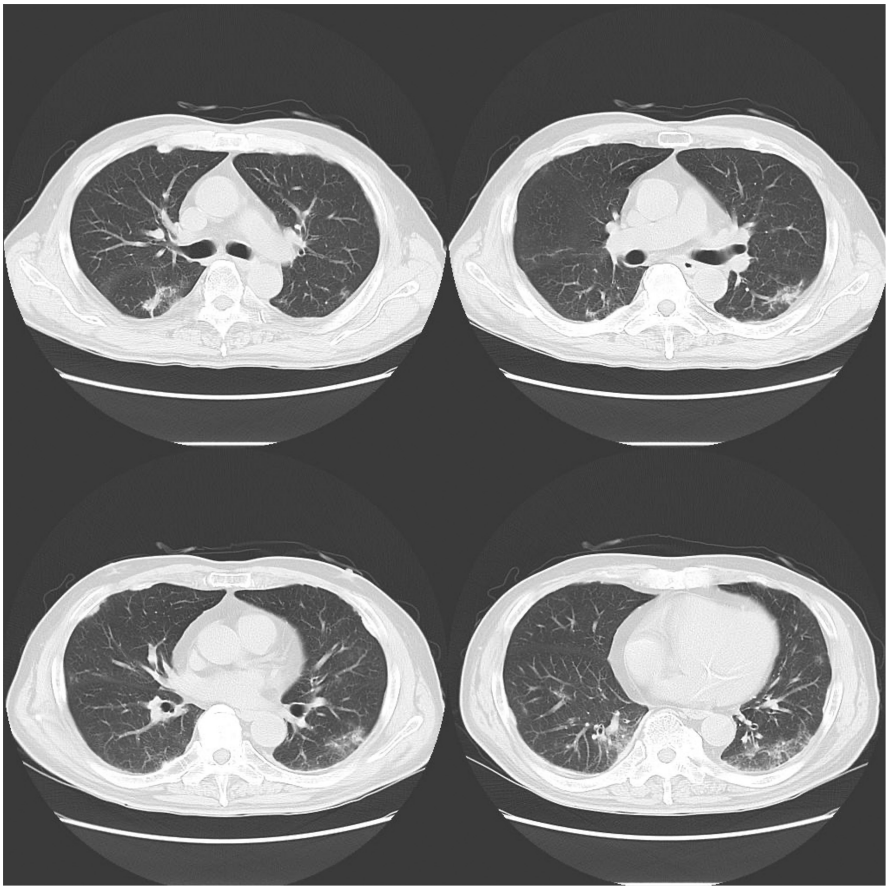


FIGURE 2 Lung computed tomography images acquired at admission.

2 | DISCUSSION

In this report, we presented the case of a patient with B-cell depletion who was diagnosed with prolonged SARS-CoV-2 infection and treated by HaH care; however, he eventually required hospital admission. Although the patient did not have severe hypoxia and seemed to have a mild or moderate illness, his symptoms persisted for over 1 month. In our analysis, the subgenomic PCR test detection rate of the canonical transcript was associated with viral load and viral activity and could not detect all of (9 of 9) the canonical transcripts, indicating that viral tests were unable to demonstrate adequate evidence of prolonged SARS-CoV-2 infection.[7] However, we finally made a conclusive diagnosis of prolonged SARS-CoV-2 infection for the following reasons: (1) the patient had high-risk factors of prolonged infection, including weakened protective humoral immune systems; (2) the patient's symptoms, including fever, fatigue, sweating, and respiratory symptoms, and relapse of his condition within 72 h after stopping remdesivir administration followed by resolution within 72 h after resuming remdesivir administration; and (3) negative results of blood and urine culture and in-hospital radiographic examination.

Several public health bureaus, including the National Health Service in the United Kingdom and the National Institutes of Health in the United States, define patients treated with B-cell depletion therapy as susceptible to the highest risk or requiring prioritized treatment.[8,9] Prior observational studies have shown an association between patients treated with B-cell depletion therapy and prolonged and severe COVID-19 infection; some of these patients experienced several months of COVID-19 infections.[10-12] This is partly because such patients did not develop detectable SARS-CoV-2 antibodies even after vaccination. However, there are no standard guidelines for prolonged COVID-19 patients. Thus, some experts administered remdesivir for more than 10 days for immunodeficient patients.[13-15] Other experts chose the combination therapy of antiviral drugs and monoclonal SARS-CoV-2 antibody drugs because the antibody type has a relatively longer half-life than the antiviral type, including remdesivir or nirmatrelvir–ritonavir.[14-16] Although there are many expert opinions about the treatments in patients with prolonged COVID-19, it remains unclear which treatment should be chosen by primary care physicians engaging in HaH care (i.e., antiviral drugs only, monoclonal SARS-CoV-2 antibody drugs only, or both). Moreover, it is unclear when these patients can end their isolation period. In primary care and HaH care settings, physicians cannot perform examinations to detect an active, viable virus. Furthermore, inadequate treatment and persistent infection might result

in the mutation of the SARS-CoV-2 virus.[17] Therefore, in cases where bed capacity is overwhelmed and patients are forced to receive HaH care, the primary care physician providing HaH care should remain cautious of the following points to consider: (1) the patient's conditions that cause prolonged SARS-CoV-2 infection (e.g., patients with hematologic cancer, who received chimeric antigen receptor T-cell therapy or a hematopoietic cell transplant, with severe primary immunodeficiency, and who received severely immunosuppressive, or immunosuppressive, or immunomodulatory biologic agents), (2) using monoclonal SARS-CoV-2 antibody drugs for such immunosuppressive patients, and (3) when the patients should end their isolation period (usually more than 10 days) even if their symptoms are resolved. In particular, to decide the isolation period, we recommend that primary care physicians do not hesitate to perform viral testing, including Ct-value of RT-PCR, subgenomic PCR, and viral culture, with consulting infectious disease specialists. The Ct-value of RT-PCR is more rapid than the other virus tests; thus, RT-PCR and its Ct-value are practically used for quick decision-making of treatment in patients with prolonged COVID-19, and the other virus tests are often used for a definite diagnosis. Since the Ct-value differs depending on specimen quality, type, and extraction method, it cannot be directly compared between assays. However, some studies suggested that low Ct-values correlated with the possibility of positive virus culture.[18,19] Therefore, monitoring the Ct-values could be used as one of the indicators of virus viability.

We acknowledge several limitations of this report. First, this is only a case report; the causal relationships among HaH care, prolonged SARS-CoV-2 infection, hospital treatment, and the patient's recovery are unknown. Even if the patient had received in-hospital care at the beginning of his treatment course, his SARS-CoV-2 infection might have been prolonged. Second, we could not determine clear evidence of viable viruses during the course of treatment. A viral culture test was not performed due to the high Ct value, and the genome sequencing test detected only 91% of the complete genome sequence. However, the clinical course, including the association between the treatment and the patient's symptoms, suggested a prolonged SARS-CoV-2 infection.

In conclusion, this is the first reported case of HaH care for a patient with COVID-19 who had undergone B-cell depletion therapy. If primary care physicians find it unavoidable to provide HaH care to patients with COVID-19 who have undergone B-cell depletion therapy, they must take into account prolonged SARS-CoV-2 infection and carefully consider the treatment regimen and the timing of ending the patients' isolation even when their symptoms are mild. Further studies are needed to establish the treatment strategy, including the isolation period, for immunosuppressive patients in HaH care settings.

AUTHOR CONTRIBUTIONS

Yuki Miyamoto: Conceptualization; formal analysis; methodology; visualization; writing – original draft. **Yasufumi Matsumura:** Data curation; funding acquisition; investigation; resources; writing – review and editing. **Shougen Sumiyoshi:** Data curation; formal analysis; investigation; methodology; writing – review and editing. **Yoshiki Morikami:** Conceptualization; funding acquisition; methodology; writing – review and editing. **Miki Nagao:** Conceptualization; investigation; project administration; resources; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patients’ privacy.

CONSENT

We declare that written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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