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Case Report

Persistent viral shedding of severe acute respiratory syndrome coronavirus 2 after treatment with bendamustine and rituximab: A case report[☆]

Tatsuya Arai^{a,*}, Satoru Mukai^a, Ryo Kazama^b, Yoshihiko Ogawa^c, Koji Nishida^d, Kazuo Hatanaka^a, Iwao Gohma^d

^a Department of Hematology, Sakai City Medical Center, Ebaraji 1-1-1, Sakai, Osaka, 593-8304, Japan

^b Department of General Internal Medicine, Sakai City Medical Center, Ebaraji 1-1-1, Sakai, Osaka, 593-8304, Japan

^c Department of Infectious Diseases, Sakai City Medical Center, Ebaraji 1-1-1, Sakai, Osaka, 593-8304, Japan

^d Department of Respiratory Medicine, Sakai City Medical Center, Ebaraji 1-1-1, Sakai, Osaka, 593-8304, Japan



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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is detectable in nasopharyngeal specimens for up to 12–20 days regardless of the presence of chronic diseases in patients. We report a case of prolonged SARS-CoV-2 infection that lasted for more than eight weeks. The patient had persistent lymphopenia after receiving six cycles of bendamustine and rituximab (BR) therapy for follicular lymphoma; the last chemotherapy session was completed nine months before admission. The first nasopharyngeal specimen (NPS) for the SARS-CoV-2 polymerase chain reaction assay tested positive for the N501Y variant five weeks before admission. The patient's general and respiratory conditions gradually worsened; therefore, he was admitted to our hospital, and the same SARS-CoV-2 variant was subsequently identified on admission. Treatment for coronavirus disease was initiated, and the patient's condition improved; however, the NPS tested positive on day 15. The patient was discharged on day 28 and was instructed to isolate at home for a month. Hence, possible prolonged SARS-CoV-2 shedding should be considered in patients who receive BR therapy.

1. Introduction

Bendamustine and rituximab (BR) are used to treat non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Bendamustine has hematologic side effects, including profound and prolonged lymphopenia [1]. One study showed that BR therapy was associated with mortality among hospitalized patients with both coronavirus disease (COVID-19) and lymphoma [2]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA is detectable in nasopharyngeal specimens for up to 12–20 days regardless of the presence of underlying diseases in patients [3]. Some case reports have shown prolonged SARS-CoV-2 shedding in patients who underwent hematopoietic stem cell transplantation or received cellular therapies [4].

We report the case of a patient, who had received BR therapy nine months before admission, and whose condition worsened five weeks

after COVID-19 diagnosis; the patient experienced protracted shedding of SARS-CoV-2 for eight weeks. We also present a literature review of prolonged shedding of SARS-CoV-2 in patients treated with BR therapy.

2. Case report

A 71-year-old man with dyspnea was admitted to our hospital. The patient had a history of follicular lymphoma (FL grade 3A, stage IIIB), which was in complete remission. Nine months before admission, he had completed six cycles of BR therapy; he was not vaccinated for SARS-CoV-2.

Five weeks before admission, the patient experienced fatigue, and a nasopharyngeal specimen (NPS) was obtained for SARS-CoV-2 polymerase chain reaction (PCR) testing in a nearby clinic. The NPS tested positive for the SARS-CoV-2, N501Y variant, with a cycle threshold (Ct)

Abbreviations: BR, bendamustine and rituximab; COVID-19, coronavirus disease-2019; NPS, nasopharyngeal specimen; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

[☆] TA was responsible for the organization and coordination of this case report. TA, RK, YO, KN, and IG treated and diagnosed the patient. SM, YO, KH contributed to the writing of the final manuscript. All authors have read and approved the manuscript.

* Corresponding author. Sakai City Medical Center, Ebaraji 1-1-1, Sakai, Osaka, 593-8304, Japan.

E-mail address: aaaaaraitttatsuya@gmail.com (T. Arai).

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value of 29.3. At the time of diagnosis, the COVID-19 symptoms were not severe; therefore, he was isolated in his own home and treated symptomatically. Two weeks after the diagnosis, PCR testing of a NPS demonstrated persistent positivity for the N501Y variant; the Ct value was 32.6. Although he was discharged, some COVID-19 symptoms, including lethargy and dizziness, persisted. Therefore, his self-isolation was continued. On the morning of admission, the patient experienced difficulty in breathing and mild confusion; therefore, he was referred to the emergency department of our hospital.

On admission, he had a temperature of 36.4 °C, blood pressure of 110/62 mmHg, pulse rate of 77 beats per minute, respiratory rate of 22 breaths per minute, and oxygen saturation of 87% on room air; physical examination revealed decreased breath sounds at the lung base. Blood examination indicated lymphopenia (1310/ μ L) and elevated C-reactive protein levels (CRP) (3.24 mg/dL); his CD4⁺ T lymphocyte count was severely low (113/ μ L). Chest radiography revealed bilateral diffuse infiltrates, and chest computed tomography showed diffuse ground-glass opacities in the peripheral and middle lobes with consolidation in the lower lobes (Fig. 1). We used nasopharyngeal specimens (NPSs) in our hospital for the real-time PCR assay (SARS-CoV-2 ELITE MGB®Kit, Precision System Science Co., Ltd, Chiba, Japan) and detection of SARS-CoV-2 variants (VirSniP SARS B1351(484K + 501Y), Precision System Science Co., Ltd, Chiba, Japan). The specimen tested positive for SARS-CoV-2, N501Y variant with a Ct value of 21.3; the patient tested negative for both SARS-CoV-2 total antibody and SARS-CoV-2 spike protein antibody, which were measured using the electrochemiluminescent immunoassay test (Elecsys®Anti-SARS-CoV-2 S, Roche Diagnostics K.K., Tokyo, Japan). As the patient had moderate COVID-19, dexamethasone and remdesivir were administered. Oxygen therapy, which is supportive therapy, was discontinued on day 5, and his general condition gradually improved (Fig. 2). The CRP level declined to 0.82 mg/dL on day 5, but rose to 4.72 mg/dL on day 15. The patient had a mild fever but no respiratory symptoms; however, the chest radiograph showed no clear improvement compared to that obtained on admission.

We speculated that the mild fever and persistent CRP positivity were caused by prolonged and relapsed COVID-19 infection due to dexamethasone cessation. However, the CRP levels and high body temperature improved gradually without administering any additional medication for COVID-19. On day 28, the patient was afebrile and was not in cardiorespiratory distress; he was discharged and instructed to observe home isolation for another month, based on a report of persistent viral shedding that lasted for approximately two months after

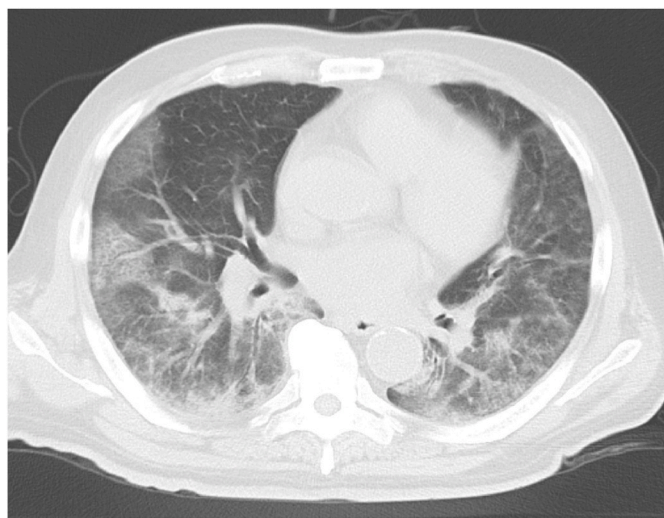


Fig. 1. Chest computed tomography revealed bilateral diffuse ground glass opacities in the peripheral and lower lobes and consolidation in the lower right lobes.

bendamustine therapy [5]. Ten days after discharge, the PCR test was reported as negative, CRP level decreased to the normal range, and chest radiography did not show any abnormal opacity. His SARS-CoV-2 antibody levels were re-tested two months after discharge; the results remained negative.

3. Discussion

The duration of viral shedding after the onset of COVID-19 is usually 20 days [3]. However, immunocompromised patients with hematologic malignancies, those undergoing chemotherapy, and especially those treated with BR, have reportedly shed the active virus for longer periods [5–8].

The reported cases of prolonged SARS-CoV-2 shedding in patients after BR therapy are shown in Table 1. There are six reported cases, including our case. The hematological malignancies in the other cases were in complete remission; however, information on disease status was unavailable for Case 3. The median duration since the last BR therapy was four months (8 days–9 months), and the median duration of SARS-CoV-2 PCR positivity was 59 days (42–111 days); one patient died of COVID-19. The favorable outcomes in these cases were attributed to the successful treatment of hematological malignancies. Previous studies indicate that certain risk factors confer poor prognosis in COVID-19 patients with hematological disorders; these include active hematological disorders that are not in remission, receiving chemotherapy with steroids, age >70 years, and treatment with bendamustine within 12 months [2,9]. However, the patients in the reported cases had several of these risk factors; most improved because their underlying diseases were in remission. Nevertheless, further studies, including patients with COVID-19 who are receiving BR therapy, are required to confirm the accuracy of the prognostic factors.

Bendamustine belongs to the alkylating agent class of cytotoxic drugs. It contains a nitrogen mustard group, which is responsible for the alkylating activity and purine analog-like properties, and is currently used for the treatment of NHL and CLL [10]. However, it causes severe and prolonged lymphopenia and significantly decreases CD4⁺ T lymphocytes. Lymphopenia occurs in 62–79% of patients receiving BR and persists for more than three years [1].

In addition to bendamustine, the repeated administration of rituximab impairs immunoglobulin (Ig) G and IgM production. Rituximab is an anti-CD20 chimeric monoclonal antibody and depletes pre-plasma B-cells, which may subsequently reduce the re-population of antibody-secreting plasma cells, leading to hypogammaglobulinemia [11]. Most patients with COVID-19 develop SARS-CoV-2 IgM and IgG antibodies within 20 days of symptom onset [12]. However, Reza et al. reported that patients treated with rituximab did not acquire anti-SARS-CoV-2 total antibodies or anti-SARS-CoV-2 S-receptor binding domain proteins, IgG, IgA, and IgM, 10 weeks after the onset of symptoms [13]. Lymphopenia was detected in our patient during a regular outpatient clinic visit. Similarly, he had a significantly low CD4 lymphocyte count on day 8 of admission; additionally, he had impaired production of SARS-CoV-2 antibodies and SARS-CoV-2 spike protein antibodies. Considering the prolonged SARS-CoV-2 shedding following BR, the patient is instructed to undergo home isolation for a month after discharge.

This report has certain limitations. Viral culture for SARS-CoV-2 could not be performed during hospitalization; therefore, we could not confirm whether the pneumonia on admission was SARS-CoV-2 pneumonia or post-COVID-19 organizing pneumonia (OP). However, post-COVID-19 OP usually develops a few weeks after the appearance of the first COVID-19 symptoms [14]. Hence, we considered that it took a much longer time for the patient to develop post-COVID-19 OP. Moreover, the Ct value was lower on admission than it was a few weeks before; the Ct value is the number of cycles necessary to detect the virus. Thus, the lower the Ct value of a patient's sample, the higher the viral load; conversely, the higher it is, the lower the viral load. In general, the

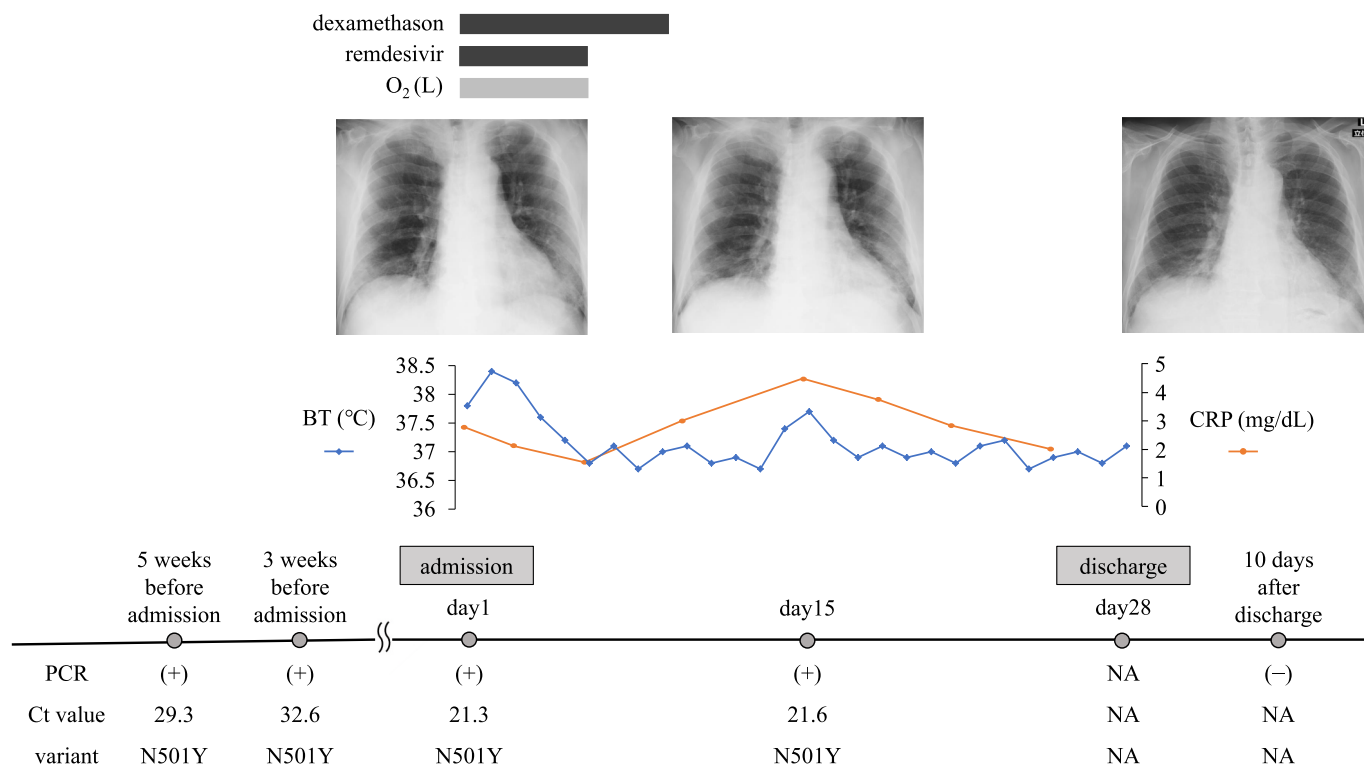


Fig. 2. Patient course timeline. We administered 10 mg of dexamethasone for 10 days and 200 mg of remdesivir on admission, followed by 100 mg daily for another four days. Oxygen supplementation was needed at a rate of 4, 2, and 1 L/min on days 1–3, 2, and 5, respectively. BT, body temperature (left, in °C); CRP, C-reactive protein (right, in mg/dL); NA, not available; Ct, cycle threshold; PCR, polymerase chain reaction.

Table 1

Cases of prolonged SARS-CoV-2 shedding in patients after BR therapy. Ref, reference; M, male; F, female; FL, follicular lymphoma; MCL, myeloid cell leukemia; WM/LPL, Waldenström macroglobulinemia/LPL; CLL, chronic lymphocytic leukemia; NA, not available; C, ciclesonide; F, favipiravir; H, hyperimmune plasma infusion; D, dexamethasone; R, remdesivir.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
age/sex	47 M	NA	NA	62F	74 M	71 M
underlying disease	FL	MCL	WM/LPL	FL	CLL	FL
Status	CR	NA	NA	CR	CR	CR
last BR therapy before COVID-19	4 months	17 days	8 days	NA	5 months	9 months
duration of PCR positive for SARS-CoV-2	59 days	42 days	56 days	66 days	111 days	above 8 weeks
treatment for COVID-19	C, F	NA	NA	H, D, R	H, D	D, R
Outcome	cure	death	cure	Cure	cure	cure
References	[5]	[6]	[6]	[7]	[8]	This case

Ct value is often approximately 20 during the early stage of SARS-CoV-2 infection, including that caused by the N501Y variant; the number increases to over 35 approximately two weeks later [15]. Therefore, the lower Ct values indicated SARS-CoV-2 replication in the patient; in addition, the lower value increased the likelihood of virus-related OP over post-COVID-19 OP.

Here, we report a case of persistent SARS-CoV-2 infection in a patient with a hematological malignancy who received BR therapy nine months before the COVID-19 diagnosis. Therefore, possible prolonged SARS-CoV-2 shedding should be considered in patients with COVID-19 who were previously treated with BR therapy.

Consent for publication

The patient provided informed consent for the publication of this report.

Authorship statement

All authors meet the ICMJE authorship criteria.

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Declaration of competing interest

None.

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