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Journal of Infection and Chemotherapy 28 (2022) 329–332

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Case Report

Recovery from severe persistent COVID-19 without evidence of an anti-SARS-CoV-2 antibody response in a man with mantle cell lymphoma treated with rituximab

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Immunocompromised state
Lymphoma
Antibody
Rituximab

ABSTRACT

Lymphoma has been reported to worsen the prognosis of COVID-19 partly because it disturbs the normal production of antibodies. We treated a man with mantle cell lymphoma treated with rituximab, who developed severe COVID-19 with viral shedding that lasted for 78 days. He stayed in the intensive care unit for 28 days and did not respond to any treatment against COVID-19. His increased oxygen demand at rest eventually resolved despite the absence of anti-SARS-CoV-2-IgG. This case illustrates that recovery from COVID-19 can occur without antibody production, and that even patients with an inability to produce antibodies can recover from severe COVID-19. It also illustrates that lymphoma patients who develop severe COVID-19 while on rituximab therapy can recover from a prolonged viral shedding state if the acute lung injury can be overcome.

1. Introduction

Lymphoma has been reported to worsen the prognosis of coronavirus disease (COVID-19) because its non-functional lymphocytes and the depletion of normal lymphocytes by chemotherapy leads to immune dysfunction [1]. Given the high efficacy of COVID-19 vaccines [2], neutralizing antibodies must be advantageous for recovery from COVID-19. However, the immune mechanism related to the eradication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains unclear. We report a case of severe COVID-19 in a man with mantle cell lymphoma (MCL) that had been treated with rituximab, who recovered without a significant increase in anti-SARS-CoV-2 antibodies, after being PCR positive for 78 days.

2. Case report

A 75-year-old man who was on maintenance therapy for MCL visited our hospital with a 2-day history of fever. He had been given rituximab 3 months previously. He tested positive for nasopharyngeal SARS-CoV-2 antigen, and was hospitalized considering his hematological malignancy (day 2). He tested positive for nasopharyngeal SARS-CoV-2 PCR test the next day (cycle threshold (Ct) value: E14.11).

Dexamethasone 4 mg was started on day 6 for his persistent fever up to 38 °C. On day 10, he started to require oxygen therapy (3 L/min by nasal cannula). On day 11, his oxygen demand increased to 10 L/min using a non-rebreathing mask. Nasal high-flow therapy (50 L/min, FiO_2: 0.50) was started on the same day. Administration of remdesivir (200 mg on day 1, followed by 100 mg administered daily on days 2 through 10) for 10 days, and steroid pulse therapy (methylprednisolone 1 g for 3 days) was started. His respiratory failure did not improve, and he was admitted to the intensive care unit (ICU) on day 15. After that, intravenous immunoglobulin therapy (IVIG) 12.5 g was administered once a day from day 21–25; he was given a second 10-day course of remdesivir from day 27, ivermectin 12 mg single administration on day 29, and interferon beta-1b (IFN-β) 9.6 million IU on alternate days from day 30–42 were administered (Fig. 1). Tapered methylprednisolone was administered until day 36.

Despite these therapies, his respiratory condition did not improve significantly. The SARS-CoV-2 PCR test remained positive, and COVID-IgG (Abbott SARS-CoV-2 IgG test), which is an anti-SARS-CoV-2 nucleocapsid protein antibody, did not become elevated (Table 1). During his stay in the ICU, he developed a pneumothorax on day 15, gastrointestinal hemorrhage on day 26, and a urinary tract infection on day 38. Even though the use of convalescent plasma (CP) was planned for the

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https://doi.org/10.1016/j.jiac.2021.11.018
Received 21 June 2021; Received in revised form 6 November 2021; Accepted 20 November 2021
Available online 25 November 2021
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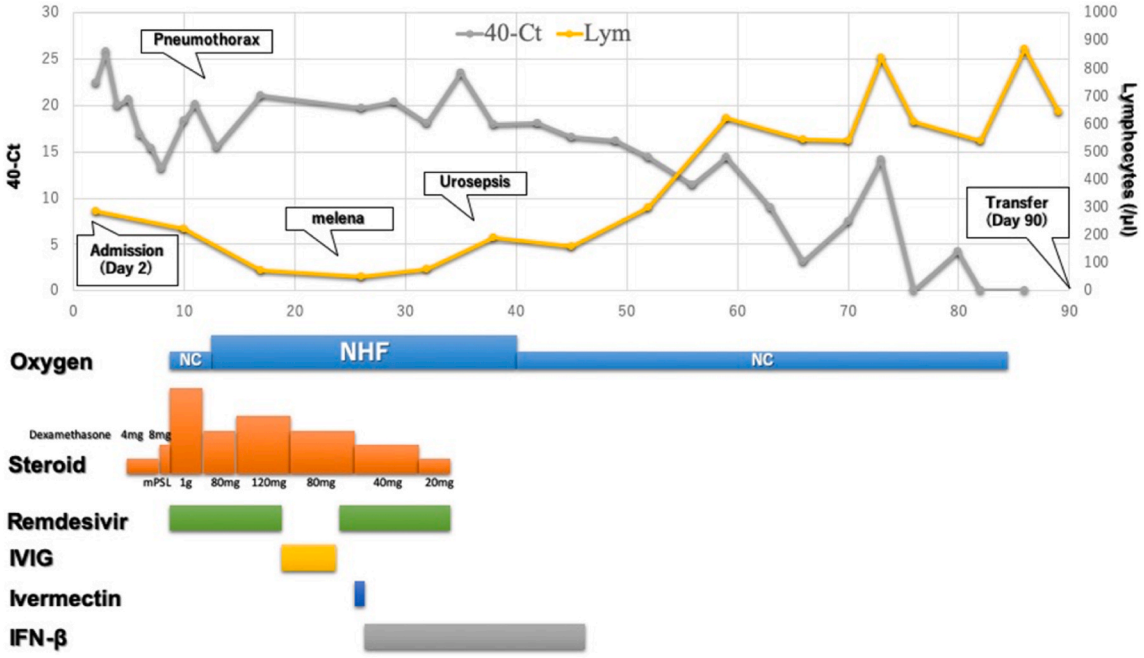

Fig. 1. Clinical course according to the SARS-CoV-2 PCR the cycle threshold (Ct) value (viral load) and the peripheral lymphocyte countViral load is inversely proportional to the CT value. A Ct value of 40 was the cutoff for a positive result.
Ct, cycle threshold; IFN-β, interferon beta-1b; IVIG, intravenous immunoglobulin; lym, lymphocytes; NC, nasal cannula; NHF, nasal high-flow.

Table 1
The dynamics of IgG and anti-SARS-CoV-2 antibody.

Date	Day2	Day8	Day14	Day21	Day25	Day32	Day40	Day47	Day54	Day62	Day69	Day73	Day79	Day83	Day86
IgG (mg/dl)	959	NA	NA	NA	NA	NA	NA	621	596	560	533	NA	NA	564	NA
COVID-IgG	0.02	0.01	0.01	0.01	0.05	0.03	0.02	0.01	0.01	0.02	0.02	0.02	0.02	0.03	0.02
COVID-IgG Quant	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	40.0	NA	NA	NA

The cutoff value for anti-nucleocapsid protein is 1.40, and for spike protein 50.0.
COVID-IgG, anti-SARS-CoV-2 nucleocapsid protein antibody; COVID-IgG Quant, anti-SARS-CoV-2 spike protein antibody; NA, not assessed.

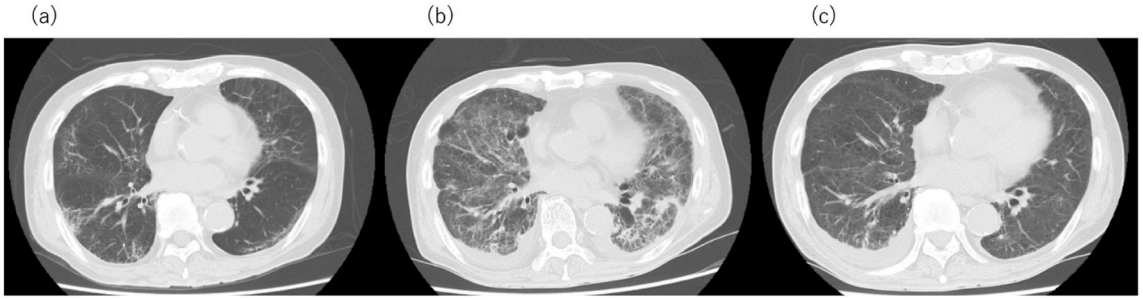

Fig. 2. Serial chest computed tomography (CT) findings
(a) day 15, (b) day 49, and (c) day 86.
The bilateral ground grass opacities and reticular shadows are less marked on day 15 (a), than on day 49 (b) despite the higher oxygen demand at rest. Without any specific treatment, the CT findings have improved by day 86 (c).

eradication of SARS-CoV-2, he withdrew from nasal high-flow oxygen therapy on day 42, and was discharged from the ICU on day 43, and his oxygen demand gradually decreased.

Computed tomography (CT) on day 49 (oxygen demand: 1 L/min) revealed worsening bilateral ground-glass opacity and reticular shadows compared to that on day 15 (Fig. 2). Despite the CT findings, his respiration status continued to gradually improve. The PCR test result was negative for the first time on day 76. Anti-SARS-CoV-2 spike protein antibody (Abbott SARS-CoV-2 IgG II Quant test) was detectable on day 73 slightly increased, but was below the cutoff. On day 78, the PCR test was positive once again, but on days 80 and 84, two consecutive negative PCR test results were confirmed. His SARS-CoV-2 IgG remained negative until day 86. His need for supplemental oxygen at rest disappeared on day 87. He was transferred to another hospital for intensive rehabilitation on day 89. Anti-SARS-CoV-2 antibody tests remained negative throughout the course of his illness.

3. Discussion

This case illustrates two clinical issues. First, MCL patients on

rituximab therapy who develop severe COVID-19 can become SARS-CoV-2 PCR-negative after being persistently positive for a prolonged period. Second, the patient recovered without any increase in anti-SARS-CoV-2 IgG, which illustrates that lymphoma patients who develop severe COVID-19 while on rituximab therapy can recover from a prolonged viral shedding state if the acute lung injury could be overcome.

Several cases of prolonged PCR positivity have been reported in patients with lymphoma. One lymphoma patient was found to be SARS-CoV-2 PCR positive on day 156, when he was readmitted due to progression of his lymphoma, but without any symptoms related to COVID-19. This patient received home hospice care and did not have any subsequent negative PCR test result [3]. Another patient with a history of autologous stem cell transplantation for lymphoma and non-severe COVID-19, who was given CP on day 40, remained PCR positive for 74 days [4]. Negative PCR test results were not confirmed, but the patient improved clinically. Poor outcomes of hemato-oncology patients with COVID-19 have been reported [5], while B-cell depletion may also provide an explanation for the moderate symptoms, as the lack of antibody-producing B cells may prevent activation of the complement system [6]. Although survival of COVID-19 patients with hematologic malignancies who have been given rituximab therapy has been reported [7], poor outcomes have also been reported in MCL patients who develop COVID-19 while on rituximab therapy [8,9]. Despite the lack of antibody-producing B cells, our patient had severe symptoms and was considered to have a very poor prognosis. To our knowledge, there have been no previous case reports of lymphoma patients who developed severe COVID-19 while on rituximab therapy, with a negative SARS-CoV-2 PCR result after a period of prolonged SARS-CoV-2 PCR positivity as long as 78 days.

Our patient recovered without any increase in anti-SARS-CoV-2 IgG, which suggests that lymphoma patients on rituximab therapy who develop severe COVID-19 can recover from a prolonged viral shedding state if the acute lung injury could be overcome. In his clinical course, antiviral therapy, including two courses of remdesivir, seemed ineffective at first. We planned to administer CP to our patient for his continuous viral shedding because successful treatment with CP has been reported in some other cases of COVID-19 in patients with lymphoma and prolonged viral shedding [10], but our patient recovered without the use of CP. The effectiveness of antiviral therapy for our patient is uncertain even though he finally recovered from severe respiratory failure. Over the whole clinical course of our patient's illness, his anti-SARS-CoV-2 nucleocapsid protein IgG did not increase, and the level of anti-SARS-CoV-2 spike protein IgG on day 73 was below the detection threshold. A serological response to COVID-19 has been reported in patients with hematological malignancies who have not received rituximab within 6 months before the diagnosis of COVID-19 [7]. For our patient, steroid pulse therapy was started on day 9. This and the prior use of rituximab may have led to the continuous viral shedding due to the suppression of cellular and humoral immunity. The recovery of our patient's cellular immunity may have contributed to the eradication of the virus because his respiratory status recovered as his peripheral lymphocyte count increased. At the time of discharge, his lymphocyte count was higher than that at the time of admission, partly because the effect of steroid pulse therapy and rituximab had worn off. One study reported that 78% of PCR-positive patients with undetectable antibodies showed T-cell immunity against SARS-CoV-2 [11]. Another case report described the recovery of a patient with nodal marginal zone lymphoma who developed COVID-19 while on rituximab therapy [6]. The patient had a protracted disease course, which was thought to be due to the B-cell depletion. The patient had an adequate number of $CD4^+$ and $CD8^+$ T cells, and the T cells might have contributed to the control of infection. The eradication of the virus in our case might have been achieved by the same mechanism. Regardless of the immune mechanism, the clinical course in our case suggests that COVID-19 might not become chronic even in patients with severe immunodeficiency who are unable to produce antibodies.

The presence of neutralizing antibody is thought to be essential for preventing COVID-19, given that COVID-19 vaccines have been shown to be effective at preventing the disease [2]. However, as our case indicated, the inability to produce sufficient antibodies does not necessarily lead to the inability to eradicate SARS-CoV-2. A few studies showed that B-cell depletion and a defective humoral immune response may have a limited impact on the clinical outcome of COVID-19 [7,12]. Another study evaluated serological and T-cell responses after complete COVID-19 mRNA vaccination in hemato-oncology patients, and found that anti-CD 20 treatment was an independent predictor for seroconversion. Notably, 74% of the seronegative patients had a T-cell immune response [13]. These studies indicate that neutralizing antibodies are not always necessary for SARS-CoV-2 eradication. At the same time, our patient's clinical course suggests that host immune response against SARS-CoV-2 could be more related than the viral toxicity itself to the development of COVID-19, considering that prolonged viral shedding did not keep causing severe lung injury after the initial aggravation of the disease.

In conclusion, a man with immunodeficiency due to being given rituximab therapy for MCL developed severe COVID-19 and recovered clinically after persistent PCR positivity, without any demonstrable increase in anti-SARS-CoV-2 antibodies. This case suggests that even patients with an inability to produce antibodies can recover from severe COVID-19 if the severe phase of the disease can be overcome, and that COVID-19 does not necessarily become a chronic infectious disease. Further studies are needed to clarify the immune mechanisms of recovery from COVID-19.

Author statement

All authors meet the ICMJE authorship criteria; Hiroshi Horiuchi was responsible for the conception of the work, interpretation of data and draft the work. Hiroaki Sasaki, Kazuhito Miyazaki, Nobuyuki Miyata, Yukihiro Yoshimura, Natsuo Tachikawa were responsible for the design of the work and the analysis of data. All authors revised this work critically and contributed to the writing of the final manuscript. All authors agreed to be accountable for all aspects of the work.

Funding

The authors received no funding to write this report.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgments

We thank Tomonori Nakazato for making plans to treat the patient with convalescent plasma.

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