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A Fatal Breakthrough COVID-19 Case Following Bendamustine-Rituximab Therapy

Kohei Kamegai, Noriko Iwamoto, Tomiteru Togano, Kenji Maeda, Yuki Takamatsu, Yusuke Miyazato, Masahiro Ishikane, Masashi Mizokami, Masaya Sugiyama, Shun Iida, Sho Miyamoto, Tadaki Suzuki, Norio Ohmagari

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A B S T R A C T

Although messenger ribonucleic acid vaccines are substantially effective toward SARS-CoV-2 infection, patients with hematologic malignancies are still prone to the virus. Herein, we report a fatal case of breakthrough SARS-CoV-2 Delta variant infection in a patient with mucosa-associated lymphoid tissue lymphoma with remission by bendamustine-rituximab (BR) therapy completed a year ago. The serologic study revealed impaired responsiveness toward vaccines and prolonged high viral load after infection. BR therapy seemingly induced an immune escape. Prevention and treatment strategies for such vulnerable patients should be clarified immediately.

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Introduction

Patients with hematologic malignancy are at high risk for developing critical COVID-19 because of immunologic unresponsiveness toward SARS-CoV-2 vaccines (García-Suárez et al., 2020; Greenberger et al., 2021). Establishing strategies for treating such patients has not yet been addressed. We report a fatal, critical case of COVID-19 after two messenger ribonucleic acid (mRNA) vaccine doses, which has been validated by detailed serologic, virologic, and cytokine kinetic studies.

Case report

Herein, we present an Asian man in his 70s, who had received six courses of bendamustine-rituximab (BR) therapy (rituximab 375 mg/m² [day 1], bendamustine 90 mg/m² [days 1 and 2]) for stage 3 mucosa-associated lymphoid tissue (MALT) lymphoma. Chemotherapy was completed 1 year before hospital admission. Positron emission tomography/computed tomography (PET/CT) performed 8 months before the admission revealed a complete metabolic response of the lymphoma lesions, and there was no evidence of relapse since then. His total lymphocyte count and total serum IgG level were within normal limits during outpatient visits.

His clinical course is shown in Supplementary Figure. The patient developed a fever at home 11 days after his second dose of the mRNA vaccine BNT162b2 (disease day 0). On disease day 10, he was transferred by ambulance from home to our hospital owing to his worsened status. On arrival, his oxygen saturation was 56% while he was breathing ambient air. We started remdesivir, 2 mg/kg per day methylprednisolone, and a single dose of 8 mg/kg tocilizumab. He required a noninvasive, positive-pressure ventilator for hypoxemia. On disease day 19, his oxygen level abruptly dropped, and intubation was needed. On disease day 26, soon after extubation, he developed pneumothorax and acute respiratory distress syndrome. He died on disease day 31.

Laboratory data

Before admission, even after receiving the BR regimen, his total serum IgG level and total lymphocyte counts were approxi-
mately within the normal limits. During his admission due to severe COVID-19, his lymphocyte counts considerably dropped to less than 200/mm³. The serum SARS-CoV-2-neutralizing activity was determined in vitro with wild-type SARS-CoV-2 (Phylogenetic Assignment of Named Global Outbreak [PANGO] lineage B) and transmembrane protease serine 2-overexpressing VeroE6 cells, as previously described (Maeda et al., 2021). The serum neutralizing activity on admission (disease day 10) was under the detection limit (50% neutralizing titer [NT₅₀] < 20-fold) even 3 weeks after the second dose of BNT162b2. The activity increased by disease day 19 and slightly decreased by disease day 27, with NT₅₀ values of 360-fold and 170-fold, respectively, compared with the NT₅₀ value of 850-fold of the best 2% of 340 neutralizing activity-determined convalescent plasma samples (Takamatsu et al., 2022).

Elevated interferon-lambda 3 (IFN-λ3), followed by a surge in interleukin-6 (IL-6) and low C-C motif chemokine ligand 17 (CCL17), all of which are strong predictors of critical COVID-19 (Sugiyama et al., 2021), were detected on admission.

Reverse transcription-quantitative polymerase chain reaction, whole viral genome sequencing, and viral isolation were performed (Supplementary material). The infectious virus (SARS-CoV-2 Delta variant, PANGO lineage AY.29, Global Initiative on Sharing All Influenza Data [GISAID] Accession ID: EPI_ISL_7999852) was isolated only from the nasopharyngeal swab sample collected on disease day 10 (sample A), whereas no further virus isolation was possible from the nasopharyngeal swab sample collected after admission (disease days 27 and 29). Several mix alleles were found in the specimens collected on disease day 27 (sample B) and disease day 29 (sample C); although, the isolated virus from sample A had none (Supplementary Table).

Discussion

Our patient died of a fatal course after receiving two doses of an mRNA SARS-CoV-2 vaccine. The blood test results that were described previously indicated that the patient failed to acquire sufficient anti-SARS-CoV-2-neutralizing antibodies and immunologic responses even after 2 doses of BNT-162b2 vaccination, with undetectable serum neutralizing activity and anti-SARS-CoV-2-Spike IgG (Table). An increase in SARS-CoV-2-neutralizing activity was observed 19 days after the infection as a booster effect.

We attribute this fatal case to four causes: (i) impaired responsiveness toward SARS-CoV-2 vaccine, (ii) prolonged high SARS-CoV-2 viral load, (iii) difficulties in controlling T-cell immunodeficiency and cytokine storm, and (iv) the possibility of bacterial superinfection. The patient had received bendamustine, a purine analog that dramatically reduces the function of CD4+ T-cell (Gaffter-Gvili and Pollack, 2016). We suggest lymphoma is responsible for (i) (Agha et al., 2021), whereas bendamustine is responsible for (ii) and (iii), and rituximab is responsible for (i), (ii), and (iii). The four causes are discussed below.

First, in this patient, even at 3 weeks after the second dose of BNT162b2, the serum SARS-CoV-2-neutralizing activity was below the detection limit. It has been reported that only 44–79% of patients with B cell lymphoma produce sufficient antibodies after completing two doses of SARS-CoV-2 vaccines (Greenberger et al., 2021). Rituximab is an anti-CD20 monoclonal antibody that significantly depletes B cells. In general, the rituximab-induced reduction of B cells persists no longer than 6 months after therapy completion (McLaughlin et al., 1998). According to another report, rituximab also reduces functional T-cell response after vaccination (Nazi et al., 2013). A cohort study in Japan reported that even beyond a year after the anti-CD20 treatment, approximately 40% of the individuals had only acquired a limited amount of anti-SARS-CoV-2-IgG antibodies after two doses of BNT162b2 compared with healthy individuals (Okamoto et al., 2022). Furthermore, it is possible that Delta variant mutations, such as L452R, can escape cell-mediated immunity; although, SARS-CoV-2 mRNA vaccines generally generate a neutralizing response in 95% of recipients (Planas et al., 2021), which may have influenced the lack of detectable SARS-CoV-2-neutralizing activity. These results imply that chemotherapies, such as BR therapy, critically compromise the immune system.

Second, a high SARS-CoV-2 viral load was observed until 1 month after onset. Several reports have showed that patients with profound immunosuppression may shed viable SARS-CoV-2 for a prolonged period (Aydillo et al., 2020), although the details of the virologic mechanism are not known. To the best of our knowledge, the mixed alleles found in this patient have not been reported to have any effect on immune escape. Further case series and virological studies are needed in this regard.

Third, elevated IFN-λ3 and IL-6 and severe lymphopenia as a manifestation of the tumultuous cytokine storm, were detected. These results suggest that a severe and uncontrolled cytokine storm resulted from the patient’s immunologic unresponsiveness, which led to his death.

Fourth, although tocilizumab and steroids are effective in suppressing host inflammatory response phase, they can give rise to the risk for superinfection, such as ventilator-associated bacterial pneumonia, significantly (Abani et al., 2021). In this case, we could
not deny the downsides of these immunosuppressors even though we used adequately broad-spectrum antibiotics.

COVID-19 treatment and prevention strategies for patients with hematologic diseases are not well established. The effectiveness of the mRNA vaccine in patients with hematologic malignancies seems restricted. Herishanu et al (2021) reported that in 172 patients with chronic lymphocytic leukemia, the antibody response rate after the third BNT162b2 mRNA vaccine was only 23.8%.

On the other hand, some articles indicate potential effectiveness of early deployment of convalescent plasma and monoclonal antibody therapies.

Hueso et al reported successful treatment with convalescent plasma in 17 patients with profound B cell lymphopenia due to anti-CD20 therapy (Hueso et al., 2020). Daher et al successfully treated a patient with COVID-19 with B cell aplasia using bamlanivimab, an FDA-approved neutralizing antibody, targeting the S spike (Daher et al., 2021). Drouin et al reported successful clearance of unpredictedly prolonged SARS-CoV-2 infection after B cell depletion therapy using an antipsike monoclonal antibody (Drouin et al., 2021).

Effectiveness of SARS-CoV-2 neutralizing antibodies after anti-CD20 therapies are still unclear as previously mentioned, and further investigation is needed to set up the strategies for those vulnerable people.

In conclusion, because the patients with hematologic malignancies are reasonably vulnerable to COVID-19 viral infection, further investigations are needed to establish prevention strategies. Promoting thorough surveillance of mixed alleles could play an essential role in detecting unknown aggravating factors.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Disclaimers

This article does not necessarily reflect the opinions of the Centers for Disease Control and Prevention or the institutions with which the authors are affiliated.

Biographical Sketch

Dr. Kamegai, the lead author, is an infectious diseases specialist at the Disease Control and Prevention Center (National Center for Global Health and Medicine, Tokyo, Japan). His research interests include emerging infectious diseases and public health.

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Ethical Approval Statement

The guardian of this patient provided written informed consent to have the patient’s anonymized clinical information to be published.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.ijid.2022.04.058.

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