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LETTER TO THE EDITOR

Patients with B-cell lymphoma receiving anti-CD20 monoclonal antibody-containing chemotherapies and seroreactive patterns in response to COVID-19 vaccination

Tohru Inaba[1] · Keita Okumura[2] · Chika Maekura[3] · Ayako Muramatsu[3] · Tsutomu Kobayashi[3] · Junya Kuroda[3] · Yoko Nukui[1]

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To the editor

We read the previous report by Funakoshi et al. about the limited increase in IgG anti-spike 1 (S1) protein following BNT 162b2 mRNA COVID-19 vaccination after anti-CD20 monoclonal antibody (MoAb) [1]. We have also examined IgM and IgG antibodies against SARS-CoV-2 nucleocapsid (N), S1, and neutralizing antibody (Nab) using an iFLASH Immunoassay Analyzer and respective reagents (Shenzhen YHLO Biotech, Shenzhen, China) in various individuals. Here, we present interesting data obtained from patients with follicular lymphoma (FL) receiving anti-CD20 MoAb before infection with SARS-CoV-2.

Case 1 was a male in his 70s with refractory FL treated for 8 years. He was infected with SARS-CoV-2 5 days after the 37th course of rituximab (R)-containing chemotherapy and developed severe pneumonia. He had never received a SARS-CoV-2 vaccine and died of respiratory failure 10 weeks (+ 10w) after the diagnosis of COVID-19. PCR for the SARS-CoV-2 E-gene was repeatedly positive. All anti-SARS-CoV-2 antibody tests had been persistently negative (< 10 AU/mL).

✉ Tohru Inaba
inaba178@koto.kpu-m.ac.jp

[1] Department of Infection Control and Laboratory Medicine, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

[2] Faculty of Clinical Laboratory, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

[3] Division of Hematology and Oncology, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

Case 2 was a male in his 70s with newly diagnosed FL. He had not received COVID-19 vaccination, and he was infected with SARS-CoV-2 7 days after the initial course of R-CHOP. After interruption of R-CHOP, he received comprehensive therapy for COVID-19. He developed sustained pneumonia, but all antibodies except IgM-S1 became positive + 4w after onset.

Case 3 was a female in her 60s who had been diagnosed with FL 3 years earlier and received six courses of R-containing chemotherapies. She experienced recurrence and received six courses of obinutuzumab–CHOP for 2 years without relapse. She also received SARS-CoV-2 vaccination twice 1 year after the last course of chemotherapy, but experienced breakthrough infection 8 weeks after the second vaccination. She experienced moderate COVID-19 pneumonia, but her condition improved without any subsequent complications. At + 2w after onset of infection, her serum sample was positive for IgM-S1 and Nab. In contrast, IgG-N, IgM-N, and IgG-S1 were consistently negative.

Case 4 was a non-infected healthy individual who had received SARS-CoV-2 vaccination twice without any severe adverse effects.

SARS-CoV-2 mRNA vaccination promotes production of anti-S Ab, including S1 as well as the receptor binding domain (RBD), and neutralizes the binding of RBD to the human angiotensin-converting enzyme 2 receptor. Therefore, anti-N antibodies are only produced in affected patients as a marker for past SARS-CoV-2 infection. Nevertheless, only Case 2 was seropositive for anti-N antibodies among the three affected cases (Cases 1–3). On the other hand, Case 3 had already acquired both IgM-S1 and Nab + 2w after infection, as well as Case 4 (non-infected vaccine recipient) at + 4w after vaccination. These findings suggest that both antibodies in Case 3 were produced by SARS-CoV-2 vaccine

before infection, although we were unable to take a sample for analysis at the onset of COVID-19. In contrast, she could produce neither anti-N antibodies nor IgG-S1 at + 4w, suggesting incomplete humoral immunity against SARS-CoV-2. The mechanism of class-switch disturbance of anti-S1 antibodies in Case 3 is unclear, but such disturbance may not be serious, at least in this case.

COVID-19 patients with malignant lymphoma have poor clinical outcomes, especially when undergoing R-based chemotherapies [2]. Moreover, there have been several reports of impaired humoral response to SARS-CoV-2 mRNA vaccination in patients receiving anti-CD20 MoAb [1, 3]. Indeed, Case 3 could not acquire IgG-S1 at + 4w after onset, which was + 12w after the 2nd vaccination, and we did not evaluate her T-cell-mediated immunity to SARS-CoV-2. Nevertheless, she had a high serum titer of Nab against SARS-CoV-2 at + 2w after onset, probably due to vaccine-induced IgM-S1, which enabled her to recover from COVID-19 pneumonia despite her persistently negative IgG-S1 level.

In conclusion, we believe that the humoral effect of SARS-CoV-2 mRNA vaccination should not be evaluated solely based on IgG-S1 or IgG-RBD. Evaluation of a larger number of patients will be necessary to clarify this issue.

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