Discordant SARS-CoV-2 spike protein receptor binding domain IgG and neutralization after B-cell depletion

Numerous publications have reported that patients receiving B-cell-depleting therapies do not mount humoral responses to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccination.[1-3] B-cell recovery following B-cell depleting therapies is variable, with B-cell aplasia often lasting 9 months or longer. It remains unclear when patients who have previously received B-cell depleting therapies are capable of mounting a functional humoral response to vaccination.

We report the case of an 87-year-old woman who developed coronavirus disease (COVID-19) pneumonia shortly after initiating rituximab + etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (R-EPOCH) chemotherapy for highly aggressive diffuse large B-cell lymphoma with 'double-hit' biology (IgH-Myc and IgH-BCL2 translocations) (Figure 1). Following a 6-week treatment delay to allow for recovery from pneumonia, she had a complete metabolic remission and completed an additional five cycles of R-EPOCH. Her lymphoma remains in remission. Surprisingly, despite the dose of rituximab, she mounted an IgG response to the nucleocapsid region of SARS-CoV-2, (AdviseDx SARS-CoV-2 IgG II assay; Abbott) which was detectable 1 month after infection and was sustained for at least 7 months.

Six months after her final dose of anti-CD20 therapy, the patient received her first of several doses of the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine. As expected in the setting of ongoing B-cell depletion, she did not mount a humoral vaccine response after two doses as measured by semi-quantitative IgG to spike protein receptor binding

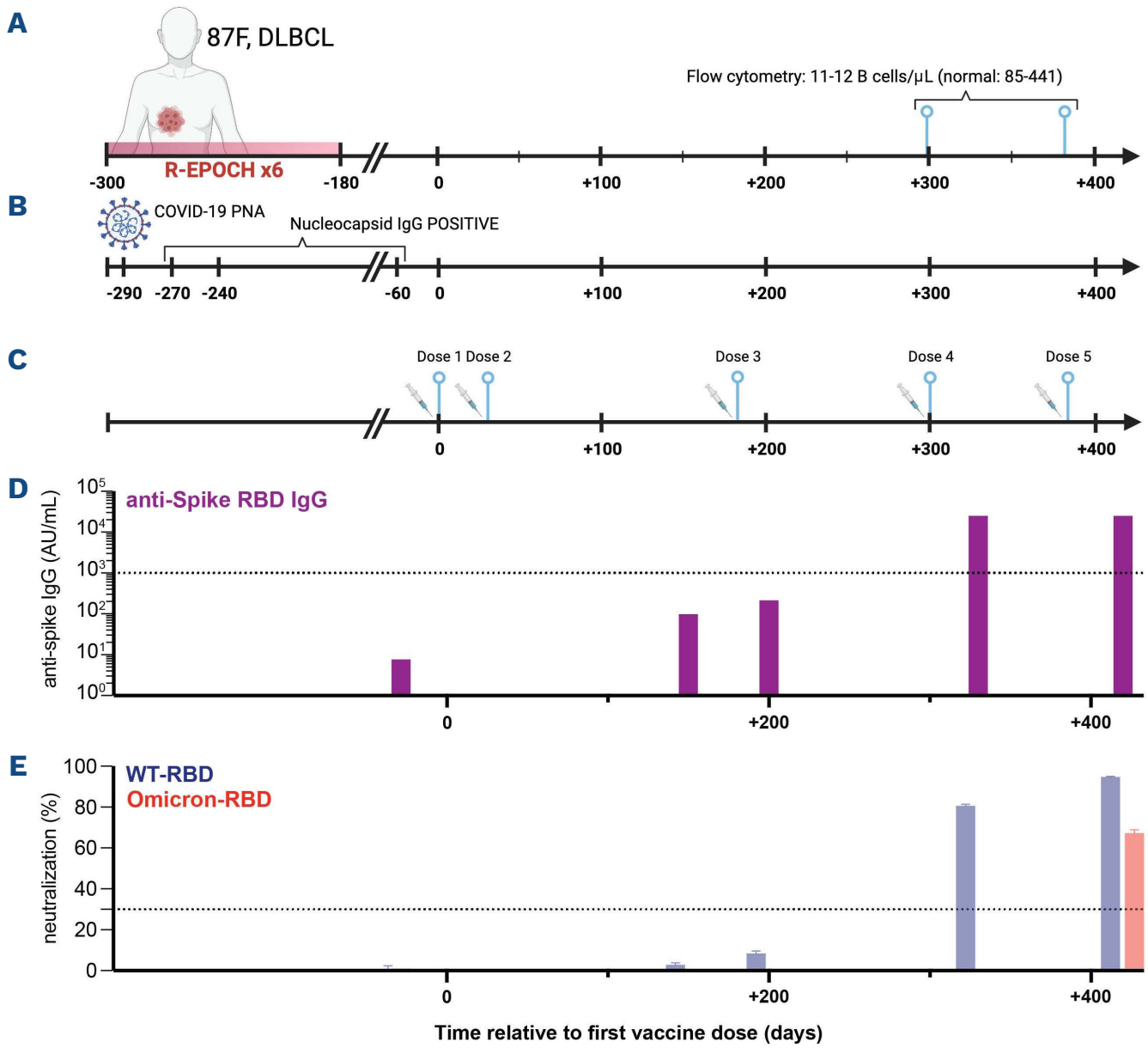

Figure 1. Schematic showing the timeline relative to the first vaccine dose in days. (A) Treatment and B-cell recovery by flow cytometry. (B) Time of infection. (D) Doses of vaccine. (E) Anti-spike receptor binding domain IgG levels. (F) Neutralizing assays to wild-type and Omicron variant SARS-CoV-2. F: female; DLBCL: diffuse large B-cell lymphoma; R-EPOCH: rituximab + etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; WT: wild-type.

domain (RBD). Her third dose, administered 1 year after her final dose of anti-CD20, resulted in only a low-titer quantitative IgG response with no neutralizing activity. Despite flow cytometry analysis of her peripheral blood mononuclear cells showing minimal B-cell reconstitution ($CD19^+$ cells 11/μL), she independently sought out and received a fourth vaccine dose 4 months after her third dose. Surprisingly, her anti-spike RBD IgG titer rose to >25,000 AU/mL with high neutralizing activity (80%) against the wild-type RBD but minimal neutralizing activity (below the limit of detection) against the Omicron variant (SARS-CoV-2 surrogate virus neutralization test kit [Genescript]) Given this improvement, she received a fifth vaccine dose 10 weeks after her fourth dose and demonstrated not only deepening (95% neutralization of WT-RBD) but diversification (66% neutralization against Omicron-RBD) of her humoral antibody response.

These data strongly suggest that patients with a history of anti-CD20 antibody treatment may mount functional humoral immune responses to SARS-CoV-2 vaccines even in the setting of minimal quantitative B-cell recovery. However, this response may require several rounds of vaccination. Furthermore, functional immunity, particularly against the Omicron variants, cannot be inferred from currently available spike IgG antibody titers, which may therefore provide false reassurance about protection in this high-risk population.

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Contributions

AN and SAV conceived the study, generated data, interpreted data and wrote the manuscript.

Data-sharing statement

Anonymized data are available to independent researchers through a standard process, which includes an internal feasibility assessment and scientific review process. Any data release is subject to the participant's consent.

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