Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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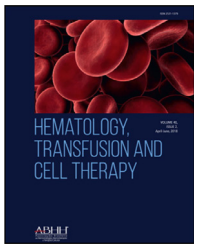

Letter to the Editor

Autoimmune hemolytic anemia and COVID-19 vaccination

Dear Editor,

Mesina recently described a patient with a history of autoimmune hemolytic anemia (AIHA) who acutely relapsed following a booster dose of the SARS-CoV-2 mRNA-1273 vaccine.[1] In addition to the case description, the author thoughtfully outlined possible etiologic mechanisms responsible for the potential hematologic complications of existing COVID-19 vaccines. However, in discussing AIHA, the author erroneously concluded that only 2 types of AIHA exist (warm and cold), omitting mixed AIHA, which is associated with a combination of warm and cold autoantibodies, and paroxysmal cold hemoglobinuria, an autoimmune disorder characterized by a biphasic IgG autoantibody that binds to the P antigen on red blood cells (RBCs) in the cold (peripheral tissues) and then fixes complement and dissociates following exposure to warm (core temperature), resulting in complement-mediated hemolysis.[2] Furthermore, the author stated that "cold AIHA involves IgM antibodies with the maximal reaction at temperatures < 4°C." While cold agglutinins classically react optimally at temperatures well below body temperature (e.g., 4° C), cold autoantibodies with a broad thermal amplitude (i.e., those that react at temperatures closer to physiologic temperature), are more likely to induce clinically significant hemolysis.[3]

Mesina also effectively reviewed the literature describing 6 additional cases of AIHA following SARS-CoV-2 vaccination, 3 of which were associated with the mRNA-1273 vaccine, 2 with the BNT16B2b2 mRNA vaccine, and in 1 case, the mRNA vaccine type was not reported; however, details regarding the patients' risk factors and past medical history are unknown. Our previous study[4] also highlighted 4 cases of AIHA potentially associated with SARS-CoV-2 vaccination, 2 of which[5,6] were not included in the author's current review, 1 associated with the BNT16B2b2 mRNA vaccine and 1 with the mRNA-1273 vaccine. Similar to Mesina's report, prior studies have highlighted the possibility that SARS-CoV-2 infection and/or vaccination may be associated with relapse or acute worsening of underlying hemolytic anemias.[7]

Moreover, in addition to the inclusion of these cases, I queried the United States (US) Centers for Disease Control's (CDC) Vaccine Adverse Event Reporting System (VAERS)[8] as of June 4, 2022 to determine if potential cases of AIHA have been reported. The VAERS database is a passive, national surveillance system maintained by the CDC and the US Food and Drug Administration (FDA) implemented to detect adverse events that are potentially associated with vaccines authorized or licensed by the FDA. Events may be submitted by any individual, and while its passive nature and variability in data availability are limitations, its national scope and requirements for reporting serious adverse events make it a useful tool for assessing the possibility of rare adverse events not identified in clinical trials.

Search of the VAERS database for SARS-CoV-2 vaccine-associated AIHA utilized the keywords "haemolysis", "haemolytic anaemia", and "cold agglutinins". All SARS-CoV-2 vaccines available in the VAERS database were included in the query. A total of 107 AIHA reports were identified. Following exclusion of duplicate reports, cases with concurrent SARS-CoV-2 infection, and cases with inadequate information, 17 (12 females, 5 males) contained sufficient details to represent potential cases of new or relapsed hemolytic anemia associated with SARS-CoV-2 vaccination. Inclusion criteria for AIHA determination included a reported acute drop in hemoglobin and/or hematocrit following SARS-CoV-2 vaccination in conjunction with at least 2 new abnormal laboratory findings: elevated total and indirect bilirubin, elevated lactate dehydrogenase, decreased haptoglobin, or a positive direct antiglobulin test.

The median (interquartile) age of the 17 patients was 60 years (32 years), 9 of whom received the BNT16B2b2 mRNA vaccine, and 8 received the mRNA-1273 vaccine. Hemolysis occurred following the first dose in 8 patients, the second dose in 8 patients, and the third dose in 1 patient. The onset of hemolysis ranged from 1 day after the first dose (BNT16B2b2 mRNA vaccine) to 48 days after the second dose (mRNA-1273 vaccine). Similar to the patient described by Mesina, several patients in the VAERS database had predisposing risk factors for hemolytic anemia, including thymic carcinoma on pembrolizumab (1), chronic lymphocytic leukemia (1), paroxysmal

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nocturnal hemoglobinuria on ravulizumab (3), and warm AIHA in remission (1). The median hemoglobin nadir was 5.4 g/dL (1.8 g/dL). Unfortunately, only 5 reports described the type of AIHA (3 warm AIHA and 2 cold AIHA).

The results from the US CDC VAERS database support prior studies and the case presented by Mesina that SARS-CoV-2 mRNA vaccines may rarely be associated with AIHA and other types of hemolytic anemia, particularly in patients with predisposing risk factors. Further mechanistic studies are warranted, and patients with significant risk factors should be cognizant of the signs and symptoms of AIHA following SARS-CoV-2 vaccination.

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Conflicts of interest

The author declares no conflicts of interest.

REFERENCES

1. Mesina FZ. Severe relapsed autoimmune hemolytic anemia after booster with mRNA-1273 COVID-19 vaccine. Hematol Transfus Cell Ther. 2022. https://doi.org/10.1016/j.htct.2022.05.001.
2. Shanbhag S, Spivak J. Paroxysmal cold hemoglobinuria. Hematol Oncol Clin North Am. 2015;29(3):473–8. https://doi.org/10.1016/j.hoc.2015.01.004.
3. Hill A, Hill QA. Autoimmune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2018;2018(1):382–9. https://doi.org/10.1182/asheducation-2018.1.382.
4. Jacobs JW, Booth GS. COVID-19 and immune-mediated RBC destruction. Am J Clin Pathol. 2021: aqab210. https://doi.org/10.1093/ajcp/aqab210.
5. Gaignard ME, Lieberherr S, Schoenenberger A, Benz R. Autoimmune hematologic disorders in two patients after mRNA COVID-19 Vaccine. Hemasphere. 2021;5(8):e618.. https://doi.org/10.1097/HS9.0000000000000618. Published 2021 Jul 13.
6. Aoun SA, Motabi I. Cold agglutinin disease after COVID-19 vaccine. Br J Haematol. 2021;195(5):650. https://doi.org/10.1111/bjh.17674.
7. Fattizzo B, Pasquale R, Bellani V, Barcellini W, Kulasekararaj AG. Complement mediated hemolytic anemias in the COVID-19 era: case series and review of the literature. Front Immunol. 2021;12:791429. https://doi.org/10.3389/fimmu.2021.791429.
8. United States Department of Health and Human Services (DHHS), Public health service (PHS), centers for disease control (CDC) /food and drug administration (FDA), vaccine adverse event reporting system (VAERS) 1990 - 05/27/2022, CDC WONDER On-line database. Accessed at http://wonder.cdc.gov/vaers.html on Jun 4, 2022.

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