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LETTER TO THE EDITOR

A case of severe autoimmune hemolytic anemia after a receipt of a first dose of SARS-CoV-2 vaccine

Dear Editors,

SARS-CoV-2 mRNA vaccine made by Pfizer and BioNTech was approved by the US Food and Drug Administration for use under an Emergency Use Authorization for active immunization to prevent coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on December 11, 2020.[1] Intolerance reactions to the vaccine identified in the initial study were usually transient and mild to moderate.[2] More serious and rare cases of anaphylaxis were reported following the emergency authorization with widespread vaccination efforts.[3] Later, the occurrence of immune thrombocytopenia and thromboembolic events in vaccine recipients (from different manufacturers) reached attention in general press[4] and in medical literature.[5,6] This is the first case published in the scientific literature of an individual with symptomatic, severe autoimmune hemolytic anemia diagnosed in the third week after receiving Pfizer-BioNTech Covid-19 vaccine, with recovery after corticosteroid therapy.

1 | CASE REPORT

The patient, in this case, is an 84-year-old man, a Vietnam War veteran of Greek-Turkish descent, whose medical history is significant for major depression/anxiety, prostate cancer (status post remote prostatectomy), colon cancer (status post remote laparoscopic right hemicolectomy with patent anastomosis and no evidence for recurrence on recent colonoscopy within the last year), nonocclusive coronary artery disease, hypertension, emphysema, trace cryoglobulinemia (evaluated by Hematology two years ago and considered clinically insignificant), evidence for duodenitis on recent endoscopy (within 6 months), chronic alcohol consumption, and mild chronic anemia with baseline hemoglobin of 13.3 g/dL 4 months prior to presentation (reference range, 13.5-17.5 g/dL).

He received the first dose of Pfizer-BioNTech BNT16B2b2 mRNA vaccine through the Veterans Administration system in early 2021.

On day 19 post-vaccine, the patient presented to his primary clinic with increased urinary frequency and dizziness. Urine analysis showed a small amount of bilirubin and few bacteria but no WBC or RBC. Urine culture was positive for 10 000-50 000 col/mL of Enterobacter cloacae. The patient was initiated on oral ciprofloxacin, of which he took 5 doses but then later self-discontinued due to worsening symptoms. (Other chronic, scheduled medications included atorvastatin, cholecalciferol, cyanocobalamin, finasteride, metoprolol SR, sertraline, and ocuvite capsule).

Worsening of the patient's chronic anemia was also noted during the appointment. Hemoglobin level was now 8.8 g/dL, MCV 107 fL (reference range, 80-100 fL), and reticulocyte count 0.163 mill/μL (reference range, 0.010-0.110 mill/μL). The patient was referred to outpatient hematology, but his symptoms worsened before his scheduled appointment.

These symptoms included dizziness/vertigo, nausea, anorexia, shortness of breath, chest pain, palpitations, "ashen" appearance, and dark urine, ultimately causing an emergency presentation to our hospital and inpatient admission 5 days after his initial visit to the outpatient clinic. The patient appeared pale, but his vital signs including oxygenation were normal. Frequent PVCs were noted on cardiac examination and on otherwise normal EKG. Rest of the physical examination was normal. Chest radiograph was clear.

Admission hemoglobin was now noted to be 5.6 g/dL and on repeat draw, 4.9 g/dL. Further abnormalities noted on peripheral blood included leukocytosis of 18.0 thou/cu mm with neutrophilia (reference range, 4.5-11.0 thou/cu mm), MCV of 124 fL, and reticulocyte of greater than 19.0% (reference range, 0.5%-2%), with elliptocytes and polychromasia. Ferritin was elevated at 561.5 ng/mL (reference range, 22.0-275.0 ng/mL). LDH was elevated at 503 IU/L (reference range, 125-220 IU/L). Haptoglobin was less than 8.00 mg/dL (reference range, 30-215 mg/dL). Glucose 6 phosphate dehydrogenase level was increased at 802 U/10E12 RBC (reference range, 127-427 U/10E12 RBC). B12 level was 329 pg/mL (reference range, 180-914 pg/dL). Total bilirubin was elevated at 3.3 mg/dL with indirect bilirubin of 2.8 mg/dL (reference range, 0.2-1.2 mg/dL and 0.2-0.8 mg/dL, respectively). The rest of the liver function tests was normal. COVID-19 testing of a nasopharyngeal specimen using a PCR method was negative. Peripheral blood morphology was consistent with a leukoerythroblastic reaction with marked macrocytic anemia and marked reticulocytosis (19%), along with moderate absolute neutrophilia and monocytosis. Interestingly, there was no morphologic evidence of hemolysis. The direct antiglobulin test (DAT) was positive for DAT ANTI-IGG and DAT polyspecific AHG, and negative for DAT ANTI-C3.

Inpatient hematology consultation was obtained, concluding that autoimmune hemolytic anemia indeed is present. The patient was given a single dose of methylprednisolone 1000 mg IV in the evening of admission and started on prednisone 1 mg/kg

(60 mg/d) the day after, with a recommended outpatient taper (reducing the prednisone dose by 10 mg/wk). The patient was also transfused with 2 units of packed red blood cells upon admission. With these treatments, the patient's hemoglobin increased to 7.7 g/dL on the second hospital day and remained stable at discharge on the third hospital day (hemoglobin level at discharge was 7.3 g/dL) as well as during the follow-up in the outpatient clinic (8.2 g/dL 2 days after discharge and 9.0 g/dL 1 week following the discharge).

A second COVID-19 vaccination was not advised at this point due to the occurrence of autoimmune hemolytic anemia in the weeks following the first dose. The event was reported as a possible vaccine-related side effect through the FDA's Vaccine Adverse Event Reporting System (VAERS). The patient was scheduled for a close outpatient follow-up with his primary internal medicine provider as well as with his hematologist.

2 | DISCUSSION

As COVID-19 large-scale vaccination efforts are underway and millions of vaccines have been delivered, reports about possible rare reactions or side effects have accumulated. A series of reports described new cases of immune thrombocytopenia or vaccine-induced immune thrombotic thrombocytopenia (VITT) in the first weeks after administration of vaccines from several manufacturers, some with fatal outcomes.[4–8] A direct role of COVID-19 genetic vaccines in spurring autoimmune response against host proteins—as the detection of high levels of antibodies to platelet factor 4 in almost all cases of VITT may suggest—has been proposed.[9] It appears plausible that a similar SARS-CoV-2 vaccine-induced host response could lead to destruction of erythrocytes and hemolysis.

Statistically, however, when examined against the background of natural occurrence, these clinical thromboembolic events appeared coincidental (ie, not increased beyond the expected incidence rate in the general population) and less likely linked to the vaccine itself.[6] Thus far, the only evidence for a link between the COVID-19 vaccines and possible hematological side effects remains only circumstantial and relies heavily on temporal association. Additional supporting evidence comes from (a) ruling out other common conditions or causes, (b) similarity to other suggested adverse effects of the vaccine—such as VITT, which shares similar timeline, proposed mechanism, and response to treatment with the case of autoimmune hemolytic anemia presented here,[6] and (c) the fact that described condition (such as autoimmune hemolytic anemia in this case) can occur as a complication of the COVID-19 infection itself.[10]

Here, I am reporting a temporal relationship of a case of severe autoimmune hemolytic anemia with a receipt of a first dose of Pfizer-BioNTech COVID-19 vaccine. As mentioned, autoimmune hemolytic anemia has been described as a complication of the COVID-19 infection itself. It has not, however, to my knowledge, been reported in the scientific literature to occur after COVID-19 vaccination. The timeline of the onset of hemolysis within the first three weeks post-vaccination is comparable to that of immune thrombocytopenia. Similarly, the occurrence after the initial dose of SARS-CoV-2 vaccine (and not after the second one), the rapidity and severity of the red blood cell drop, and the favorable response to corticosteroid treatment are comparable between the two conditions. The patient at the time of presentation did not have any evidence for active autoimmune disease, lymphoproliferative disorder or infectious process, or other conditions commonly associated with secondary autoimmune hemolytic anemia such as exposure to toxins or medications. An association between ciprofloxacin, prescribed shortly before the patient's autoimmune hemolytic anemia diagnosis, has been carefully examined as such a relation had been documented previously.[11] The fact that laboratory indices such as hemoglobin decline, macrocytosis, and reticulocytosis pointed toward hemolysis *prior* to the initiation of the antibiotic all speak against such association in this case.

In conclusion, the purpose of reporting a case of serious autoimmune hemolytic anemia that has developed in the absence of other likely causes shortly after a receipt of an initial SARS-CoV-2 vaccine is to raise awareness about a possible, rare, and previously unreported hematological side effect of the vaccine. It does not provide proof of a causative relationship but rather serves to alert the clinicians to this possible association, so that they can obtain laboratory evidence of hemolysis should individuals with a sudden hemoglobin drop post SARS-CoV-2 vaccine present to their practice.

KEYWORDS

autoimmune hemolytic anemia, COVID-19 vaccine

CONFLICT OF INTEREST

The author has no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. *Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization Review Memorandum*. U.S. Food and Drug Administration. www.fda.gov. Accessed December 11, 2020.
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med*. 2020;383:2603-2615.
3. CDC COVID-19 Response team, Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine - United States, December 14-23, 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70:46-51.
4. Grady D, Mazzei P. *Doctor's death after Covid vaccine is being investigated*. The New York Times. Published January 12, 2021.
5. Tarawneh O, Tarawneh H. Immune thrombocytopenia in a 22-year-old post Covid-19 vaccine. *Am J Hematol*. 2021;96:E133-E134.
6. Lee EJ, Cines DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol*. 2021;96:534-537.
7. Wise J. Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. *BMJ*. 2021;372:n699.
8. Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. *N Engl J Med*. 2021;384:1964-1965.
9. Cines DB, Bustle JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med*. 2021;384(23):2254-2256.
10. Lazarian G, Quinquenel A, Bellal M, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol*. 2020;190:29-31.
11. Mackay AD, Mehta A. Autoimmune haemolytic anaemia associated with ciprofloxacin. *Clin Lab Haem*. 1995;17:97-98.