Case Report

Acute Thrombotic Thrombocytopenic Purpura: Rare and Life-Threatening Side Effect of Recent BNT-162b2 COVID-19 Vaccination

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Abstract

Description

Thrombotic thrombocytopenic purpura (TTP) is a rare, potentially life-threatening disorder characterized by uncontrolled and spontaneous clot formation throughout the body. Known secondary causes of TTP include malignancy, bone marrow transplantation, pregnancy, various medications, and HIV infection. TTP in the setting of COVID-19 vaccination is rare and not well reported. Reported cases have been confined primarily to the AstraZeneca and Johnson and Johnson COVID-19 Vaccines. TTP in the setting of Pfizer BNT-162b2 vaccination has only recently been reported. We present a patient with no obvious risk factors for TTP who presented with acute altered mental status and was found to have objective evidence of TTP. To our knowledge, there are very few reported cases of TTP in the setting of a recent Pfizer COVID-19 vaccination.

Keywords

COVID-19 vaccines; BNT162 vaccines; BNT-162b2; thrombotic thrombocytopenia; thrombotic thrombocytopenic purpura; TTP; idiopathic thrombocytopenic purpura; drug-related side effects and adverse reactions; SARS-CoV-2

Introduction

The United States (US) Food and Drug Administration (FDA) issued an emergency use authorization (EUA) of the Pfizer COVID-19 vaccine for individuals ages 16 years or older, on December 11, 2020.[1] The age bracket was later extended to include children from 5-15 years of age under the EUA.[2] This was the first marketed vaccine in the US for the prevention of SARS-CoV-2[1] and as of now, more than 75% of US adults have received at least a single shot of one of the three authorized COVID-19 vaccines.[3] To date, over 200 million Pfizer BNT-162b2 vaccinations have been administered worldwide. As one of the first vaccinations to obtain FDA approval in the US, this mRNA vaccine has an important role in the prevention and mitigation of the COVID-19 pandemic. Since the beginning of the pandemic, a plethora of research and case reports have been published regarding additional specific adverse effects of various COVID-19 vaccines. In preliminary studies, the most common serious adverse events reported were appendicitis, acute myocardial infarction, and cerebrovascular accident which are found to have a higher incidence in the vaccination groups versus the placebo group, with the overall incidence being 0.6% of patients in the vaccination group.[4] Thrombotic thrombocytopenic purpura (TTP) was reported as a consequence of COVID-19 infection itself[5], but recent reports suggest that TTP may be associated with recent Pfizer vaccine administration.[6-9] Phenomena of thrombocytopenia with thrombotic events of possible vaccine-induced thrombotic thrombocytopenia (VITT) were reportedly associated with the Johnson and Johnson and AstraZeneca vaccines, which are not BNT-162b2 vaccines.[10] Presentation of

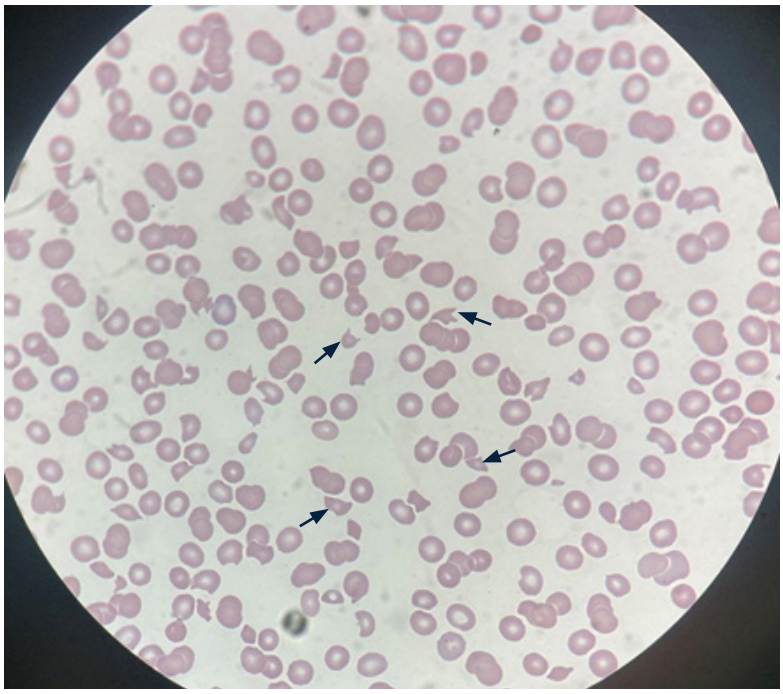

Figure 1. An image of a peripheral smear indicates florid schistocytes (some highlighted with black arrows), nucleated red blood cells, and rouleaux formations (40X magnification).

TTP can involve a pentad of findings of fever, microangiopathic hemolytic anemia (MAHA) with schistocyte formation, thrombocytopenia, renal dysfunction, and changes in mental status, although the presence of all 5 symptoms overall is quite rare.[8] To our knowledge, this is one of very few reported cases of BNT-162b2 vaccine-associated TTP worldwide.

Case Presentation

We present a case of a 75-year-old male of Indian descent with a past medical history of hypertension and diabetes mellitus who presented to the hospital with a complaint of altered mental status, associated with difficulty speaking since the morning on the day of presentation. The patient was otherwise in good health with no active complaints until the morning of the presentation. His home medications included losartan, glimepiride, metformin, and sitagliptin. There was no reported history of any recent sick contacts or exposure to someone who tested positive for COVID-19, recent travel, changes in home medication, substance abuse, history of trauma, or any recent hospitalization. The patient was, however, administered his second dose of the BNT-162b2 vaccine 23 days prior to the current presentation. On admission, a stroke alert was called out of concern from the endorsed symptoms. Initial vital signs were stable. A preliminary neurological exam was notable for mild dysarthria, slurred speech, and slight right lower extremity drift. Computerized tomography (CT) of the head and CT angiogram (CTA) of the head and neck were negative for intracranial hemorrhage, large vessel occlusion, or any other acute findings. The patient was outside the window for tissue plasminogen activator therapy and subsequently was admitted for further management.

Initial blood work showed hemoglobin of 8.1 g/dL (reference range: 12-17 g/dL), platelets of 18 x 10^9/L (reference range: 150-400 x 10^9/L), aspartate transaminase (AST) of 255 U/L (reference range: <37 U/L), alanine transaminase (ALT) of 222 U/L (reference range: <78 U/L), prothrombin time of 14.5 sec (reference range: 10.2-12.9 sec), and lactate dehydrogenase (LDH) was 2356 U/L (reference range: 85-227 U/L). Blood peripheral smear was evident for schistocytes (**Figure 1**). Our working diagnosis was TTP, as there was a clinical concern of MAHA and acquired thrombocytopenia with a plasmic score of 6. During the placement of a non-tunneled dialysis catheter for emergent plasma exchange, the patient had generalized seizure-like activity with a subsequent worsen-

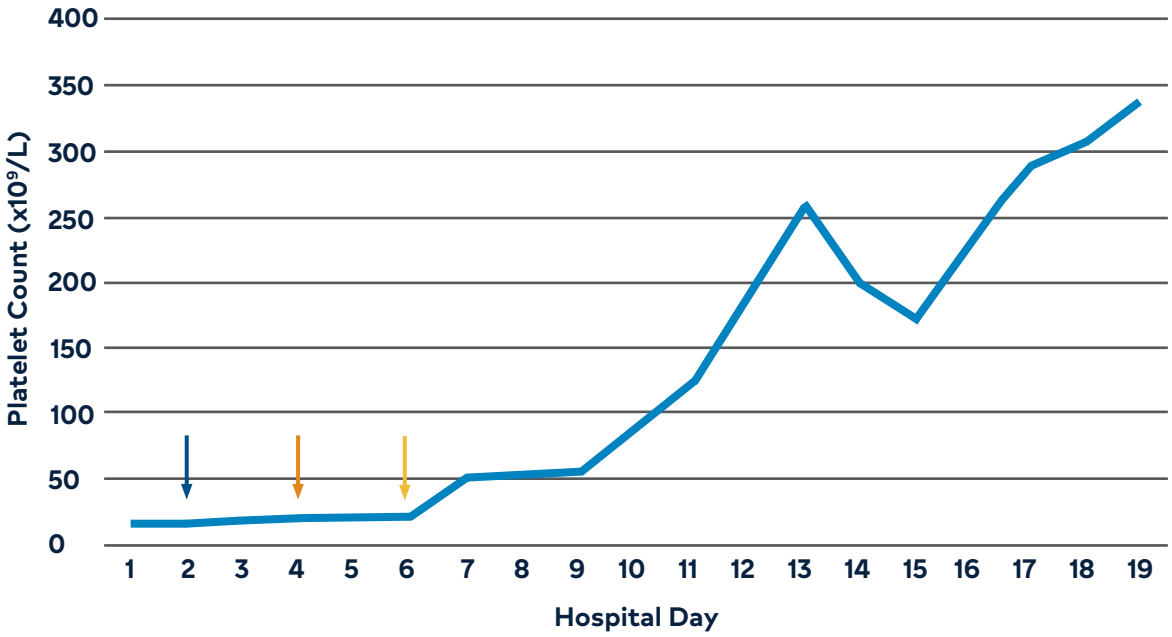

Figure 2. The trend of platelet count during the patient's hospital course (Normal platelet range: 150-400 x 109/L) is shown. The initiation of plasma exchange and steroids (blue arrow), rituximab (orange arrow), and IVIG (yellow arrow) are indicated.

ing of mentation, requiring intubation to secure the airway.

After multidisciplinary consultation, it was determined that the patient was to undergo daily plasma exchange and to start a pulse dose of intravenous (IV) methylprednisolone 1g daily. Meanwhile, a serological workup was ordered including, ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) antibody and activity level, HIV antibodies, serum protein electrophoresis, antinuclear antibody, rapid plasma reagin, PF-4 (platelet factor-4/heparin-induced thrombocytopenia [HIT]) autoantibodies, antinuclear nuclear antibody titers, and hepatitis screening along with non-contrast magnetic resonance imaging (MRI) of the brain, CTA of the chest, an echocardiogram and a liver ultrasound. These laboratory and radiological studies were ordered to rule out other potential etiologies of the patient's clinical presentation and to look for objective evidence of thrombosis. The patient continued on daily plasma exchange and pulse dose IV steroids with no clinical improvement, and platelets remained essentially unchanged, staying stable around 19-20 x 10^9/L. For his refractory clinical response to the treatment, the differential diagnosis was broadened further, to include concurrent idiopathic thrombotic purpura, and the decision was made to start IV immunoglobulin (IVIG) on day 4. Concurrently, rituximab was also started on day 4 and his platelet count started improving to 50 x 10^9/L, on day 5 of hospitalization (**Figure 2**).

The blood workup returned as negative, except for elevated ADAMTS13 antibody titer (>182 U/ml, reference range: <12 U/ml) and ADAMTS13 activity level of less than 2% (reference range: > 66.8%), confirming the diagnosis of TTP. An MRI of the brain (**Figure 3**) showed bilateral cerebral and cerebellar hemispheres infarcts, likely secondary in the setting of TTP thrombosis, although the chest CTA remained negative for pulmonary embolism, the echocardiogram read as normal biventricular function with no evidence of wall motion abnormality or intracardiac thrombus, and the liver ultrasound showed normal main portal vein flow. The patient was eventually able to tolerate spontaneous breathing trials and was finally weaned from the ventilator. Plasma exchange was reduced in frequency from daily to every other day and eventually to every 72 hours. Initial IV methylprednisolone was tapered to oral prednisone. Prophylactic trimethoprim/sulfamethoxazole was started given his prolonged high

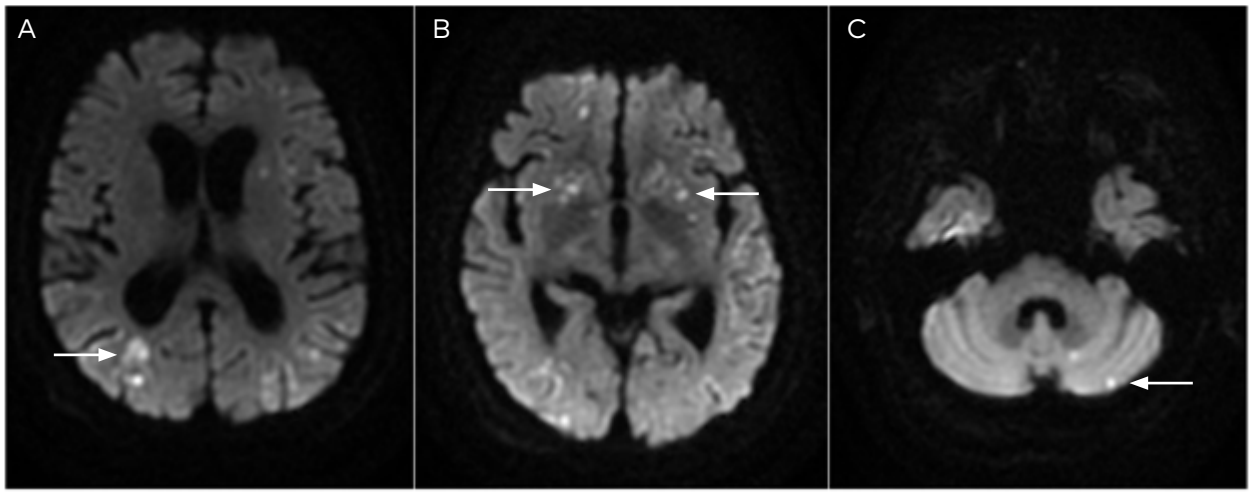

Figure 3. A magnetic resonance diffusion-weighted axial image shows multiple small foci scattered throughout both cerebral (white arrows in A and B) and cerebellar (white arrow in C) hemispheres indicating scattered punctate acute infarctions.

dose steroid use. In total, he received 4 doses of rituximab (375 mg/m^2 once weekly infusions) and IVIG. He was finally discharged to an inpatient rehabilitation center, where he stayed for 14 days and was discharged home after the removal of the temporary dialysis catheter. To ensure the stability of his platelet count, it was monitored through the course of the patient's stay and was reported as 170 x 10^9/L on the day of discharge from the hospital and as 219 x 10^9/L on the day of discharge from the rehabilitation center. His platelet count was found to be within the normal range on his most recent outpatient visit, 6 months following the discharge from the rehabilitation center.

Discussion

TTP is a rare, life-threatening disorder associated with thrombocytopenia, microangiopathic hemolytic anemia, and thrombotic events secondary to underlying inherited or acquired deficiency of von-Willebrand factor (vWF)-cleaving protease ADAMTS13. The severely reduced ADAMTS13 activity (generally less than 10%) leads to ultra-large multimers of vWF because of its insufficient processing. This larger molecular structure gets disheveled while passing through the microcirculation system, where it triggers unwanted aggregation of platelets, and finally a thrombosis.[11,12] Prompt recognition and empiric treatment are crucial, as TTP is almost always fatal if not treated. Treatment focuses on plasma exchange, which removes the vWF-multimer complexes from the circulation. Other concurrent strategies used include high-dose IV steroids and rituximab. With timely diagnosis and appropriate treatment, survival rates range anywhere from 60 to 90%. TTP is predominantly found in females and those of African descent and the median age of presentation is typically around 40 years. It is unusual for TTP to present in the elderly, especially over the age of 70 years; this case was unusual as the patient was a male, 75 years of age, and of Indian descent.[9] Congenital TTP is typically caused by autoantibodies or a mutation against ADAMTS13. Acquired TTP often occurs in the setting of concurrent organ transplantation, malignancy, pregnancy, autoimmune diseases (especially systemic lupus erythematosus [SLE])[8,9], or medications, such as mitomycin C, quinine, cyclosporine, ticlodipine, or clopidogeral, among others.[8,9,13] Our patient had none of these risk factors, and the workup for other causes was negative.

The BNT-162b2 vaccine was the first FDA-approved vaccine for the prevention of SARS-Cov-2. It was initially targeted for individuals ages 16 years and older, to be administered in 2 doses 21 days apart, and is now authorized, through EUA for ages 5 years and over.[2] Recently, the FDA recommended a third (booster dose) for ages 12 years and older, at least 5 months after completion of the primary BNT-162b2 vaccine series.[2] The most common reported side effects include pain at the injection site, myalgias, headache, fevers, and nausea.[4] Previously known safety concerns with the use of mRNA vaccines include: local, or systemic

inflammatory responses,[12,14] and the possibility of thrombus formation, potentially because mRNA causes platelet-independent direct activation of coagulation factors. The same hypothesis was extended as a probable cause for thromboembolic events in cancer patients. mRNA vaccines induce immune complexes containing RNA-binding proteins, triggering plasmacytoid dendritic cells via toll-like receptors (TLR), leading to an elevation in serum type-1 interferon (IFN) immune activity.[11] The type-1 IFN system, which plays an important role in innate and adaptive immunity, is associated with the production of autoantibodies against RNA-binding proteins[16] in various autoimmune diseases including SLE. Drug[17] and inflammation-induced[18] type-1 IFN responses are also well-documented triggers for thrombotic microangiopathy[17], including TTP due to the acquired deficiency of ADAMTS13.[11]

Further reports have been published depicting more uncommon side effects of the vaccines for COVID-19. Preliminary studies suggested evidence of a vaccine-induced thrombotic thrombocytopenia (VITT) following Astra-Zeneca and Johnson and Johnson vaccination, which are not mRNA vaccines.[10,19] The diagnostic criteria for VITT include the evidence of COVID-19 vaccination within the last 4 to 42 days, any thrombotic event, platelet count < 150 x 10^9/L, positive PF4 (HIT) assay, and D-dimer of greater than 4 times the upper normal limit.[10] In the present case, the HIT assay was negative, and therefore we assumed VITT was a less likely mechanism in our patient. Moreover, the patient's lack of clinical improvement raised a possible concern for autoimmune hemolysis with concomitant immune-thrombocytopenia and the decision was made to start IVIG on day 6 of hospitalization. Although IVIG was also used as an adjuvant therapy, in TTP refractory to plasma exchange, its first-line use has not been thoroughly established.[20]

The pathophysiology of vaccine-induced TTP is not well understood. The first case report on vaccine-induced TTP was published in 1960, involving the typhoid vaccine. Since then, there have been other reported cases involving influenza, pneumococcal, and H1N1 vaccines among others.[5,6] It is thought to potentially occur through proposed mechanisms such as increased vWF-release from the endothelium[7] or due to molecular mimicry from vaccine antigens.[9] Further studies are needed to confirm these hypotheses.

Conclusion

TTP is a life-threatening disorder that needs to be treated emergently with plasma exchange while awaiting further test results. With the increased administration of COVID-19 vaccinations, more serious side effects are being reported. In the present case, as there was no objective evidence for concurrent infection, immunocompromised conditions, a genetic component, an autoimmune process, or malignancy, we believe the recently administered Pfizer BNT-162b2 vaccination presented the most likely cause of his diagnosis. TTP is a rare side effect, with only 5 reported cases globally in the setting of the recent Pfizer BNT-162b2 vaccination.[6-9,21] Therapy relies upon plasma exchange, with further mitigation from steroids and potentially rituximab. IVIG may be used as an adjuvant to enhance clinical success however, its role in the first episode of TTP has yet to be established. Through this case report we hope to bring greater awareness to TTP as a significant potential complication of COVID-19 vaccination, in particular the Pfizer BNT-162b2 vaccine. With further clinical and laboratory research, this association can be better understood.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

1. US Food and Drug Administration. Pfizer-BioNTech COVID-19 Vaccines: Comirnaty and Pfizer-BioNTech COVID-19 Vaccine. 2021. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccines
2. COMIRNATY® (COVID-19 Vaccine, mRNA). Pfizer; 2022. https://www.comirnaty.com/
3. United States Census Bureau. Household Pulse Survey COVID-19 Vaccination Tracker. December 22, 2021. https://www.census.gov/library/visualizations/interactive/household-pulse-survey-covid-19-vaccination-tracker.html
4. Pfizer-BioNTech COVID-19 Vaccine Overview and Safety (also known as COMIRNATY). 2021.
5. Karabulut K, Andronikashvili A, Kapici AH. Recurrence of thrombotic thrombocytopenic purpura after mRNA-1273 COVID-19 vaccine administered shortly after COVID-19. *Case Rep Hematol*. 2021;2021:4130138. doi:10.1155/2021/4130138
6. de Bruijn S, Maes MB, De Waele L, Vanhoorelbeke K, Gadisseur A. First report of a de novo iTTP episode associated with an mRNA-based anti-COVID-19 vaccination. *J Thromb Haemost*. 2021;19(8):2014-2018. doi:10.1111/jth.15418
7. Ruhe J, Schnetzke U, Kentouche K, et al. Acquired thrombotic thrombocytopenic purpura after first vaccination dose of BNT162b2 mRNA COVID-19 vaccine. *Ann Hematol*. 2022;101(3):717-719. doi:10.1007/s00277-021-04584-y
8. Waqar SHB, Khan AA, Memon S. Thrombotic thrombocytopenic purpura: a new menace after COVID bnt162b2 vaccine. *Int J Hematol*. 2021;114(5):626-629. doi:10.1007/s12185-021-03190-y
9. Chamarti K, Dar K, Reddy A, Gundlapalli A, Mourning D, Bajaj K. Thrombotic thrombocytopenic purpura presentation in an elderly gentleman following COVID vaccine circumstances. *Cureus*. 2021;13(7):e16619.
10. Bussel JB, Connors JM, Cines DB, et al. Thrombosis with Thrombocytopenia Syndrome (also termed Vaccine-induced Thrombotic Thrombocytopenia) 2021. Last updated: January 28, 2022 https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia
11. Edgar CE, Terrell DR, Vesely SK, et al. Ribosomal and immune transcripts associate with relapse in acquired ADAMTS13-deficient thrombotic thrombocytopenic purpura. *PLoS One*. 2015;10(2):e0117614. doi:10.1371/journal.pone.0117614
12. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov*. 2018;17(4):261-279. doi:10.1038/nrd.2017.243
13. Medina PJ, Sipols JM, George JN. Drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Curr Opin Hematol*. 2001;8(5):286-293. doi:10.1097/00062752-200109000-00004
14. Pepini T, Pulichino AM, Carsillo T, et al. Induction of an IFN-mediated antiviral response by a self-amplifying RNA vaccine: implications for vaccine design. *J Immunol*. 2017;198(10):4012-4024. doi:10.4049/jimmunol.1601877
15. Kannemeier C, Shibamiya A, Nakazawa F, et al. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. *Proc Natl Acad Sci U S A*. 2007;104(15):6388-6393. doi:10.1073/pnas.0608647104
16. Niewold TB, Hua J, Lehman TJ, Harley JB, Crow MK. High serum IFN-alpha activity is a heritable risk factor for systemic lupus erythematosus. *Genes Immun*. 2007;8(6):492-502. doi:10.1038/sj.gene.6364408
17. Pisoni R, Ruggenenti P, Remuzzi G. Drug-induced thrombotic microangiopathy: incidence, prevention and management. *Drug Saf*. 2001;24(7):491-501. doi:10.2165/00002018-200124070-00002
18. Swisher KK, Doan JT, Vesely SK, et al. Pancreatitis preceding acute episodes of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: report of five patients with a systematic review of published reports. *Haematologica*. 2007;92(7):936-943. doi:10.3324/haematol.10963
19. Greinacher A, Langer F, Makris M, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT): update on diagnosis and management considering different resources. *J Thromb Haemost*. 2022;20(1):149-156. doi:10.1111/jth.15572
20. Ding J, Baer MR, Hess JR, Zimrin AB. Intravenous immunoglobulin as salvage therapy for refractory thrombotic thrombocytopenic purpura. *Am J Hematol*. 2018;93(3):E77-E79. doi:10.1002/ajh.25007
21. Jasaraj RB, Shrestha DB, Gaire S, Kassem M. Immune thrombocytopenic purpura following Pfizer-BioNTech COVID-19 vaccine in an elderly female. *Cureus*. 2021;13(8):e16871. doi:10.7759/cureus.16871