



Thrombotic thrombocytopenic purpura: a new menace after COVID bnt162b2 vaccine

Syed Hamza Bin Waqar¹ · Anosh Aslam Khan² · Shehzeen Memon²

Received: 19 May 2021 / Revised: 2 July 2021 / Accepted: 9 July 2021 / Published online: 15 July 2021

© This is a U.S. government work and not under copyright protection in the U.S.; foreign copyright protection may apply 2021

Abstract

Thrombotic thrombocytopenic purpura (TTP) is a known menace in hematology and is quite rare in practice with known triggers. Lately, in the COVID-19 pandemic, hematology has seen a new pathology amongst which TTP associated with COVID-19 messenger RNA (mRNA) vaccine is unique. We report a case of a 69-year-old male with multiple comorbidities who presented to the hospital with severe fatigue and shortness of breath. Labs were significant for thrombocytopenia, anemia, and hemolysis with schistocytes consistent with TTP with a second dose of BNT162b2 mRNA vaccine as a likely culprit been documented.

Keywords COVID-19 · Vaccine · TTP · Thrombosis · Thrombocytopenia

Case description

A 69-year-old male with a known medical history of hypertension, chronic kidney disease, HIV on anti-retroviral therapy (ART), chronic hepatitis B, two prior episodes of deep vein thrombosis managed with daily oral warfarin, presented to the emergency department with primary complaints of severe fatigue and new onset of shortness of breath for past three days. The shortness of breath was progressive, limiting his ability to walk and even talk in complete sentences without stopping to catch his breath. He denied any inciting event. There was no association with fever, chills, night sweats, weight loss, headaches, vision changes, cough, sputum chest pain, abdominal pain, rash, bleeding, bruising, edema, focal weakness, or changes in bowel or urinary habits. The patient received a second dose of BNT162b2 mRNA vaccine one week before the onset of concerning symptoms.

On examination, the patient was afebrile and hemodynamically stable with oxygen saturation of 96% at room air. The patient appeared frail and tired but in no apparent

distress. A thorough examination was unremarkable with no neurological deficits. An initial baseline laboratory workup was sent (Table 1), which revealed anemia, thrombocytopenia, and elevated bilirubin. Of note, patient had a normal hemoglobin and platelet count with no evidence of hemolysis on the labs prior to admission. Von Willebrand factor assay was not sent during our workup of TTP.

The CD4 T-cell count of the patient was 354 with undetectable viral load, showing compliance of the patient to ART medications. Further blood workup (Table 2) showed elevated reticulocyte count of 2.8% (Reference: 0.5–1%), elevated lactate dehydrogenase, low haptoglobin level of 10 (Reference: 50–220 mg/dL) and indirect bilirubin of 1.4 mg/dL. Peripheral smear was remarkable for normocytic, normochromic red blood cells with polychromasia, an ample number of spherocytes and schistocytes, along with a decreased number of platelets without any evidence of clumping. All these findings were consistent with the hemolytic phenomenon. Henceforth, a tentative diagnosis of Thrombotic Thrombocytopenic Purpura (TTP) was made. Of note, computed tomography of the chest with contrast was performed for pulmonary embolism concerns, which was normal. The PLASMIC score for estimating ADAMTS13 deficiency was seven, indicating a high risk of severe deficiency. An urgent decision was made to initiate plasma exchange therapy. Since the patient's HIV status is stable with a CD4 count above 200, the trigger of TTP was presumed to be recent vaccination.

✉ Syed Hamza Bin Waqar
Syed.waqar@downstate.edu

¹ Department of Internal Medicine, Downstate Medical Center, State University of New York (SUNY), 186 Lenox Rd, Apartment 1H, NYC, Brooklyn, NY 11226, USA

² Department of Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan

Table 1 Laboratory results of the patient on presentation

Component	reference range	Labs 1 month prior to presentation	Patient's labs at day 1 of presentation
WBC	4.50–10.90 K/uL	4.7	8.25
HGB	14.0–18.0 g/dL	15	9.3
HCT	42.0–52.0%	46	29.5
MCV	78.0–95.0 fL	92	89.4
Platelet count	130–400 K/uL	374	22
Sodium	136–146 mmol/L	138	139
Potassium	3.5–5.0 mmol/L	4.2	4.1
Chloride	98–106 mmol/L	101	102
CO ₂	24–31 mmol/L	25	26
BUN	8.0–23.0 mg/dL	18	29.0
Creatinine	0.70–1.20 mg/dL	1.98	2.01
Calcium	8.8–10.2 mg/dL	9.1	9.0
Albumin	3.3–6.1 g/dL	4.0	4.4
Total Protein	6.4–8.3 g/dL	7.4	8.3
Total Bilirubin	0.0–1.2 mg/dL	0.2	1.8
Alkaline Phosphatase	35–145 U/L	23	110
ALT (SGPT)	0–41 U/L	19	22
AST (SGOT)	10–50 U/L	26	35

Table 2 Hematological parameters

Components	Reference Range	Presentation Day	Day 1*	Day 2*	Day 3*	Day 4*	Day 5*
Prothrombin Time (PT)	9.4–12.5 s	69.5	51.0	15.2	14.6	14.8	
INR	0.8–1.2 ratio	6.0	4.3	1.3	1.2	1.2	
Platelet's count	130–400 K/uL	22	19	61	133	164	199
activated partial thromboplastin time (aPTT)	25–37 s	41	25	24		24	
Lactate Dehydrogenase (LDH)	135–225 U/L	1229	1333	652	394	316	262
D-Dimer	0–243 ng/mL	136	225	985	629		
Fibrinogen	200–393 mg/dL	509	318	287	485		
Total Bilirubin	0.0–1.2 mg/dL	1.8	1.5	1.2	0.6	0.7	0.9

*Hematological labs were trended on the same days after each session of plasmapheresis

The patient received five plasmapheresis sessions along with daily trending of hematological profile. Pulse prednisone of 1 mg/kg (60 mg) IV was also given along the plasmapheresis sessions. ADAMTS13 activity was below 2% and anti-ADAMTS13 antibodies (titer > 90 UI/ml) were detected, hence confirming acquired TTP. The platelet count was considerably improved by the fifth session (Table 2). After that, we started prednisone taper. The patient got discharged after the first dose of rituximab infusion and the next four doses scheduled in our out-patient infusion center.

Discussion

TTP is a rare disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia, often with or without neurological or renal abnormalities with the complete pentad seen in only one-third of the patients [1]. Generally, thrombocytopenia is attributed to infection, bone marrow suppression, lack of nutrition, genetic causes, or autoimmune processes, for instance, immune thrombotic

thrombocytopenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or disseminated vascular coagulation [2]; however, our patient's characteristic symptoms and peripheral blood smear point to a very diagnosis of TTP. TTP is classified into two types: congenital and acquired [1]. Congenital or primary TTP mainly occurs due to a mutation or autoantibodies directed to the *ADAMTS13* gene. In contrast, acquired TTP is associated with autoimmune diseases, such as systemic lupus erythematosus and scleroderma, pregnancy, transplantation, neoplasms, or antineoplastic drugs [1, 2]. We also need to mention that the patients infected with COVID-19 can develop excess pro-coagulant factors with thrombosis and concomitant association of thrombocytopenia, pathogenesis not fully understood and likely multifactorial [3].

The pandemic of coronavirus disease 2019 (SARS-CoV2) presented new challenges that humbled the genius minds in the medical and scientific world, acknowledging the gravity of the situation and working towards its amelioration. Different companies, hence, used various techniques ranging from using viral nucleic acids or sub-units of the virus SARS-CoV2 to using an inactivated or live attenuated virus or viral vectors to create vaccines in the hope of curbing this rampage all over the globe [4]. Vaccines, like infections, activate the defensive immunity of a person by mediating an immune response which could eventually trigger the development of an autoimmune disorder like immune thrombocytopenic purpura (ITP) or thrombotic thrombocytopenic purpura (TTP) [5] or Guillain–Barre syndrome [1]. Previous cases have been recorded in the medical literature giving rise to the terminology of ‘vaccine-induced prothrombotic immune thrombocytopenia’ (VIPIT) or ‘vaccine-induced thrombosis with thrombocytopenia (VITT) which is a rare disorder that affects one individual in 1 million people around the world [6]. Studies suggest a possible presence of vaccinal antigens against *ADAMTS13* specific gene, responsible for creating a robust immune response [6]. In the elderly population post-pneumococcal vaccination, cases of thrombocytopenic purpura have been registered with an indication of antigens present in the vaccine against the *ADAMTS 13* gene [1]. Antibodies against platelet-factor 4 (PF4) have been found in VIPIT like the heparin complexes formed in heparin-induced thrombocytopenic purpura, hinting at analogous immune mechanisms [7]. However, being a novel disease, literature on the adverse effects of the SARS-CoV2 (COVID-19) vaccination is still scarce.

Reports on Ad26.COV2.S vaccine reported symptoms like bilateral lower leg edema and shortness of breath, along with thrombotic thrombocytopenic events in women aged less than 60 years [8].

Yocum [9] and Sissa [10] reported women with co-morbidities in a similar age group as our patient presenting with similar symptoms within a month of administration of the

Ad26.COV2.S and BNT162b2 mRNA vaccines, respectively, indicating the presence of a possible diagnosis of VIPIT that was treated efficiently with plasmapheresis in both cases. Of note, in the latter case involving BNT162b2, the patient suffered from relapse precisely six days after the second dosage of COVID vaccine, just as in our case—although our patient never had TTP before. TTP is commonly treated with plasmapheresis, chemotherapeutics, for example, vincristine and corticosteroids with splenectomy kept as a last resort in case of refractory disease [1].

Further studies are, however, needed to verify possible associations between microangiopathic, thrombocytopenic thrombotic disorders and the administration of vaccines against COVID-19, so the menace can be nipped in the bud before the presumptive rewarding efforts go in vain.

Author contributions All authors participated in analysis, designing intellectual content, final approval of version and are accountable for the integrity of their work. Guarantor: Syed Hamza Bin Waqar.

Declarations

Conflict of interest We have nothing to disclose.

References

1. Kojima Y, Ohashi H, Nakamura T, Nakamura H, Yamamoto H, Miyata Y, et al. Acute thrombotic thrombocytopenic purpura after pneumococcal vaccination. *Blood Coagul Fibrinol*. 2014;25(5):512–4. <https://doi.org/10.1097/MBC.0000000000000058>.
2. Perricone C, Ceccarelli F, Neshet G, Borella E, Odeh Q, Conti F, et al. Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases. *Immunol Res*. 2014;60(2–3):226–35. <https://doi.org/10.1007/s12026-014-8597-x>.
3. Althaus K, Marini I, Zlamal J, Pelzl L, Singh A, Häberle H, et al. Antibody-induced procoagulant platelets in severe COVID-19 infection. *Blood*. 2021;137(8):1061–71. <https://doi.org/10.1182/blood.2020008762>.
4. Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. *Immunity*. 2020;52(4):583–9. <https://doi.org/10.1016/j.immuni.2020.03.007>.
5. Brodin-Sartorius A, Guebre-Egziabher F, Fouque D, Cozon G, Villar E, Laville M, et al. Recurrent idiopathic thrombotic thrombocytopenic purpura: a role for vaccination in disease relapse? *Am J Kidney Dis*. 2006;48(3):31–4. <https://doi.org/10.1053/j.ajkd.2006.04.090>.
6. Pai M, Grill A, Ivers N, Maltsev A, Miller KJ, Razak F, et al. Vaccine induced prothrombotic immune thrombocytopenia VIPIT following AstraZeneca COVID-19 vaccination. *Science Briefs of the Ontario COVID-19 Science Advisory Table*. (2021); 1(17). <https://doi.org/10.47326/ocsat.2021.02.17.1.0>
7. von Hundelshausen P, Lorenz R, Siess W, Weber C. Vaccine-induced immune thrombotic thrombocytopenia (VITT): targeting patho-mechanisms with Bruton tyrosine kinase inhibitors. *Thromb Haemost*. 2021. <https://doi.org/10.1055/a-1481-3039>.

8. Shay DK, Gee J, Su JR, Myers TR, Marques P, Liu R, et al. Safety monitoring of the Janssen (Johnson & Johnson) COVID-19 vaccine—United States, March–April 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70(18):680–4.
9. Yocum A, Simon EL. Thrombotic thrombocytopenic. Purpura after Ad26 COV2-S vaccination. *Am J Emerg Med.* 2021;S0735–6757(21):00376–84. <https://doi.org/10.1016/j.ajem.2021.05.001>.
10. Sissa C, Al-Khaffaf A, Frattini F, Gaiardoni R, Mimiola E, Montorsi P, et al. Relapse of thrombotic thrombocytopenic purpura after COVID-19 vaccine. *Transfus Apher Sci.* 2021. <https://doi.org/10.1016/j.transci.2021.103145>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.