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CASE REPORT

Recurrence of Thrombotic Thrombocytopenic Purpura After Vaccination with mRNA-1273 COVID-19 vaccine

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, and ischemic organ damage. Several cases of TTP associated with administration of COVID-19 vaccines have been reported. We report a case of a 63-year-old woman with a past medical history of hypertension, diabetes mellitus, chronic kidney disease, HIV infection, and remote history of TTP who presented with several days of shortness of breath on exertion, chest tightness, low-grade fever, and bruising thirty-three days after receiving the second dose of the mRNA-1273 COVID-19 vaccine. Thrombocytopenia and hemolytic anemia with schistocytes were noted on testing, and ADAMTS13 activity was <5%. Temporizing treatment with fresh frozen plasma was started immediately on presentation, and treatment was continued with daily therapeutic plasma exchange and corticosteroids. TTP should be considered in patients who present with thrombocytopenia after COVID-19 vaccination, especially if there is a past history of TTP.

Keywords: Thrombotic thrombocytopenic purpura, COVID-19, mRNA-1273 vaccine

1. Introduction

The COVID-19 pandemic, caused by the wide transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in millions of deaths around the world. Multiple vaccines have been developed in an attempt to halt the spreading of the disease. Many of the available vaccines have proved to be efficacious and safe,[1–4] with mRNA vaccine trials showing efficacy above 90% in preventing COVID-19. These vaccines have a crucial role in the effort to combat COVID-19 expansion, but continuous evaluation of their safety and possible adverse effects is warranted.

Thrombotic thrombocytopenic purpura (TTP) is a rare disease caused by acquired or inherited decrease in ADAMTS13 activity. ADAMTS13 is a protease that cleaves von Willebrand factor multimers in smaller molecules. Decreased activity of this enzyme results in platelet aggregation and thrombi formation. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and organ damage of varying degrees. TTP can potentially have a high mortality rate, but survival improves drastically if treatment with therapeutic plasma exchange and immunosuppressive medications is started promptly.[5]

We present a case of TTP recurrence thirty-three days after receiving her second dose of mRNA-1273 COVID-19 vaccine.

2. Case presentation

A 63-year-old woman with a past medical history of hypertension, diabetes mellitus, chronic kidney disease stage III, HIV infection on antiretroviral treatment, and history of TTP twelve years before this encounter, presented with several days of shortness of breath on exertion and associated chest tightness with no radiation. Additionally, she reported low-grade fever up to 99.2° and bruising at the areas where she administered her insulin

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injections. She was alert and oriented and denied confusion, dysuria, hematuria, changes in urinary frequency, nausea, vomiting, abdominal pain, diarrhea, cough, wheezing, rash, and joint pain. She received her second dose of the mRNA-1273 COVID-19 vaccine thirty-three days before presentation. The list of her medications included emtricitabine, tenofovir, dolutegravir/lamivudine, rilpivirine, amlodipine, losartan, hydrochlorothiazide, insulin glargine and ergocalciferol, Her initial TTP episode was not clearly associated with a specific cause.

Blood pressure was 133/65 mmHg and heart rate was 99 beats per minute. Respiratory rate was 20 breaths per minute and oxygen saturation was 100% on room air. The patient was afebrile with a temperature of 98.6°. On physical examination, heart rhythm was regular, breath sounds were clear bilaterally, and the abdomen was soft with no tenderness or guarding. Neurologic examination, including mental status examination, was normal. Scleral icterus was noted and hematomas were found on the anterior abdomen and the right thigh. No petechiae were noted. Electrocardiogram and chest x-ray showed no acute abnormalities.

Laboratory testing revealed anemia (hemoglobin level: 7.1 g/dL, range: 11.9−15.7 g/dL) and thrombocytopenia (platelets level: 12 K/μL, range: 153−367 K/μL). White blood cell count was normal at 9.2 K/mcL (range: 4.5−11 K/mcL). Reticulocyte percentage was elevated at 8.15% (range: 0.59−2.79%). Schistocytes, microcytes, basophilic stippling, polychromasia, and hyper-segmented neutrophiles were noted on peripheral blood smear. Indirect bilirubin (6.5 mg/dL, range: 0−1.1 mg/dL) and LDH (3765 units/L, range: 313−618 units/L) were elevated, and haptoglobin levels were low. The peripheral smear findings, elevated reticulocyte percentage, indirect bilirubin, and LDH levels, and decreased haptoglobin levels were indicative of microangiopathic hemolytic anemia. Electrolytes were normal with Na 138 mmol/L (range: 137−145 mmol/L), K 4 mmol/L (range: 3.5−5.1 mmol/L), Ca 9.5 mg/dL (range: 8.4−10.2 mg/dL), phosphorus 3.6 mmol/L (range: 2.5−4.5 mmol/L), Mg 1.7 mg/dL (range: 1.6−2.3 mg/dL). Serum creatinine (1.59 mg/dL, range: 0.7−1.5 mg/dL) and BUN (21 mg/dL, range: 7−17 mg/dL) levels were elevated, but close to this patient's baseline. Estimated glomerular filtration rate was 40 ml/min/1.73 m^2. Coagulation studies showed no abnormalities. Fibrinogen levels were normal. Troponin levels were initially elevated at 0.041 ng/ml (range: 0−0.034 ng/ml) but normalized on two repeat tests. A molecular COVID-19 test was negative.

PLASMIC score was 6, consistent with 62−82% likelihood of severe deficiency of ADAMTS13 activity. In light of the high PLASMIC score and the history of TTP in the past, a diagnosis of TTP was presumed. ADAMTS13 levels were ordered and temporizing treatment with fresh frozen plasma was started immediately, due to unavailability of plasma exchange at the time of admission. Treatment with daily therapeutic plasma exchange and oral prednisone 1 mg/kg was started the following day. Rituximab was not used, because of a hypersensitivity reaction after receiving this medication for the treatment of the previous TTP episode.

ADAMTS13 activity returned <5%, confirming the diagnosis of TTP. Hemoglobin, platelet count, indirect bilirubin, haptoglobin, LDH, and ADAMTS13 were monitored (Table 1) to assess for remission. HIV RNA was undetectable. The trigger of this TTP episode was presumed to be the recent vaccination. The patient was discharged on a prednisone taper regimen, after eight days of hospitalization, with plans to continue treatment with plasma exchange on an outpatient basis. Unfortunately, she passed away six days after discharge due to unknown cause.

3. Discussion

TTP is a rare disease, with an incidence of 2−6 per million,[6] characterized by thrombocytopenia, microangiopathic hemolytic anemia, and ischemia of various organs, including the kidneys and the nervous system. The pathogenesis of the disease involves decreased ADAMTS13 activity, which results in accumulation of large von Willebrand factor multimers on endothelial cells. Activation of platelets results in thrombosis, with consequent hemolysis, tissue ischemia, and thrombocytopenia. Decreased

Table 1. Laboratory monitoring during hospitalization.

Laboratory test	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Reference range
Hemoglobin	7.1	5.2	9.8	10.7	10.4	10.5	10.6	10.8	11.9−15.7 g/dL
Platelets	12	12	41	86	121	155	201	174	153−367 K/μL
LDH	3565	1177		551	464	429	540	477	313-618 u/L
Haptoglobin	<20			38	63	57	69	62	30−178 mg/dL
Indirect Bilirubin	6.5	3.7							0−1.1 mg/dL
ADAMTS13	<5%		10%		16%				≥61%

Table 2. Thrombotic thrombocytopenic purpura cases associated with COVID-19 vaccines.

Reference	Patient age & gender	Vaccine	Dose	Time after vaccine	ADAMTS13 activity on presentation	Treatment	Outcome
Chamarti et al.[9]	80, male	BNT162b2	2nd	2 weeks	<2%	Plasma exchange, corticosteroids, rituximab	Improvement
Alislambouli et al.[15]	61, male	BNT162b2	1st	5 days	<3%	Plasma exchange, corticosteroids, rituximab	Improvement
de Bruijn et al.[16]	38, female	BNT162b2	1st	2 weeks	Undetectable	Plasma exchange, corticosteroids, rituximab, caplacizumab	Improvement
Waqar et al.[17]	69, male	BNT162b2	2nd	1 week	<2%	Plasma exchange, corticosteroids, rituximab	Improvement
Maayan et al.[18]	40, female	BNT162b2	2nd	8 days	0%	Plasma exchange, corticosteroids, caplacizumab	Improvement
	28, male	BNT162b2	2nd	28 days	0%	Plasma exchange, corticosteroids, rituximab, caplacizumab	Improvement
	31, female	BNT162b2	1st	13 days	0%	Plasma exchange, corticosteroids, rituximab, caplacizumab	Improvement
	30, male	BNT162b2	2nd	8 days	0%	Plasma exchange, corticosteroids, rituximab, caplacizumab	Improvement
Yoshida et al.[19]	57, male	BNT162b2	1st	1 week	<0.5%	Plasma exchange, corticosteroids, rituximab	Improvement
Kirpalani et al.[20]	14, female	BNT162b2	1st	2 weeks	<1%	Plasma exchange, corticosteroids, rituximab, caplacizumab	Improvement
Sissa et al.[21]	48, female	BNT162b2	2nd	6 days	<3%	Plasma exchange, corticosteroids	Improvement
Ruhe et al.[22]	84, female	BNT162b2	1st	16 days	1.6%	Plasma exchange, corticosteroids, rituximab	Improvement
Giuffrida et al.[23]	83, female	BNT162b2	1st	14 days	<10%	Plasma exchange, corticosteroids, caplacizumab	Death
	30, female	BNT162b2	1st	8 days	<10%	Plasma exchange, corticosteroids, caplacizumab	Improvement
Guney et al.[24]	48, female	BNT162b2	1st	3 days	<0.2%	Plasma exchange, corticosteroids, rituximab	Unknown
Karabulut et al.[25]	48, male	mRNA-1273	1st	5 days	<3%	Plasma exchange, corticosteroids, rituximab	Improvement
Osmanodja et al.[26]	25, male	mRNA-1273	1st	13 days	<1%	Plasma exchange, corticosteroids, rituximab, caplacizumab	Improvement
Dykes et al.[27]	50, female	mRNA-1273	2nd	1 week	<5%	Plasma infusion	Improvement
Yocum et al.[28]	62, female	Ad26.COV2.S	1st	37 days	<12%	Plasma exchange, corticosteroids	Unknown
Al-Ahmad et al.[29]	37, male	ChAdOx1 nCoV-19	1st	3 weeks	2.6%	Plasma exchange, corticosteroids, rituximab	Improvement
Lee et al.[30]	50, female	ChAdOx1 nCoV-19	1st	12 days	0%	Plasma exchange, corticosteroids, rituximab	Improvement
Wang et al.[31]	75, male	ChAdOx1 nCoV-19	1st	30 days	0.8%	Plasma exchange	Improvement

ADAMTS13 activity may be congenital (5%), due to biallelic mutations in the ADAMTS13 gene, or acquired (95%), due to autoantibodies targeting the ADAMTS13 enzyme. Medications (e.g. clopidogrel, ticlodipine, cyclosporin) and infections, such as HIV, have been recognized as possible triggers.[5] Definitive diagnosis is based on decreased ADAMTS13 activity levels (<10 u/dL or < 10% of normal activity), but empiric treatment should be started before ADAMTS13 activity levels are available, based on high clinical suspicion for TTP or increased likelihood of severe ADAMTS13 deficiency based on clinical scores (PLASMIC, French).[6] TTP is treated with plasma exchange and corticosteroids. Rituximab and caplacizumab can also be added.[7] Mortality is 90% without treatment, but survival is significantly increased with prompt treatment. Recurrence rate is 20–50% after successful treatment.[8]

COVID-19 vaccines provoke an immune response in order to protect from infection and severe disease. A potential side effect could be autoimmunity, such as immune-mediated TTP. The pathogenesis is not clear but the possible involved mechanisms are molecular mimicry and aberrant activation of the immune system.[9] TTP cases associated with other vaccines, including influenza,[10–12] pneumococcus,[13] and rabies,[14] have been reported.

Cases of COVID-19 vaccine-associated TTP have also been reported.[9,15–31] Like our case, four of these reports are relapses in patients with a prior history of acquired TTP.[18,21,25] History of HIV infection was not reported for any of these relapsing acquired TTP cases. Additionally, there is one report of a flare of congenital TTP after vaccination.[27] Most of these cases are associated with the BNT162b2 mRNA vaccine. However, the mRNA-1273 vaccine, the Ad26.COV2.S vaccine, and the ChAdOx1 nCoV-19 vaccine have also been associated with TTP. Patients presented 3–37 days after the 1st or 2nd dose of the vaccine. Therapeutic plasma exchange was used in the management of 21 patients and plasma infusion was used in one case of congenital TTP.[27] Corticosteroids were used in 20 cases, rituximab in 15 cases, and caplacizumab in 9 cases. Only one death was reported.[23] The case-reports of TTP associated with COVID-19 vaccines are summarized in Table 2.

4. Conclusion

Surveillance for possible vaccine adverse events is continuous and reports of side effects may increase as vaccine administration becomes wider. Currently, reports of TTP cases in association with these vaccines are very limited, and more data are needed to assess for any causal effect. Based on our case and other reported cases, we recommend considering TTP in patients presenting with thrombocytopenia after COVID-19 vaccination, especially if they have prior history of TTP.

Conflict of interest

No potential conflict of interest was reported by the authors.

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