

CASE REPORT

Successful treatment of vaccine-induced thrombotic thrombocytopenia in a patient with contraindication to standard-of-care early anticoagulation: A case report

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Abstract

Vaccine-induced thrombotic thrombocytopenia (VITT) is a rare yet fatal side effect associated with adenoviral vector vaccines for coronavirus disease of 2019. We report a case of VITT in a previously healthy 43-year-old woman occurring 10 days after receiving the Johnson and Johnson (Ad26.COV2.S) vaccine. She presented with right-sided weakness, aphasia, and left gaze deviation. Computed tomography angiography of the head and neck revealed complete occlusion of the left internal carotid artery, left anterior carotid artery, and left middle cerebral artery with hemorrhagic conversion and midline shift. Pertinent laboratory results revealed acute thrombocytopenia and an elevated d-dimer level. She tested positive for platelet factor 4 (PF-4) antibodies, and a Doppler ultrasound revealed a deep vein thrombosis of the right femoral and popliteal veins. With these findings and the timing of vaccine administration, she had met the full criteria for VITT. While the crucial immediate treatment of VITT is therapeutic anticoagulation, its application for this case was contraindicated due to evolving hemorrhage and the need for an urgent decompressive craniectomy. An inferior vena cava filter was inserted, and intravenous immunoglobulin was administered, resulting in a suboptimal rise in platelet counts. She was then successfully treated with the addition of high-dose steroids and rituximab, eventually displaying therapeutic anticoagulation more than 2 weeks after the diagnosis. Two years after this diagnosis, she had slowly recovered from VITT. Her PF-4 antibodies are negative, and she remains only on prophylactic anticoagulation. This case highlights the importance of early recognition of symptoms to establish the correct diagnosis and the complexities of acute treatment of VITT in patients with contraindications to early therapeutic anticoagulation.

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1. Background

The coronavirus disease of 2019 (COVID-19) has resulted in over six million deaths, leading to the development and administration of several vaccines. The Johnson and

Johnson (Ad26.COV2.S) and the AstraZeneca (ChAdOx1 nCoV-19) vaccines are adenoviral vector vaccines, while the Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) vaccines are messenger RNA (mRNA)-based vaccines. It is estimated that thirteen billion vaccine doses have been administered to reduce morbidity and mortality of COVID-19.¹ Since the introduction of the COVID-19 vaccines in 2020, common side effects, such as local injection effects, fever, chills, and malaise, have been reported. One of the rare and more fatal side effects is the development of vaccine-induced thrombotic thrombocytopenia (VITT). VITT is characterized by the development of thrombosis, thrombocytopenia, and antibodies to platelet factor 4 (PF-4)-complexes within 42 days of administration of the vaccine. It is also more commonly reported in those with viral vector vaccines.² As of December 2021, the incidence of VITT in those who received Ad26.COV2.S is 1 in 263,000 individuals.³ Once VITT is suspected or confirmed, the mainstay of treatment is the immediate initiation of therapeutic anticoagulation.

Herein, we present a case of a young, healthy female who developed VITT after receiving the Johnson and Johnson (Ad26.COV2.S) vaccine. The patient developed severe thrombocytopenia, deep vein thrombosis (DVT), and thrombotic stroke complicated by hemorrhagic conversion. Therefore, upfront anticoagulation was contraindicated. This case outlines the severity and complexities of treating this rare condition.

2. Case presentation

We report the case of a 43-year-old woman who was admitted to the hospital after being found obtunded at home, presenting with right-sided weakness, left gaze deviation, and aphasia. Computed tomography angiography of the head and neck revealed complete occlusion of the left internal carotid artery (ICA), left anterior carotid artery (ACA), and left middle cerebral artery (MCA). Subsequent magnetic resonance imaging of the brain revealed restriction diffusion of the left ACA and MCA territories. Computed tomography (CT) of the head, conducted later in the day, revealed a rightward midline shift and anterior subfalcine herniation, with no evidence of hemorrhagic transformation.

The patient received the Johnson and Johnson COVID-19 vaccine 10 days before admission. Initial complete blood count (CBC) revealed a white blood cell count of $7.1 \times 10^3/\mu\text{L}$, hemoglobin of 15.4 g/dL, hematocrit of 44.9%, platelets of $73 \times 10^3/\mu\text{L}$, and mean corpuscular volume of 103.2 fL. Moreover, the prothrombin time was 11.9 s; the international normalized ratio was 1.1; the partial prothrombin time was 25.9 s; the absolute

reticulocyte count was $0.113 \times 10^6/\text{mm}^3$; fibrinogen level was 331 mg/dL; d-dimer level was 4.3 $\mu\text{gFEU/mL}$; lactate dehydrogenase level was 175 units/L; and haptoglobin level was 182 mg/dL. A CBC obtained a month before the admission was normal. The blood smear was reviewed by the hematology team, revealing stomatocytes, few spherocytes, and no schistocytes or platelet clumping.

The head CT of the patient (Figure 1), obtained the following day, revealed an evolving left ICA infarct with petechial hemorrhagic transformation in the anterior inferior basal ganglia and progression with rightward midline with early left uncal and transtentorial herniations. The patient was placed on hypertonic saline and given two units of platelets with minimal improvements in platelet count, i.e., from 75 to $78 \times 10^3/\mu\text{L}$. Venous Doppler of her lower extremities revealed a DVT of the right femoral vein and right popliteal vein. She underwent decompressive hemicraniectomy and expansile duraplasty with neurosurgery. She had an inferior vena cava filter placed, given her DVT and inability to receive therapeutic anticoagulation due to a major stroke with hemorrhagic conversion.

As there was high suspicion of VITT, heparin-induced thrombocytopenia (HIT) antibodies were also measured from the serotonin release assay. A full hypercoagulable workup testing reported negative indications for antiphospholipid syndrome, factor V Leiden mutation, prothrombin II mutation, proteins C and S, antithrombin III, JAK2 mutation, and paroxysmal nocturnal hematuria. Given the high suspicion of VITT and contraindication to therapeutic anticoagulation, the patient was given intravenous immunoglobulin (IVIG) at 1 g/kg daily for 2 days. As



Figure 1. Head computed tomography on presentation. Left middle cerebral artery (MCA) and anterior carotid artery (ACA) displayed acute or early subacute infarct with overlying sulcal effacement, left ventricular effacement, rightward midline shift, and an anterior subfalcine herniation of 5 mm. The hypodense proximal left ACA and MCA vessels reflect intraluminal thrombi. No hemorrhagic transformation was observed.

observed in Figure 2, there was no initial improvement in the platelet count. She was then given 10 mg of dexamethasone 3 times a day for concerns of laryngeal edema, exhibiting some improvement in platelet count (i.e., to $91 \times 10^3/\mu\text{L}$) the next day. She was subsequently extubated, and her PF-4 antibody results came back positive, with an optical density (OD) of 1.58. She was given an additional dose of IVIG, which steadily increased the platelet count to $137 \times 10^3/\mu\text{L}$, but the patient was still unable to receive a full dose of anticoagulation. Therefore, she was started on a 4-day course of 40 mg dexamethasone daily and given a dose of 1000 mg rituximab for long-term control. The patient's platelet count eventually normalized to $173 \times 10^3/\mu\text{L}$, and a prophylactic dose of non-heparin-containing anticoagulation with 2.5 mg fondaparinux daily was started. A repeated assessment of HIT antibodies reported an elevated OD of 1.642 for PF-4 antibodies. The patient was given a total of four doses of rituximab weekly and was successfully able to start therapeutic anticoagulation with 7.5 mg of fondaparinux; she was then discharged to a rehabilitation facility. Two months after her initial presentation, the anticoagulation agent was changed to 5 mg apixaban twice a day. A year and a half after the initial diagnosis, the patient's d-dimer levels normalized, but her HIT antibodies were still weakly positive at OD 0.388. It was only 2 years after the original diagnosis that the patient's HIT antibody test came back negative. Anticoagulation was reduced accordingly to a prophylactic dose of 2.5 mg apixaban twice a day (BID).

3. Discussion

Herein, we describe the case of a 43-year-old woman with a confirmed diagnosis of VITT after presenting acutely altered mental status and right-sided hemiplegia. Further testing revealed severe thrombotic stroke, venous thromboembolism (VTE), and acute thrombocytopenia.

This case highlights the importance of early recognition and management of rare complications in patients receiving COVID-19 vaccines, particularly in a patient with contraindications to upfront anticoagulation.

VITT is defined by the collective manifestations of venous or arterial thrombosis, thrombocytopenia, and antibodies to PF4-complexes, and its clinical presentation varies based on the sites of thromboses. Unusual sites of thromboses are common in VITT patients. In addition, VITT patients may develop intense headaches with cerebral venous sinus thrombosis, abdominal or back pain in portal vein thrombosis, shortness of breath with pulmonary embolism, leg pain and swelling in deep venous thrombosis, chest pain in myocardial infarction, and limb changes in limb ischemia, as well as altered mental status, vision changes, and focal neurological deficits with cerebrovascular events.² Bleeding is also common with thrombocytopenia. An age of <50 years old is the only known risk factor. Incidence of VITT was generally equal among gender groups except for 30 – 49 years old, wherein females were more affected. There have been no prevailing comorbidities or thrombotic risk factors identified.³ This was also apparent in a systemic review of 22 patients with acute ischemic stroke from VITT. The patients were mostly females younger than 60 years old, with 30% of them having other sites of thrombosis and 95% of them receiving viral vector vaccines.⁴ Our patient fit within this description, and only had a history of hypertension without known thrombophilic risk factors.

The pathophysiology of VITT is akin to HIT, although having a specific mechanism for each case. A proposed theory is that the DNA and mRNA components released from the vaccine trigger the production of PF4 antibodies, leading to the formation of immunoglobulin G (IgG) anti-PF4-heparin antibodies and IgG heparin-PF4 immune

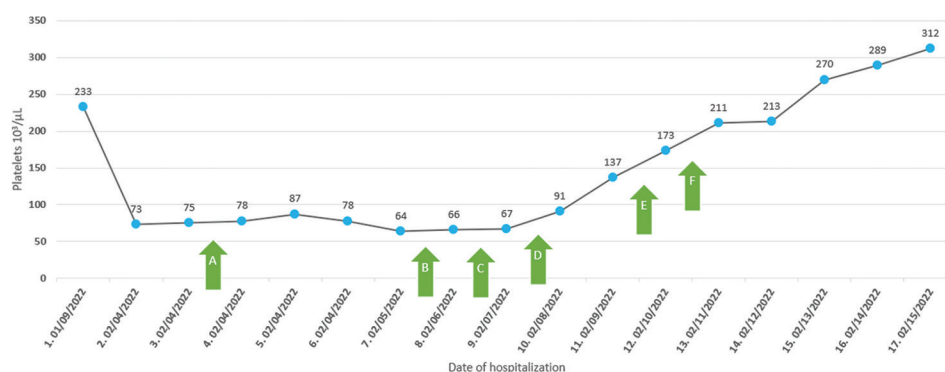


Figure 2. Line graph depicting the platelet trend of this patient during hospitalization. Data point 1 (i.e., September 01, 2022) indicates platelet count before presentation/hospitalization. Green arrows indicate intervention: (A) two units of platelets; (B) one dose of 1 g/kg intravenous immunoglobulin (IVIG); (C) one dose of 1 g/kg IVIG; (D) started on 10 mg dexamethasone 3 times a day for laryngeal edema; (E) one dose of 1000 mg rituximab and started 40 mg dexamethasone daily over a 4-day course; (F) started a prophylactic dose of 2.5 mg of fondaparinux daily.

complexes. These complexes then bind to the Fc receptor on platelets, starting a cascade that eventually leads to marked platelet activation and thrombotic events.^{2,5,6}

The suggested workup from the American Society of Hematology includes Centers for disease control, a review of the peripheral blood smear to rule out pseudothrombocytopenia from platelet clumping, symptom-based imaging to detect thrombosis, fibrinogen, and d-dimer, and PF4-HIT enzyme-linked immunosorbent assay (ELISA). The definitive diagnosis of VITT requires the fulfillment of all five criteria: (i) administration of COVID vaccine 4 – 42 days before symptom onset, (ii) thrombocytopenia (platelet count $<150 \times 10^9/L$), (iii) positive PF4-HIT ELISA, (iv) markedly elevated d-dimer (>4 times the upper limit of normal) levels, and (v) development of thrombosis.⁶ The reported patient met all the criteria, with the onset of VITT 10 days after her COVID-19 vaccination.

The acute treatment of VITT (or suspected VITT) involves the immediate initiation of therapeutic anticoagulation. Its management approach is largely based on HIT. Thus, the preference is to administer non-heparin-containing anticoagulants, such as direct oral anticoagulants, parenteral direct thrombin inhibitors, or fondaparinux, for at least 3 months. A large cohort from the United Kingdom reported mortality rates of 20% versus 16% in those who received heparin-containing and non-heparin-containing agents, respectively.⁵ However, this difference was not apparent in a subsequent meta-analysis.⁷ Platelet transfusions are generally avoided and thought to aggravate thrombotic events, except in acute bleeding and before emergent surgeries. In this patient, platelet transfusions were administered due to the ongoing hemorrhagic conversion of her stroke and in preparation for decompressive hemicraniectomy. We did not observe a clinical decline of her stroke or VTE after platelet transfusion. Another approach for acute VITT management is the administration of high-dose IVIG at 1 g/kg/day for 2 days to suppress antibody-mediated platelet activation and mediate the downregulation of antibody/PF4-complexes. Corticosteroids have been administered along with IVIG in some cases or in place of IVIG (if IVIG is not available).^{2,6,8} In this case, corticosteroids were initially administered for laryngeal edema and continued due to a suboptimal increase in platelets after IVIG.

In select refractory cases to anticoagulation, IVIG, and steroids, the use of plasma exchange, eculizumab, or rituximab may offer some benefit. These have been anecdotal, reported in case series, or extrapolated from HIT treatment. Patriquin *et al.* reported three refractory VITT cases, wherein plasma exchange was given over

5 – 7 days, with one receiving concurrent IVIG and the other receiving rituximab. All three cases had no further thrombotic events, and two patients recovered.⁹ Two of five patients in a case series from Germany improved with the administration of eculizumab, one of whom developed thrombotic microangiopathy.¹⁰ The use of rituximab has been less favored due to its slow onset of action and potential dampening of the immune system; however, it remains a viable treatment option in refractory cases. Our patient received four weekly doses of rituximab along with dexamethasone, which improved her platelet counts. She did not develop secondary infections despite her prolonged hospital stay.

A common type of thrombosis for those with VITT is cerebral vein sinus thrombosis (CVST), often seen in 50% of VITT cases. Approximately 30 – 40% of CVST patients develop secondary intracranial hemorrhage, which poses additional treatment challenges for these patients.⁵ Clinical data on the treatment of CVST cases are limited, but several reports suggested the use of mechanical thrombectomy. Chew *et al.* used mechanical thrombectomy in seven cases of refractory VITT. Six of the seven patients underwent successful recanalization; three patients were discharged with good functional outcomes; one was sent to rehabilitation; two died due to severe mass effects.¹¹

Earlier cohort studies in mid-2021 reported VITT mortality rates of 22%, even reaching 73% for those with severe thrombocytopenia and intracranial hemorrhage.⁵ The most recent data from Australia have reported a 5% mortality rate, reflecting the medical community's better understanding and management of this syndrome.⁸

4. Conclusion

While the development of VITT is rare, it corresponds with increased morbidity and mortality. Thus, a high level of suspicion followed by prompt investigation and treatment initiation of anticoagulation and IVIG are warranted for better patient outcomes. Many VITT patients are at a high risk of life-threatening hemorrhage from thrombosis and thrombocytopenia, warranting further investigation into refractory VITT cases.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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All authors contributed equally to the work.

Ethics approval and consent to participate

The patient gave consent to participate in this study.

Consent for publication

The authors have concealed any information that may identify the patient.

Availability of data

Data supporting the findings of this study are available within the article.

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