Case Report

A rare case of vaccine-induced immune thrombosis and thrombocytopenia and approach to management

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ABSTRACT

Background: The use of the COVID-19 vaccines Vaxzevria from AstraZeneca and Covishield from Janssen has been associated with sporadic reports of thrombosis with thrombocytopenia, a complication referred to as vaccine-induced immune thrombocytopenia (VITT) or vaccine-induced prothrombotic immune thrombocytopenia. It presents commonly as cerebral sinus venous thrombosis (CSVT), within 4–30 days of vaccination. Females under 55 years of age are considered to be especially at high risk. Mortality up to 50% has been reported in some countries. Identification of early warning signs and symptoms with prompt medical intervention is crucial.

Case Description: We report here a case of VITT in a young female who presented 11 days after receiving the first dose of the Covishield vaccine, with severe headache and hemiparesis. She was diagnosed with CSVT with a large intraparenchymal bleed, requiring decompressive craniectomy and extended period on mechanical ventilation.

Conclusion: The patient was successfully treated with intravenous immunoglobulin and discharged after 19 days in ICU. Although she was left with long-term neurological deficits, an early presentation and a multidisciplinary approach to management contributed toward a relatively short stay in hospital and avoided mortality.

Keywords: Autoimmune heparin-induced thrombocytopenia, Cerebral venous sinus thrombosis, Platelet-factor 4 antibodies, Vaccine-induced immune thrombosis and thrombocytopenia, Vaccine-induced prothrombotic immune thrombocytopenia

INTRODUCTION

Vaccine-induced immune thrombotic thrombocytopenia (VITT)⁵ otherwise known as vaccine-induced prothrombotic immune thrombocytopenia⁶ is a very rare prothrombotic disorder that has been reported following vaccination with the adenovirus vector-based vaccines ChAdOx1 nCoV-19 from AstraZeneca/Oxford (marketed as Vaxzevria and Covishield) and Ad26.COV2.S from Janssen (Johnson and Johnson). It should be suspected when a patient develops symptoms such as severe headache, blurred vision, vomiting, altered sensorium, focal neurological deficits, abdominal pain, leg pain, and/or swelling or dyspnea, 4–30 days after vaccination.⁶ We report a case of VITT admitted at a tertiary care, referral ICU in June 2021.
CASE REPORT

The patient is a 32-year-old female who presented with 3 days of headache associated with blurring of vision and giddiness. She also had weakness on the left upper and lower limb from 1 day. The family reported history of the patient receiving her first dose of Covishield vaccine 11 days before admission. She was unmarried, an active cigarette smoker, with no history of comorbidities or medications, nor any similar episodes in the past.

On examination, she was conscious and oriented, with heart rate of 76/min, respiratory rate of 22/min, blood pressure of 110/70 mmHg, oxygen saturation of 94% on room air, a normal Glasgow Coma Scale score, and normal pupils. Limb power was 2/5 and 3/5 on the left upper and lower limbs, respectively. A magnetic resonance imaging (MRI) of brain [Figure 1a] showed a large right parietal hemorrhage with mild adjacent peri-focal edema, causing mass effect on adjacent right lateral ventricle and locoregional effacement of sulci and gyri, with a mid-line shift of 5 mm to the left. CT venogram [Figure 1b] and 3D volume rendering technique [Figure 1c] showed thrombosis of the left transverse and sigmoid sinuses and partial thrombosis of superior sagittal sinus. Following neurology review, she was started on 100 ml of 20% mannitol every 6 h, 200 ml of 3% saline every 6 h, intravenous levetiracetam 500 mg twice daily, and therapeutic dose of enoxaparin 40 mg twice daily subcutaneously, with close neuromonitoring in ICU. A work-up for pro-coagulant disorders was sent including factor V Leiden mutation, protein C and S deficiency, vasculitis, and anti-phospholipid antibody syndrome. Her initial coagulation parameters were normal, with platelet count of $120 \times 10^9$/L. Vitamin B12 was low at 40 pg/ml (reference range 180–914 pg/ml), which was corrected with intravenous cyanocobalamin 5000 mcg once daily for 5 days.

On day 2 in ICU, her sensorium acutely deteriorated and a CT brain showed significant increase in the right parietal hematoma and worsening midline shift of 10 mm [Figure 1d]. She underwent emergency right parietal decompressive hemicraniectomy with evacuation of the intracranial hematoma [Figure 1e], following which she remained intubated, on mechanical ventilation and sedated. The same day, her platelet count was noted to drop to $105 \times 10^9$/L, with a further fall to $69 \times 10^9$/L on day 3 [Figure 2]. Fibrinogen was normal (2.6 mg/dl and 4.0 mg/dl, on days 2 and 3, respectively). Initial d-dimer was 1105 ng/ml (normal <250 ng/ml) and 1101 ng/ml on day 2. Pro-coagulant work-up returned normal. The possibility of VITT was considered and enzyme-linked immunosorbent assay (ELISA) for platelet factor-4 antibody was sent for, which was found raised at 15.2 IU/ml (reference range 0–12 IU/ml). After hematology review, enoxaparin was substituted with injection fondaparinux 7.5 mg subcutaneously once daily, with instructions to stop it in case of platelet count drop below $50 \times 10^9$/L or bleeding manifestations. She was given intravenous immunoglobulin (IVIG) 1 g/kg once daily for

Figure 1: (a) MRI brain T2-weighted-GRE axial view showing right parietal hemorrhage. (b) MR venogram 2D TOF MIP coronal view showing complete thrombosis of the left transverse and sigmoid sinuses and partial thrombosis of superior sagittal sinus. (c) CT venogram 3D volume rendering technique showing complete thrombosis of the left transverse and sigmoid sinuses and partial thrombosis of superior sagittal sinus. (d) CT brain axial view showing increase in midline shift. (e) CT axial view after right parietal decompression craniectomy.
2 days. There was a gradual rise in platelet count over the next few days, increasing up to $252 \times 10^9$ on by day 11 of admission.

She underwent percutaneous tracheostomy on day 5 of admission, anticipating prolonged need for airway protection due to slow neurological recovery. Her sensorium started improving by day 6 and she was gradually weaned off ventilator. By day 10, she was conscious, oriented, breathing on room air through the tracheostomy, and communicating by writing. Her left lower limb power had improved to 4/5 although upper limb remained weak with power 3/5. By day 17, the tracheostomy was decannulated after assessing her cough and swallowing reflexes. She was monitored for another 2 days and discharged with home neurorehabilitation services, on tablet dabigatran 150 mg twice daily until the next review.

**DISCUSSION**

Worldwide, data on thrombotic events following COVID vaccination continues to evolve but initial studies show that the incidence of VITT varies widely according to age, gender, type and timing of vaccine, and across different geographies.[1,3-5] Individuals below 50 years of age are at higher risk, with median age of 40.5 years, ranging between 21 and 77 years.[3-5] Females accounted for 67–80% of cases. VITT usually occurs within 4–28 days of vaccination, but may be seen up to 42 days.[1] It most commonly causes thrombosis of cerebral venous sinuses, followed by that of splanchnic veins, deep veins of legs, pulmonary veins, and cerebral arteries, although some patients had two or more sites involved.[3-6] The incidence following the AstraZeneca vaccine is about 1 case/73,000 recipients in a Canadian report,[1] 3.6 cases/million in a US study,[2] 8.6 cases/million in Germany and France, and in the UK, 3.9 cases/million.[5] The incidence following the Janssen vaccine is lesser at 0.9 cases/million recipients.[2] Incidence after the second vaccine dose has remained the same.[1] VITT has been more commonly associated with the adenovirus vector-based vaccines than mRNA vaccines.[3-5] Mortality associated with VITT also varies between countries ranging between 20% and 50%.[1,3,5]

Symptoms are mostly neurological, as in the present case, including severe and persistent headache, blurred vision, vomiting, seizures, focal neurological deficits, and altered sensorium.[3] Nonneurological symptoms include dyspnea, chest pain, persistent pain abdomen, and leg pain. Many cases are left with serious long-term morbidity, including neurologic deficits.[1] However, flulike symptoms such as joint and muscle pain or headache are common soon after vaccination and are not a cause for concern.[8] Our patient had two additional prothrombotic, modifiable risk factors of cigarette smoking and Vitamin B12 deficiency. Other common prothrombotic risk factors identified are hormonal contraceptive usage and thrombophilic status.[3]

The underlying pathophysiology resembles that of heparin-induced thrombocytopenia (HIT), a prothrombotic disorder resulting from IgG-specific antibodies against platelet-factor 4 (PF4)-heparin complexes, causing platelet activation through the FcγRIIA receptor on the platelets.[5] These anti-PF4 antibodies appear about 4–16 days after vaccination and might be provoked by the inflammatory stimulus of the vaccination or by the vaccine itself, cross-reacting with PF4 and platelets. However, unlike in the classical HIT, thrombosis in VITT occurs in the absence of known previous exposure to heparin, leading to the term “spontaneous” or autoimmune HIT. VITT also presents with a more severe thrombocytopenia, higher incidence of disseminated intravascular coagulation, and atypical thrombotic events.[1]

The British Society for Haematology[9] and the Society of Thrombosis and Haemostasis Research (GTH)[8] have issued management guidelines for this rare complication. Successful treatment requires a multidisciplinary approach, as in this case, which involved intensive care, hematology, neurology,
and neurosurgery. It is important to investigate any recently vaccinated patient with symptoms suggestive of VITT with serial monitoring of platelet count, d-dimer, prothrombin time, partial thromboplastin time, and fibrinogen [Figure 3]. Any deranged result should be followed up by anti-PF4 assay by ELISA. A positive test for anti-PF4 is confirmatory,[6] while a negative test in a case with a high index of suspicion for VITT can be further worked up with heparin-induced platelet activation assay or serotonin-release assay.[7,8,10] Imaging tests, specific to symptoms, such as CT or MRI, can further help in diagnosis and management.[6,8]

Treatment parallels that of autoimmune HIT and mainly involves IVIG 1 g/kg once daily for 2 days, which improves the platelet count within days, as seen in our patient, by limiting antibody-mediated platelet clearance and platelet activation by immune complexes.[4,9] Concurrent anticoagulation with a nonheparin-based drug is required, such as factor Xa inhibitors (fondaparinux or danaparoid), direct thrombin inhibitors (argatroban or bivalirudin), and novel oral anticoagulants (apixaban, rivaroxaban, and dabigatran) with monitoring for bleeding or worsening thrombocytopenia.[5,6,8,9] Low dose of argatroban is favored when platelet count is below 30 × 10^9/L. Platelet transfusion should be avoided as it can trigger further thrombosis, but, if necessary, should be done after IVIG transfusion. Plasma exchange and high-dose steroids are indicated in cases unresponsive to IVIG. Bruton tyrosine kinase inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, which are able to block the FCγRIIA receptor-mediated platelet activation, have been proposed as an alternative treatment option for VITT. Cryoprecipitate or fibrinogen concentrates may be given to maintain fibrinogen above 1.5 g/l. Anticoagulation is continued on discharge until platelet count, D-dimer, and fibrinogen are normal and PF4 antibodies are negative. Patients who developed VITT following the first dose of the AstraZeneca vaccine are advised to not take the second dose.[9]

CONCLUSION

Although COVID vaccination can lead to this very rare, life-threatening thrombotic complication, most regulatory bodies advice that the benefits far outweigh the risks. Awareness of warning signs after vaccination and early medical treatment at a multidisciplinary specialty center, as well as modification of prothrombotic risk factors would help in preventing high morbidity and mortality.

Declaration of patient consent

Patient’s consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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