

Vaccine-induced thrombosis and thrombocytopenia (VITT); Exploring the unknown

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ABSTRACT

Vaccination is supposed to be the most reliable means to end the COVID 19 pandemic, but recently there have been reports of thrombosis and thrombocytopenia in patients receiving the vaccine especially ChAdOx1 nCoV-19 (AstraZeneca University of Oxford and Serum Institute of India). This has been termed as vaccine-induced immune thrombotic thrombocytopenia (VITT), thrombosis with thrombocytopenia syndrome (TTS) and vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). This is a challenging situation and patients are treated with Fondaparinux and Rivaroxaban after thrombocytopenia is corrected. Herewith, we report a case of VITT who presented to our hospital and was successfully treated over a weeks' time.

Keywords: Immune, thrombocytopenia, thrombosis, vaccination

Introduction

When the world was struck by the SARS-CoV-2 pandemic with severe morbidity and mortality across the globe, the world was looking up at scientists to come up with an effective vaccine. They came up with vaccines produced from diverse technologies on a war footing. However, beginning in late February 2021, adverse events like immune thrombocytopenia and bleeding with or without thrombosis came to light after exposure to the recombinant chimpanzee adenoviral vector vaccines like ChAdOx1 nCoV-19 (Covishield/AstraZeneca)^[1] and Ad26.COV2.S (Janssen/Johnson and Johnson).^[2] Both thrombosis and thrombocytopenia usually occurred between 5 and 45 days,^[3] after vaccination. Thrombosis occurred at unusual sites like portal vein, hepatic veins, splanchnic vein, mesenteric veins and cerebral venous sinuses. This was associated with thrombocytopenia with average platelet count varying

between 20,000 and 30,000 cubic mm. As the thrombosis with concurrent thrombocytopenia was triggered by a vaccine, the condition was termed as Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT). The overall incidence of VITT appeared to be approximately 1 case per 500,000 vaccine doses administered. The treatment is challenging and includes immunoglobulins with non-heparin anti-coagulation.

Case Presentation

A 50-year-old lady was admitted with a history of a non-itchy petechial rash over her body. She had taken her first dose of Covishield vaccine about 3 weeks prior. RT-PCR for SARS-CoV-2 was negative. Complete blood count was unremarkable except for severe thrombocytopenia (platelet count was 3,000/cu mm). Her other biochemical parameters were as shown in the Table 1. Considering the antecedent history of vaccination, the possibility of VITT was considered. Test for anti PF4-HITT ELISA was reported positive. In the meantime, she was treated with Methyl prednisolone 1 gm once daily intravenously (IV) for 3 days, IVIG 1 gm/kg IV for 2 days and Methyl cobalamin 500 mcg IV × 5 days followed by oral 1,500 mcg/day. Her platelet response to the combination of IVIG and steroid was dramatic.

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Table 1: Investigations

Parameter	On admission	Day 2	Day 5	Normal range
C-Reactive protein	2.8 mg/dl	0.98 mg/dl	1.56 mg/dl	0.08-.79 mg/dl
D-Dimer test	2880 ng FEU/ml	2440 ng FEU/ml	2000 ng FEU/ml	0-500 ng FEU/ml
Plasma Fibrinogen	170 mg/dl	400 mg/dl		180-360 mg/dl
Haemoglobin	11.0 gm/dl	10.8 gm/dl	11.3 gm/dl	11.5-16.5 gm/dl
Platelet count	3000 per cu mm	8000 per cu mm	156000 per cu mm	150,000-450,000 per cu mm
ANA (Antinuclear antibodies)	Negative			
Dengue Virus card test	Negative			
Serum albumin	4.34 gm/dl			3.5-5.2 gm/dl
Serum globulin	2.76 gm/dl			2.5-3.5 gm/dl
Reticulocyte percentage	3.1%			0.5-2%
INR (International normalized ratio)	0.99 sec	1.01 sec	1.21 sec	0.8-1.2 sec
Vitamin B12	84 pg/ml			180-914 pg/ml
APTT (Activated Partial Thromboplastin Time)	26.3 sec			22-36 sec
LDH (Lactate Dehydrogenase)	452 U/I			208-378 n U/I

It rose from 3,000 to 1.56 lakhs on the fifth day. The petechial rashes disappeared gradually. D-dimer levels fell to 2,000 ng/FEU/ml. Her screening for thrombosis (portal, hepatic veins and deep veins of the legs) did not reveal any evidence of the same. After her platelets rose to safe levels, she was treated with injection Fondaparinaux 7.5 mg once daily subcutaneously for 5 days and finally switched over to oral Rivaroxaban 10 mg once daily. She was discharged in a stable condition and advised to follow-up in the outpatient department. Four weeks later she was asymptomatic; her platelet count was 2.6 lakhs. D-dimer had decreased to 1000 ng/FEU/ml. At 12 weeks, her platelets were normal and D-dimer level was less than 500 ng/FEU/ml. Rivaroxaban was subsequently stopped.

Discussion

VITT is a condition akin to heparin-induced thrombocytopenia and is associated with prior administration of the Ad26.COV2.S from Johnson and Johnson/Janssen and ChAdOx1 from AstraZeneca COVID-19 vaccines and without exposure to heparin. Both vaccines utilize recombinant adenoviral vectors encoding the SARS-CoV-2 spike protein. The incidence of VITT ranges widely from one case per 26,000 to one case per 127,000 doses of AstraZeneca/COVISHIELD administered in countries like Norway and Denmark reporting the highest rates.

VITT is characterized by the presence of two conditions simultaneously—thrombosis (often at unusual sites like the cerebral veins, hepatic veins or splanchnic veins) and thrombocytopenia. The incidence of VITT is not known, but it appears to be extremely rare.

Most of the reported cases occurred between 5 and 42 days following vaccination. Most patients who developed VITT were less than 60 years and were females.^[3] However, both men and women have been diagnosed with VITT following the administration of AstraZeneca vaccine in other parts of the world. Our patient was also a 50-year-old lady with no apparent pro-thrombotic condition except her obesity. There is

no evidence as of now that patients with a previous history of thrombosis, thrombophilic disorder, or prior HIT are at increased risk for VITT.

The five criteria for “Definitive” VITT are:

1. Development of symptoms 4–42 days after exposure to COVID vaccine.
2. Venous or arterial thrombosis at any site.
3. Thrombocytopenia (platelet count $<150 \times 10^9/L$).
4. Positive platelet-factor 4 heparin-induced thrombocytopenia (PF4 HIT) by ELISA.
5. D-dimer elevated at least four times the upper limit of normal.

Our patient met four out of the five criteria for VITT. She did not have evidence of arterial/venous thrombus on Doppler ultrasound of abdomen. However, the possibility of silent cortical vein thrombosis could not be ruled out. She had high levels of D-dimer and low levels of fibrinogen, which signified systemic activation of the coagulation system. The possibility of immune thrombocytopenia was considered but elevated D-dimer levels could not be explained by ITP.

The pathophysiology of VITT is similar to that of HIT, a pro-thrombotic condition arising from platelet activation due to IgG-specific antibodies against PF4-heparin polyanion complexes binding to the FcγRIIA receptor on the platelets.^[4] The exact mechanism by which the adenovirus vaccines trigger development of new antibodies is not known. Probably, components of the vaccine-like virus proteins and free DNA bind to PF4 and produce a “neoantigen,” which then triggers antibody production against PF4.^[2] These anti-PF4 antibodies then cause “pancellular” activation of platelets, leucocytes, endothelial cells and coagulation factors resulting in thrombosis.

The clinical features vary depending upon the site of thrombosis with some people remaining asymptomatic. Our patient had only mild cutaneous bleed in the form of a petechial rash despite a platelet count of 3,000/cu mm. Thrombosis at multiple sites

was also reported.^[5] Overall mortality was 22%. Higher mortality was observed in case of intracerebral bleed (Odds ratio, 2.7; 95% confidence interval [CI], 1.4–5.2) and those with platelet count of less than 30,000/cu mm. Early in the thrombotic process, platelets may not fall. Hence, in the clinical background of vaccination, a very high D-dimer assay even with normal or slightly low platelet count is suggestive of an early VITT.

Treatment of VITT includes IV immune globulin G in the dose of 1 gm/kg body weight for 2 days with or without pulse corticosteroid and therapeutic doses of anticoagulation preferably a non-heparin anticoagulant. Platelet transfusions should not be given as the risk of thrombosis is increased. It should be restricted to bleeding in critical areas or in case of hemodynamic compromise. Our patient showed a good response to the combination of IV IgG and Methylprednisolone and had a haemostatic platelet count on follow-up. As she developed a life-threatening complication after the first dose of Covishield vaccine, she was advised against taking the second dose.

Conclusions

VITT develops within 4–45 days of receiving adenovirus vector-based vaccines. One should have a high index of suspicion to diagnose this condition early. If symptoms suspicious of VITT appear within the window period, complete blood count, PT (INR), activated partial thromboplastin time, serum fibrinogen, D-dimer assay and antibodies to PF4/polyanion complex by ELISA should be done along with appropriate diagnostic imaging. The condition should be suspected in the presence of thrombocytopenia with thrombosis and treatment should be initiated early with IVIG, steroids and non-heparin anticoagulants with careful monitoring.

Key points

Although the COVID 19 vaccines were produced to give us immunity against the deadly virus, they were not devoid of side effects. COVISHIELD is one such vaccine that can very rarely lead to VITT, which the clinicians must recognize quickly to save the life of the patient.

Emerging new knowledge

COVISHIELD is a commonly used vaccine against COVID 19, which interferes with the coagulation system of the body and can cause VITT.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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