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LETTER TO THE EDITOR

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SARS-CoV-2 vaccine-induced prothrombotic immune thrombocytopenia: Promoting awareness to improve patient-doctor trust

Dear Editor,

The COVID-19 pandemic has engulfed the entire world in a state of crisis. Vaccines are an important new weapon in the fight against COVID-19, and the fact that so many vaccines are proving to be effective and are being developed is very promising. However, the general public has been concerned about the possible development of side effects and the study of it is important to clarify any doubts, improve confidence and for the benefit of scientific progress.

Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) also referred to as thrombosis with thrombocytopenia syndrome is characterised by mild to severe thrombocytopenia, venous or arterial thrombosis at sites such as cerebral venous thrombosis/splanchnic thrombosis and positive PF-4 heparin enzyme-linked immunosorbent assay (ELISA).[1] It has been observed that this phenomenon has an underlying immunological mechanism similar to that of heparin-induced thrombocytopenia (HIT); however, it was reported that this is not triggered by heparin, hence it imitates spontaneous autoimmune HIT (aHIT) with the identification of antibodies to platelet factor-4 (PF4).[1,2]

HIT is a prothrombotic adverse reaction, caused by the brief production of IgG class of platelet-activating antibodies which recognise the PF4 which are cationic and bind to heparin which is polyanionic.[2] In aHIT there is uniformly positive PF4-heparin ELISAs, with the circulating PF4-reactive antibodies which activate platelets in the absence of heparin.[1] The binding of aHIT antibodies to PF4 brings in heparin-dependent antibodies to form large immune complexes thus flaring up the reaction.[2] Patients so far have presented with symptoms of headaches followed by rapid neurological deterioration after vaccination.[3] This reaction is a rarely seen and highly unique event which has been reported in patients after vaccination.[4] Other rarely recorded autoimmune diseases include Guillian Barre syndrome, which was seen in influenza vaccination.[4] The constellation of signs, symptoms, and reports seen in the patients have not been previously described in the medical literature as a possible post-vaccination reaction. Hence an association between the clinical syndrome and vaccination is suspected.[4]

There have been isolated case reports in various regions of the world involving signs of thrombotic thrombocytopenia following COVID-19 vaccination. In Table 1, we outlined the reported and published COVID-19 VIPIT[5–9] till date providing a detailed description of the events. The incidence remains largely unknown, however it appears that an incidence of 1 in 125,000 was seen after vaccination with the AstraZeneca vaccine (ChAdOx1 nCoV-19).[10] A report by Centers for Disease Control suggested an incidence of 1 in 533,333 after individuals were vaccinated with the Janssen vaccine (Ad26.COV2.S).[11] A small amount of cases have also been reported following vaccination with Moderna (mRNA-1273) and Pfizer–BioNTech (BNT162b2).[12] Based on the available literature thus far, there seems to be an increased occurance of vaccine induced thrombotic thrombocytopenia in young female patients.

VIPIT patients usually presents with arterial/venous clots or with cerebral sinus vein thrombosis. The suspicious symptoms include severe and persistent headache, focal neurological symptoms, breathlessness and chest pain, seizures, blurred vision, abdominal pain, swelling, redness or pallor of limbs. If a patient presents with a normal platelet count and thrombosis after vaccination, they might be at an early stage of VIPIT, therefore it is required to give special attention, to avoid complications and be able to catch rare dangerous cases in a prompt manner. Most VIPIT cases present within 30 days post vaccination, therefore patients presenting with the above listed symptoms in a similar timeline, must be suspected of having VIPIT. The diagnosis of VIPIT must satisfy all these criteria—recent COVID-19 vaccine, venous or arterial thrombosis (can be cerebral/abdominal), positive PF4 HIT ELISA. In case of suspicion of VIPIT, an immediate a complete blood count (include platelet count) should be performed and imaging for thrombosis would be suggested depending upon the patient's symptoms. Regarding treatment, intravenous immune immunoglobin and nonheparin anticoagulants are recommended. Heparin and platelet transfusions are instead contraindicated until VIPIT has been ruled out.

In conclusion, it is important to monitor patients presenting with the above described symptoms in all cases but particular attention is required when patients report a history of recent COVID-19 vaccination. Patients that present with similar symptoms and normal full blood count might be at the early stages of the side effect, therefore they should also be continuously monitored to avoid fatality. Awareness of the side effects and the protocols established to provide the best possible care is

TABLE 1 A detailed description of the reported and published COVID-19 VITC

Vaccine	Country	No of Patients	Age	Gender	Complications	Management	Outcome
Pfizer-BioNTech BNT16B2b2 mRNA vaccine (Tarawneh et al.)	USA	1	22	Male	Widespread petechiae and gum bleeding	Dexamethasone 40 mg daily for 4 days, platelet transfusion, and intravenous immunoglobulin (IVIG) at 1 g/kg for 2 days	Recovered
Adenoviral (ChAdOx1) vector-based COVID-19 vaccine (AZD1222) (Blauenfeldt et al.)	Norway and Denmark	1	60	Female	CVT, bilateral adrenal hemorrhages, subcapsular renal hematoma	Hydrocortisone 100 mg three times daily as substitution therapy, platelet transfusion, cefuroxime	Death
Ad26.COV2.S vaccine (Johnson & Johnson/Janssen) (Muir et al.)	USA	1	48	Female	CVT, splanchnic vein thrombosis	Unfractionated heparin, IVIG (1 g/kg)	Critically ill
ChAdOx1 nCov-19 Vaccine (AstraZeneca) (Greinacher et al.)	Germany and Austria	11	Median age of 36 (range of 22-49)	9 Female and 2 Male	9—CVT, 3—splanchnic vein thrombosis, 3—pulmonary embolism	Intravenous antibiotics, low molecular weight heparin (enoxaparin), red blood cell and platelet transfusions, prothrombin complex concentrates, recombinant factor VIIa	Six died, four recovered, and one not reported
mRNA-1273 Moderna Covid-19 vaccine (Toom et al.)	USA	1	26	Female	Diffuse petechiae, oral ecchymosis	Dexamethasone 40 mg intravenously daily for four days, IVIG 1 mg/kg for 3 days	Recovered

fundamental, to avoid fatalities and to reassure patients that they are always at the centre of the work of healthcare professionals during this crisis.

Tarun K. Suvvari[1]
Eshwar Rajesh[2]
Reewen G. D Silva[3]
Anna C. Corriero[4]
L. V. Simhachalam Kutikuppala[1]

[1]*Dr. N.T.R. University of Health Sciences, Vijayawada, India*
[2]*Madras Medical College, Chennai, India*
[3]*Belagavi Institute of Medical Sciences, Belagavi, India*
[4]*Anglia Ruskin University School of Medicine, Cambridge, UK*

Correspondence
Tarun K. Suvvari, Dr. N.T.R. University of Health Sciences, Vijayawada, Andhra Pradesh 520004, India.
Email: tarunkumarsuvvari234@gmail.com

ORCID

Tarun K. Suvvari http://orcid.org/0000-0003-0063-0339
Eshwar Rajesh http://orcid.org/0000-0002-2057-017X
Reewen G. D Silva http://orcid.org/0000-0002-5335-8204
Anna C. Corriero http://orcid.org/0000-0001-9687-3997
L. V. Simhachalam Kutikuppala http://orcid.org/0000-0002-5685-6049

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