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Thrombotic thrombocytopenia due to SARS-CoV-2 vaccination

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■ ABSTRACT

Vaccine-induced thrombotic thrombocytopenia (VITT) has been reported after vaccination with the AstraZeneca ChAdOx1 nCoV-19 and the Johnson and Johnson Ad26.COV2.S vaccines. This manuscript provides a brief overview of reported cases, clinical and laboratory features, and current understanding of the pathogenesis of VITT. The author also poses unanswered questions and identifies directions for future study.

■ INTRODUCTION

The global SARS-CoV-2 pandemic has resulted in more than 150 million confirmed infections and 3 million deaths (<https://covid19.who.int>). The scope of the pandemic has led to an unprecedented effort to develop effective vaccines. Currently, 3 vaccines have received US Food and Drug Administration emergency use authorization (EUA): the messenger RNA (mRNA)-based vaccines produced by Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2), and the adenoviral-based vaccine from Johnson and Johnson (J&J; Ad26.COV2.S). These vaccines, as well as the adenoviral vaccine ChAdOx1 nCoV-19 from AstraZeneca (AZD1222), are also authorized for use in Europe (Table 1). As of this writing, at least 133 million people in the United States have been vaccinated with a SARS-CoV-2 vaccine, and continued vaccination will play a critical role in controlling COVID-19.

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■ KEY FEATURES OF VACCINE-INDUCED THROMBOTIC THROMBOCYTOPENIA

Who is affected

Recently, several reports have documented the occurrence of a post-vaccination syndrome that has become known as vaccine-induced thrombotic thrombocytopenia (VITT).¹⁻⁴ This syndrome has been described as occurring 5 to 24 days after vaccination with the ChAdOx1 nCoV-19 vaccine, and characterized by thrombocytopenia accompanied by thrombosis, often at unusual sites. After a report of an additional case occurring after immunization with the Ad26.COV2.S vaccine,⁴ review of Ad26.COV2.S clinical trial data revealed an additional 5 cases of VITT.⁵ Of the approximately 46 cases reported in the literature to date, 40 have relatively detailed patient history and demographic information¹⁻⁵; 28 have occurred in females ranging in age from 21 to 77 (though most commonly under age 50), and only a few of these patients have been on estrogen therapy.

Clinical and laboratory features

Severe thrombocytopenia with platelet counts below $10 \times 10^9/L$ have been reported, though median nadir platelet counts are generally in the range of 20 to $30 \times 10^9/L$. Some patients, however, have demonstrated only mild thrombocytopenia. A predilection for cerebral venous sinus thrombosis (CVST) is common, occurring in 27 of 40 patients. Splanchnic thrombosis is also frequent, particularly involving the portal vein. The reasons underlying the localization of venous thrombi to these uncommon sites is unknown. In addition to venous thrombi, arterial thromboembolism, including aortoiliac thrombosis and stroke, has occurred in less than 10% of patients.^{2,3}

From a laboratory perspective, high levels of D-dimers have been reported in most patients with VITT, and in some patients have levels more than

TABLE 1**Current SARS-CoV-2 vaccines**

Vaccine	Nomenclature	Type/vector	Antigen	US approval	European approval
Moderna	mRNA-1273	mRNA in lipid nanoparticles	Stabilized, prefusion spike protein	Emergency Use Authorization (EUA)	Conditional Marketing Authorisation (CMA)
Pfizer-BioNTech	BNT162b2 (EU-Cominarty)	mRNA in lipid nanoparticles	Stabilized, prefusion spike protein	EUA	CMA
Johnson & Johnson/Janssen	Ad26.CO2-5	Adenovirus 26 (species A)	Stabilized, prefusion spike protein	EUA	CMA
Astra-Zeneca	ChAdOx1 nCoV19 (AZD1222, Vaxzevria)	Chimpanzee adenovirus (species E)	Unmodified spike protein	–	CMA

100 times higher than laboratory normal cutoffs.^{2,3} Decreased fibrinogen levels, elevated D-dimer, and prolongation of the international normalized ratio consistent with the International Society on Thrombosis and Haemostasis criteria for overt disseminated intravascular coagulation (DIC) are present in at least one-half of patients, although evidence of a consumptive coagulopathy that does not meet strict DIC criteria are present in most.

These findings are consistent with an analysis of ChAdOx1 nCoV-19-vaccinated patients by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) (<https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots>), which has reviewed 79 cases of VITT; 44 of these were characterized by CVST and thrombocytopenia, and 35 as thromboses in other veins; 51 of these cases were in women.

VITT is associated with a significant death rate, with at least 16 of 40 reported patients dying, most commonly of cerebral edema or bleeding secondary to extensive CVST. The rate of death was lower (19 of 79) in the MHRA analysis. It is not known whether any of the patients with VITT in this series have previous COVID-19.

■ SIMILARITIES WITH HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS

Heparin-induced thrombocytopenia with thrombosis (HITT) is a highly prothrombotic disorder caused by antibodies to platelet factor 4 (PF4)-heparin complexes; these antibodies appear 5 to 14 days after heparin exposure. HITT antibodies are directed toward a neopeptide on the highly cationic PF4 that

is exposed after charge-dependent binding to heparin or a related anionic glycosaminoglycan or polyanion. When PF4 and heparin are present at the proper stoichiometric concentration (approximately 1:1 for unfractionated heparin), ultralarge, highly antigenic complexes that are recognized by HITT antibodies may develop.⁶ These antibodies cause activation of platelets and monocytes through binding of these complexes through Fc gamma receptor II, and may also activate endothelial cells through binding to PF4 associated with negatively charged endothelial cell glycosaminoglycans.⁷

The occurrence of aggressive thrombosis and thrombocytopenia in SARS-CoV-2-vaccinated patients suggested similarities between VITT and HITT and led investigators to test patients for the presence of antibodies to PF4-heparin complexes. Antibodies to complexes of heparin or heparinlike polyanions (used in commercial enzyme-linked immunosorbent assay kits) bound to PF4 were observed in all patients with VITT, despite no recent exposure of these patients to heparin.⁸ Moreover, like HITT antibodies, sera and purified PF4-heparin antibodies from VITT patients caused platelet activation in a PF4-dependent manner. However, in contrast to HITT, activation of platelets by VITT sera was not enhanced in the presence of low heparin concentrations, suggesting subtle differences in the nature of the target epitope.

Taken together, the serologic and platelet studies observed in patients with VITT resemble those described in “autoimmune” HITT (aHITT), an uncommon HITT variant that encompasses several unusual syndromes including delayed-onset HITT, persisting HITT, spontaneous HITT, and severe HITT with DIC.⁹ In several of these disorders, there is no history of recent heparin exposure, and it is

believed that binding of antibodies to complexes of PF4 bound to related polyanions such as hypersulfated chondroitin sulfate, DNA, RNA, polyphosphate, or bacterial-wall components may result in a structural change in PF4 that exposes an antigenic neoepitope. In the case of VITT, it has been postulated that DNA may serve as the polyanion that binds PF4,² but this remains speculative, and the underlying mechanisms by which antigenic polyanion-PF4 complexes form in VITT remains to be determined.

■ DIAGNOSIS AND MANAGEMENT

Despite the high initial mortality associated with VITT, prompt recognition and institution of specific therapy will likely lead to better outcomes. International agencies and societies including the American Society of Hematology (ASH) (<https://www.hematology.org/covid-19>) and International Society of Thrombosis and Hemostasis (ISTH)¹⁰ have issued recommendations on diagnosis and management. A brief summary follows.

Diagnostic criteria

Key criteria for the diagnosis of VITT include the following:

- The patient has received the ChAdOx1 nCoV-19 or Ad26.SOV2.S vaccine within the last 30 days.
- Thrombocytopenia that is generally moderate to severe (platelet count $< 50 \times 10^9/L$), though in some cases it is mild, particularly in the early stage of VITT.
- Thrombosis, often involving the cerebral venous sinus or splanchnic veins. Arterial thrombosis occurs less commonly. Physicians should be aware of the clinical presentations of these events, which include severe, nonrelenting headache in CVST, and abdominal or back pain (or both) and nausea and vomiting in splanchnic thrombosis.
- Anti-PF4-heparin or PF4-polyanion antibodies, or both, assessed using a commercially approved assay. However, some rapid immunoassays and chemiluminescence assays have yielded false-negative results.³ ISTH guidelines recommend confirmation using a functional assay such as carbon 14-labeled serotonin release assay.

Initial evaluation, and the differential diagnosis

The initial evaluation of suspected VITT should include a complete blood cell count, D-dimer and fibrinogen levels, PF4-polyanion ELISA, and imaging

studies appropriate for the diagnosis of thrombosis and as dictated by symptoms.

On the surface, the diagnosis of VITT would seem relatively straightforward. However, multiple cases of immune thrombocytopenia have been described after SARS-CoV-2 vaccination, including after the Moderna and Pfizer vaccines.¹¹ Likewise, anti-PF4 antibodies are seen in a variety of clinical situations, such as after cardiovascular surgery, and are seen even in normal individuals, but these alone do not make the diagnosis of VITT.

Cornerstones of treatment

Treatment of VITT should be suggested by the clinical and laboratory findings outlined in **Table 2**. However, other potential scenarios should be considered on a case-by-case basis.

The cornerstones of treatment of VITT are intravenous immunoglobulin, usually given at a dose of 1 gm/kg for 2 days, and anticoagulation. The mechanism of intravenous immunoglobulin is presumed to be Fc gamma receptor blockade, similar to that observed in HITT, resulting in a rapid rise in the platelet count.

Although heparin has not been definitively shown to worsen outcomes, it should be avoided in patients with VITT. Nonheparin anticoagulants such as direct oral anticoagulants and argatroban are preferred, and danaparoid has been recommended in settings outside the United States.

Platelet transfusion may worsen thrombotic manifestations of VITT and should be avoided, except perhaps in the setting of life-threatening bleeding.

■ UNANSWERED QUESTIONS, DIRECTIONS FOR FUTURE INVESTIGATION

We do not yet know why VITT antibodies develop after SARS-CoV-2 vaccination. To date, VITT has developed only in patients who have received the ChAdOx1 nCoV-19 and Ad26.COV2.S vaccines, both of which employ an adenoviral vector. This has led to speculation that the adenoviral component of the vaccine may be responsible.

However, the two vaccines are built upon different vectors, the Ad26.COV2.S vaccine on an adenovirus 26 vector (Ad species A), and the ChAdOx1 nCoV-19 on a chimpanzee adenovirus vector (Ad species E). These use different receptors to gain cellular entry and likely have different biological characteristics. Moreover, the nature of the spike protein encoded by both vectors differs as well, with the Ad26.COV2 construct encoding a membrane-bound spike protein

TABLE 2**Indications for initiating treatment of suspected VITT**

Thrombocytopenia and a positive PF4-polyanion test in the presence of thrombosis

High clinical suspicion of VITT based on the presence of thrombosis and thrombocytopenia after vaccination, even when PF4-polyanion ELISA results are pending

Thrombocytopenia and a positive PF4-polyanion ELISA, with or without a very high or increasing D-dimer level, even in the absence of thrombosis

ELISA = enzyme-linked immunosorbent assay; VITT = vaccine-induced thrombotic thrombocytopenia

stabilized by two proline substitutions that does not shed the S1 fragment of the spike protein, whereas ChAdOx1 nCoV-19 encodes an unmodified S protein.

Interestingly, high-titer anti-PF4–heparin antibodies may occur in COVID-19, but these do not activate platelets, suggesting differences from VITT antibodies that have yet to be defined.¹² Likewise, IgG fractions from some patients with COVID-19 have been shown to induce Fc gamma receptor II-dependent platelet apoptosis, although the nature of these antibodies or immune complexes is unknown.¹³

Other unanswered questions include the risk of revaccination, the significance of PF4 antibodies that may develop after natural SARS-CoV-2 infection, and the patient characteristics that predispose to VITT.

Finally, the incidence of VITT must be viewed in comparison to a CVST incidence of 0.22 to 1.57 cases per 100,000 per year in the general population, which does not differ substantially from the incidence in vaccinated patients, which is estimated at 1 per 100,000 to 1 per 1,000,000 individuals.⁸ While this low incidence represents a challenge to the study of patients with VITT, it provides reassurance of the safety of SARS-CoV-2 vaccination relative to the incidence and outcomes of COVID-19 disease.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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