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Short Review

SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia

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ABSTRACT

SARS-CoV-2 vaccines have been carefully developed and significantly alleviate the global pandemic. However, a rare but severe complication after vaccination of adenoviral vector vaccines has attracted worldwide attention. It is characterized by thrombosis at unusual sites (often cerebral or abdominal), thrombocytopenia, and the presence of antibodies against platelet factor 4 (PF4), termed vaccine-induced immune thrombotic thrombocytopenia (VITT). Its pathogenesis is similar to that of heparin-induced thrombocytopenia (HIT). VITT progresses rapidly and has a high mortality rate. Clinicians and the public should raise their vigilance to this disease so that accurate and timely treatment is provided.

1. Introduction

Since the onset of the coronavirus disease (COVID-19) pandemic until the end of October 2021, there have been more than 240 million individuals diagnosed and more than 5 million deaths worldwide. Economic and social activities have been severely disrupted, and health sector has been severely impacted. A vaccine is the most effective way to prevent the infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within a year, several types of vaccines have been developed, including viral vector vaccines, nucleic acid vaccines, recombinant protein vaccines, inactivated vaccines, and billions of doses have been delivered. Massive vaccination campaigns have significantly alleviated this pandemic. However, a rare but severe thrombotic event with thrombocytopenia after the ChAdOx1 vaccine (AstraZeneca) and Ad26.COV2.S vaccine (Janssen/Johnson & Johnson) has been reported in several countries [1–7]. This complication is characterized by thrombosis at unusual sites, such as severe cerebral venous sinus thrombosis (CVST), splanchnic venous thrombosis or arterial thrombosis, increased D-dimer levels, decreased or normal fibrinogen levels, and the presence of antibodies against platelet factor 4 (PF4). It progresses rapidly, and the mortality rate can reach 20%–50%, which requires great attention [3,8–10]. Its pathogenesis is similar to that of heparin-induced thrombocytopenia (HIT). This new disease is named as "vaccine-induced immune thrombotic thrombocytopenia (VITT)" [11]. The purpose of this review is to provide an overview and the latest progress of this thrombotic incident in order to raise vigilance among the public and assist the doctors to treat the disease.

2. Epidemiology

At the beginning of April 2021, the European regulatory EudraVigilance database reported 169 cases of CVST and 53 cases of splanchnic venous thrombosis in 34 million individuals who received the first dose of ChAdOx1 vaccine in the European Economic Area (EEA) and the United Kingdom, with an overall incidence of approximately 6.5 per million, among which the incidence of CVST was 5.0 per million. The U. S. Vaccine Adverse Event Reporting System (VAERS) reported that the incidence of VITT after Ad26.COV2.S vaccine was 7 per million in women aged 18–49 years and 0.9 per million in women aged 50 years and older. In the analysis of subgroups by age (18–29, 30–39, 40–49, 50–64, and ≥65 years), the highest incidence was reported in women aged 30–39 years, with 11.8 VITT cases per million Ad26.COV2.S doses administered [8]. In the general population without any vaccination, the incidence of venous thrombosis is 1–2 cases per 1000 persons every year [12], and that of CVST is 0.22–1.57 per million. The incidence of CVST among hospitalized patients in the United States in the months of March and April 2021 was 2.4 per million [13]. The frequency of CVST in patients with COVID-19 is approximately 42.8 per million [14], which is much higher than that of vaccine-related cases. Therefore, the incidence of VITT is very low. However, VITT progresses rapidly, especially in patients with CVST, whose mortality is much higher than that of general CVST patients (about 5%–10%) [3,4,15].

The majority of VITT patients are younger than 50 years old with potential predominance of women [9,16]. The potential risk factors of VITT patients were analyzed, including obesity, hypothyroidism, oral contraceptives, hormone therapy among women, and infections [8,10].

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None of the patients had a history of thrombosis, coagulation dysfunction, or family history of thrombus, and none had been exposed to heparin before the onset of VITT [8].

3. Pathogenesis

The pathogenesis of VITT is unclear, but high levels of antibodies against PF4 have been detected in the serum of almost all patients with VITT [3]; therefore, anti-PF4 antibodies may induce thrombosis, which is similar to HIT, a well-known immune thrombotic disease. In HIT, anti-PF4 antibodies recognize multimolecular complexes formed by cationic PF4 and anionic heparin. The new complexes, containing heparin, PF4, and anti-PF4 antibodies, crosslink many FcγRIIA receptors (CD32a) on platelets. FcγRIIA, a type I transmembrane protein, can induce signaling and platelet aggregation/secretion, formation of platelet-neutrophilia and monocyte complexes, and thrombin generation [17]. As a result, platelets are activated and blood clots form [18]. The pathogenesis of VITT is similar. The study on VITT after ChAdOx1 vaccine by Greinacher et al. [19] found that vaccine components bound with PF4 on platelet surface driven by charge, and anti-PF4 antibodies from VITT patients bound with vaccine components/PF4 to form immune complexes. The immune complexes can induce activation of platelets, aggregation of neutrophils and drive thrombosis. Vaccine components and EDTA contained in the vaccine led to vascular leakage in mice after intradermal injection. Proteomics identified that approximately half of the vaccine protein components were T-Rex HEK293 cell protein associated with transfection of adenovirus. Vaccine components/PF4 complexes and the proinflammatory surroundings induced by vaccine trigger an obvious B cell response to produce high-activity anti-PF4 antibodies. Studies have shown that high titer anti-PF4 antibodies could activate platelets effectively in the presence of PF4 or DNA and polyphosphate polyanions. Anti-PF4 antibodies also stimulate neutrophils to release neutrophil extracellular traps (NETs) in a PF4-dependent manner. Procoagulant NETs biomarkers were elevated in serum of VITT patients, and abundant NETs were seen in cerebral venous thrombi from VITT patients by immunohistochemistry. Study by Holm et al. [20] also found formation of immune complexes resulted in the release of an enormous amount of innate immune response cytokines and markers of systemic inflammatory into blood, extensive degranulation of neutrophils. Activated inflammatory response can lead to tissue and endothelial damage and promote thrombosis. Anti-PF4 antibody-mediated platelet activation can be neutralized by high concentrations of heparin or polyclonal immunoglobulins, or blocked by monoclonal antibodies against FcγRIIA.

There are several differences between VITT and classic HIT. Firstly, patients with VITT had no prior exposure to heparin. The negative charge drives the binding of vaccine components to PF4. Secondly, study by Singh et al. [21] showed that VITT anti-PF4 antibodies were oligoclonal, which was similar to spontaneous HIT, while anti-PF4 antibodies from classic HIT patients were polyclonal. In addition, VITT anti-PF4 antibodies bind to PF4 at a different site from HIT. A report by Huynh et al. [22] showed that VITT anti-PF4 antibodies bound to the heparin-binding site on the PF4 tetramer; further, the heparin inhibited platelet activation by replacing VITT anti-PF4 antibodies. However, in HIT samples, the binding of anti-PF4 antibodies to PF4 was not limited to the heparin-binding site, which explained the different responses to low concentration of heparin in the two diseases [3,5].

Study by Greinacher et al. [23] showed that although SARS-CoV-2 spike protein had at least one similar epitope with PF4, anti-PF4 antibodies purified from VITT patients do not cross-react with SARS-CoV-2 spike protein, suggesting that the immune response against SARS-CoV-2 spike protein is not the trigger of VITT.

Adenoviral vector components play an important role in the formation of VITT immune complexes. Both AstraZeneca's chimpanzee ChAdOx1 vaccine and Janssen/Johnson & Johnson's human Ad26.COV2.S vaccine contain non-replicative adenoviral vectors. The Sputnik V vaccine (Gamaleya Research Institute, Russia) and Convidecia vaccine (CanSino Biologics, Academy of Military Medical Sciences, China) are also adenoviral vector vaccines. Interim analysis of the phase III clinical trial of Sputnik V showed that one patient developed deep vein thrombosis, while three developed cerebrovascular diseases (n = 16,427) [24]. No thrombotic incidents have been reported with the Convidecia vaccine. Among these vaccines, adenoviral vector of ChAdOx1 vaccine had higher electronegative surface potential than others, which may be associated with the slightly higher incidence of ChAdOx1 vaccine-related VITT [25].

4. Clinical manifestations and laboratory tests

4.1. Time of onset

The time from vaccination to the onset of VITT-related symptoms was approximately 5–30 days [26]. In the phase III trial of the Ad26.COV2.S vaccine, 44% of those vaccinated population younger than 60 years developed headache in the first week after vaccination. The symptoms appeared within 2 days and disappeared within 2 days [4]. Caution should be raised if symptoms appear more than 4 days after vaccination, especially for persistent symptoms.

4.2. Clinical manifestations

Patients with VITT mainly present one or multiple thrombosis at unusual sites, including CVST, splanchnic venous thrombosis, arterial thromboembolism, and thrombotic microangiopathy (TMA) [2]. CVST is the most common site, occurring in more than 40% of the reported patients [3–6,9,16], followed by splanchnic venous thrombosis. The most common symptom is severe headache, which worsens and is insensitive to analgesics, possibly with visual changes, nausea, and vomiting, and other symptoms include persistent abdominal pain, shortness of breath, chest pain, back pain, leg pain or swelling, petechiae, unexplained bruising or bleeding. If these symptoms occur within the time window after vaccination, emergency medical evaluation is required. Patients may also develop disseminated intravascular coagulation and diffuse bleeding. Intracranial hemorrhage occurs in approximately 20%–70% of CVST cases [3–6,9,16], which progresses rapidly and is often fatal [4]. Some patients may manifest as microangiopathic hemolysis, but this is not a common feature.

4.3. Laboratory examination

Thrombosis and hemorrhage may be found through imaging examinations. The focus is on CVST, splanchnic venous thrombosis, pulmonary embolism, and deep venous thrombosis (DVT).

Complete blood count showed thrombocytopenia, with a mean platelet count of approximately 20–40 $\times$ 10^9/L and a range of about 10–110 $\times$ 10^9/L [3–5]. D-dimer levels increased in most patients and were often greater than 2000 μg/L [27], and fibrinogen levels decreased in some patients. The international standardized ratio (INR) and activated partial thromboplastin time (APTT) were mostly within the normal range, and the level of C-reactive protein was always increased [3–5]. Blood smear indicates platelet aggregation, routine blood analyses show increased platelet volume [28].

Enzyme-linked immunosorbent assay (ELISA) for anti-PF4 antibodies showed a high level of positivity in almost all the reported patients; the optical density value (OD) was usually greater than 2.0–3.0 [3,4]. Whether the positive level of anti-PF4 antibodies detected by ELISA is associated with the risk of VITT is not clear. The serum of patients with or without the addition of PF4 can induce activation of normal platelets, and addition of PF4 can enhance platelet activation. Study by Schönborn et al. [29] showed that platelet-activation assay became negative at a median of 12 weeks, while the OD of anti-PF4 antibodies by ELISA may not turn negative completely. Non-ELISA

rapid immunoassay (RIA) showed poor specificity for VITT and is not recommended [30]. To determine VITT, samples should be collected prior to treatment.

Functional HIT assay may contribute to the diagnosis of VITT, including serotonin release assay (SRA), heparin-induced platelet activation assay (HIPA), or p-selectin expression assay (PEA) [31]. However, See et al. [4] detected the functional HIT assay in nine VITT patients with positive anti-PF4 antibodies by ELISA, and only one patient was positive for SRA and PEA. Therefore, the practicality of functional HIT assays in VITT is uncertain, and negative results cannot exclude false negatives.

Antiphospholipid antibodies were detected in some of the reported patients, most of which were negative, but several patients showed a slight elevation [4]. Lupus anticoagulant assay results were negative. The levels of complement proteins (C1q, C3, and C4) and activating products (sC5b-9) were normal in most cases, except those with hemolysis. The results of antithrombin, protein C, and protein S screening were negative, and the activities of ADAMTS13 were normal in the tested patients [4,6].

Polymerase chain reaction (PCR) was used to detect SARS-CoV-2 nucleic acids in all patients, and all were negative. Scully et al. [5] detected serological antibodies for SARS-CoV-2 nucleocapsid protein in 10 available samples, and the results were negative, which excluded recent SARS-CoV-2 infection. The levels of spike glycoprotein and receptor-binding domain (RBD) antibodies in all 10 patients were within the range of a single dose of SARS-CoV-2 vaccination.

5. Diagnosis

Diagnosis of VITT must meet the following five criteria: symptoms usually begin 5–30 days after vaccination with SARS-CoV-2 vaccine, any venous or arterial thrombosis (often cerebral or abdominal), thrombocytopenia (platelet count $< 150 \times 10^9$/L), and positive anti-PF4 antibodies (ELISA), markedly elevated D-dimer (>4 times upper limit of normal) [26,30] (Fig. 1).

Some patients developed severe headache, thrombocytopenia, markedly elevated D-dimer and high levels of anti-PF4 antibodies 5 to 20 days after SARS-CoV-2 vaccination, but there was no imaging evidence of obvious cerebral venous sinus thrombosis. Severe headache in these patients may be associated with microthrombosis in smaller cortical veins. These patients might develop typical CVST after a few days. Salih et al. defined this phenomenon as pre-VITT syndrome [32].

VITT can be excluded using negative anti-PF4 antibodies (ELISA). If thrombocytopenia with no thrombosis occurs and anti-PF4 antibodies (ELISA) are negative, immune thrombocytopenia (ITP) may occur. Negative antiphospholipid antibodies, lupus anticoagulant assay, screening for antithrombin, and normal ADAMTS13 activity may help exclude other thrombotic diseases. Tests of SARS-CoV-2 nucleic acid and nucleocapsid protein antibodies can help exclude SARS-CoV-2 infection.

6. Treatment

If VITT is diagnosed, patients should be transferred to a tertiary hospital, and the condition should be assessed in time. Pre-VITT is at imminent risk for CVST and CVST can be prevented with immediate therapy [32]. Treatment includes the following (Fig. 1).

6.1. Non-heparin anticoagulant therapy

Although no studies have shown that heparin aggravates thrombosis, hematologists strongly recommend that patients with VITT avoid heparin unless the HIT assay is negative [2,3,5,30]. Non-heparin anticoagulants are recommended for VITT patients, such as direct thrombin inhibitors (bivalirudin and argatroban), fondaparinux sodium, and direct oral anticoagulants (DOACs) (apixaban and rivaroxaban) [3]. For patients with thrombosis and severe depletion of coagulation factors, the use of anticoagulants should be carefully monitored, especially in patients with CVST, in which hemorrhage may be fatal. Patients with thrombus should be treated with anticoagulants for at least three months, as with conventional treatment for DVT.

6.2. High dose of intravenous immunoglobulin (IVIG)

A high dose of IVIG should be administered as early as possible, 1 g/

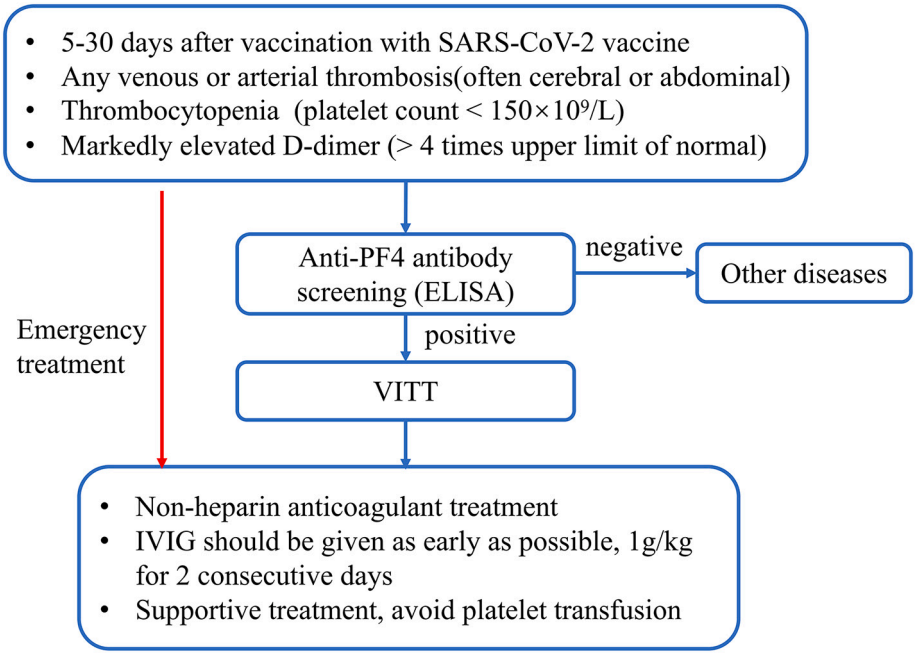

Fig. 1. Recommended procedures for diagnosis and treatment of VITT.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PF4, platelet factor 4; VITT, vaccine-induced immune thrombotic thrombocytopenia; IVIG, intravenous immunoglobulin.

kg for 2 consecutive days. IVIG can competitively inhibit platelet activation induced by immune complexes [3]. When patients develop severe thrombocytopenia and thrombosis, a high dose of IVIG can increase platelet counts rapidly and increase the safety of the anticoagulant treatment. Patients with severe bleeding or need for emergency surgery may receive IVIG urgently. IVIG can also increase fibrinogen levels and decrease D-dimer levels to reduce hypercoagulability [33]. However, the influence of IVIG on the efficacy of the SARS-CoV-2 vaccine is not fully understood. It is worth noting that there may be neutralizing antibodies against SARS-CoV-2 vaccine antigen in IVIG collected during the COVID-19 pandemic, which may reduce the efficacy of the vaccine [34], and interfere with the detection of SARS-CoV-2 antibodies [34]. Therefore, IVIG from COVID-19 pre-pandemic plasma is recommended to avoid vaccine failure. If IVIG is absent, plasma exchange may be considered [35,36].

6.3. Supportive treatment

Patients with hemorrhage or hypofibrinogenemia could be treated with fibrinogen replacement. Platelet transfusion can increase mortality in patients with HIT [37]. Based on the similarity with HIT, platelet transfusion should be avoided in VITT patients. However, patients with serious bleeding or need emergency surgery may benefit from platelet transfusion after IVIG and non-heparin anticoagulation [26,30].

6.4. Target therapy

Bruton tyrosine kinase (BTK) inhibitors have been approved for B-cell lymphoma and target multiple downstream pathways activated by FcγRIIA. BTK inhibitors have been proven to inhibit FcγRIIA-mediated cross-linking of platelet aggregation, secretion of dense granules, expression of p-selectin, and platelet-neutrophil aggregation [38]. Weber et al. [39] found that low concentrations of ibrutinib and fenebrutinib prevented platelet aggregation induced by serum from VITT patients. So BTK inhibitors are considered as potential treatment options for VITT. Eculizumab may be effective in some cases presenting with TMA, in which complement activation may be involved. The PF4/anti-PF4 complexes can activate the complement cascade [40]. Tiede et al. successfully treated a patient with eculizumab who failed anticoagulation and IVIG therapy [2].

6.5. Other treatments

Some refractory patients with deteriorating status may benefit from thrombectomy [18]. Aspirin should be avoided to treat or prevent VITT as it is ineffective in preventing platelet activation from anti-PF4 antibodies and may increase the risk of bleeding [30]. Vitamin K antagonists should be avoided in acute VITT because of the inhibition of protein C and protein S, which may aggravate thrombosis [26]. Glucocorticoids combined with IVIG have been used in some cases.

Time to start treatment: If thrombosis in unusual sites with thrombocytopenia occurs within the time window after vaccination, do not wait for the ELISA results of anti-PF4 antibodies. Start treatment immediately with non-heparin anticoagulants and high-dose IVIG [3].

7. Advice

The United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), European Medicines Agency (EMA), and Advisory Committee on Immunization Practices (ACIP) in the United States reviewed the benefits and risks of two adenoviral vector vaccines and confirmed that the risk of vaccine-related thrombosis was not higher than the background risk in the general population. In fact, infection of SARS-CoV-2 is associated with a greater risk of thrombocytopenia and thrombosis [41]. The very favorable risk-benefit ratio of vaccines was highlighted. Therefore, continued use of the two vaccines is recommended [5,8]. The benefits of SARS-CoV-2 vaccines have also been recognized worldwide, particularly in avoiding severe cases, significantly decreasing the frequency of hospitalizations, reducing virus transmission, and providing group immunity [8].

Widespread screening for anti-PF4 antibodies after vaccination is of little significance, because the incidence of VITT is extremely low. A study by Sørvoll et al. [42] recruited 492 health care workers who received a single dose of ChAdOx1 vaccine (10–35 days post vaccination). The results showed only 6 cases had positive anti-PF4 antibodies with low OD (OD $\geq$ 0.4, range 0.58–1.16), and 8 cases had a slight decline of platelet counts ($<150 \times 10^9$/L, all $> 100 \times 10^9$/L), with no thrombosis. However, doctors and the general public should be educated about the adverse effects of SARS-CoV-2 vaccines, especially severe VITT and the options of other types of vaccines, especially for women aged 18–49 years. In the case reports of CVST in the United States, the median time from the onset of symptoms to hospitalization was 7 days, and increased awareness of VITT in patients and clinicians may shorten the time to medical evaluation and treatment [4]. Clinicians who encounter suspected thrombosis and thrombocytopenia after SARS-CoV-2 vaccine should report to the pharmacovigilance department in time after considering its association with vaccine. Recipients of vaccines who develop emerging and persistent symptoms for more than 4 days after vaccination should seek medical attention as soon as possible for a timely and thorough examination.

8. Summary

SARS-CoV-2 vaccines play a key role in controlling the COVID-19 pandemic, but doctors and the public should remain vigilant for the presence of vaccine-related serious adverse effects. VITT is rare but severe, with rapid progress and a high mortality rate, requiring extensive attention. The pathogenesis and monitoring still requires further study.

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CRediT authorship contribution statement

All authors contributed to the design, writing, critical review of the manuscript, and approved it for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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