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Review

Autoimmunity roots of the thrombotic events after COVID-19 vaccination

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ABSTRACT

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Although vaccination represents the most promising way to stop or contain the coronavirus disease 2019 (COVID-19) pandemic and safety and effectiveness of available vaccines were proven, a small number of individuals who received anti-SARS-CoV-2 vaccines developed a prothrombotic syndrome. Vaccine-induced immune thrombotic thrombocytopenia (VITT) can be triggered by the adenoviral vector-based vaccine, whereas lipid nanoparticle-mRNA-based vaccines can induce rare cases of deep vein thrombosis (DVT). Although the main pathogenic mechanisms behind this rare phenomenon have not yet been identified, both host and vaccine factors might be involved, with pathology at least in part being related to the vaccine-triggered autoimmune reaction. In this review, we are considering some aspects related to pathogenesis, major risk factors, as well as peculiarities of diagnosis and treatment of this rare condition.

1. Pathogenesis

After an important journey to develop vaccines against COVID-19 to be able to control SARS-CoV-2 transmissibility and the severity of disease [1], the world has faced rare severe adverse events associated with these vaccines. SARS-CoV-2 vaccines are based on an adenoviral (Ad) vector platform for the expression of the SARS-CoV-2 spike (S) protein. However, both the chimpanzee ChAdOx1 nCoV-19 vaccine (University of Oxford/AstraZeneca) and the human Ad26.COV2·S vaccine (Janssen Pharmaceuticals/Johnson & Johnson) have recently been associated with severe thrombosis and thrombocytopenia, also known as vaccine-induced immune thrombotic thrombocytopenia (VITT) [2–5]. Additionally, the lipid nanoparticle (LNP)-mRNA based vaccines (Pfizer/BioNTech and Moderna) have induced rare cases of deep vein thrombosis (DVT) [6,7]. The main pathogenic factors behind this rare phenomenon have not yet been identified, however, both host and vaccine factors might be involved. Several questions have been raised. Why do thrombotic events appear only in a very limited number of vaccinated persons? Why are thrombotic events more frequent in females? Is thrombocytopenia related to the spike glycoprotein? Does the Ad vector induce thrombocytopenia? Is there an association between vaccinated individuals with pre-existing health conditions (individuals who underwent specific surgery, were treated with anti-PF4 antibody inducing drugs and/or with a particular haplotype more vulnerable to thrombi) and diagnosed with VITT? Do those individuals already have excessive production of pro-inflammatory cytokines? Why do post-vaccination thrombi appear at unusual sites? [8]. Although the reported cases are very rare, appearing at a rate of roughly 1/1,000,000 among vaccinated persons (VigiBase, WHO, [7,9]) in developed countries, our report aims to analyze this phenomenon and better understand its pathophysiological mechanism(s). Since this is the first time that Ad- and LNP-mRNA based vaccines have been used at such a large scale, determination of their long-term protection is critical for the identification of potentially contraindications, such as a history of blood disorders, past or present thrombocytopenia, or pre-existing immunological conditions [10]. Below are described some of the possible players involved in thrombotic events associated with COVID-19 vaccines.

Thrombotic and thrombocytopenic complications occurred in 40 individuals after the first dose of the ChAdOx1 nCoV-19 vaccine [2,4,5] and in 18 patients after the first dose of Ad26.COV2·S vaccine [3,11], of which 13 (22.4%) patients had one or more predisposing factors for thrombosis or history of previous thromboses (Table 1).

Platelets (thrombocytes), the smallest colorless blood cells with no nucleus, are characterized by the biconvex discoid (lens-shaped) shape. They are abundantly found in blood and are involved in blood clotting. In addition to the essential role platelets play in hemostasis through multiple pathways, they are pivotal in the host defense response against many human diseases. The multifunctional platelets may be involved in various abnormalities and diseases, including thrombosis, atherosclerosis, tumor progression/metastasis, stroke, and myocardial infarction induced by arterial thrombosis [12].

Using both molecular modeling (to compare the immunogenic epitopes of platelet factor-4 (PF4) and SARS-CoV-2 S protein) and purified antibodies against PF4 and S proteins, Greinacher and colleagues showed that three motifs within the SARS-CoV-2 S protein sequence share a potential immunogenic epitope with PF4. In their preprint study, they revealed that purified antibodies to PF4 are not immunogenic [13]. Of particular interest are the different magnitudes of antibody response against both PF4 and the SARS-CoV-2S protein, indicating two different immune response mechanisms [9]. The VITT patients showed strong antibody reactivity against PF4 within 5–14 days post-vaccination, presumably reflecting a secondary immune response. They found that the primary immune response is extremely unlikely to yield such high IgG reactivity (titers >1:3000). Precedence for this concept is found in the heparin-induced thrombocytopenia literature: patients who develop this complication with their first heparin exposure, develop a strong IgG immune response beginning as early as 4–5 days after exposure to heparin, which is consistent with the prior re-sensitization through naturally occurring polyanions [13,14].

Clinical observations show unusually strong pro-inflammatory symptoms in most individuals starting about eight to twelve hours post-vaccination, lasting for 12–24 h. Potentially, this inflammatory response in specific individuals (based on their genetic makeups, human leukocyte antigen (HLA) type, or pro-inflammatory conditions) may have led to the observed occurrences of severe VITT (31 patients reported in Germany). The inflammatory reactions might be reduced by reducing the ChAdOx1 nCoV-19 vaccine dose. Of note, results from a phase III study indicated that a lower dose of 2.5×10^{10} adenoviral particles administered in the first injection induced a similar antibody response compared to the currently used dose [14,15]. It is also worth noting that a lower dose of adenoviral particles could reduce platelet activation [16].

Table 1
Examples of patients with risk factors of thrombosis who received adenoviral (Ad) vector-based SARS-CoV-2 vaccines and developed VITT and their characteristics.

Gender	Age	Vaccine type	Dose	Risk factor	Thrombosis site	Ref
–	–	ChAdOx1 nCov-19	First	Type 1 von Willebrand disease Factor V Leiden Anti-cardiolipin antibodies	Splanchnic-vein, Pulmonary, Cerebral sinus	[2]
Female	37	ChAdOx1 nCoV-19	First	Oral contraceptive pill	Cortical veins, left transverse sinus, and sigmoid left sinus	[5]
Female	42	ChAdOx1 nCoV-19	First	Contraceptive vaginal ring	Cortical veins, left transverse sinus, and sigmoid left sinus	[5]
Female	54	ChAdOx1 nCoV-19	First	Hormone-replacement therapy	Cortical veins, superior sagittal sinus, both transverse sinuses, and left sigmoid sinus	[5]
–	–	ChAdOx1 nCoV-19	First	Oral contraceptive pill	–	[2]
–	–	ChAdOx1 nCoV-19	First	Deep vein thrombosis	–	[2]
Female	<60	Ad26.COV2.S	First	Obesity Hypothyroidism Oral contraceptive pill	Cerebral venous sinus thrombosis	[67]

VITT is similar to autoimmune heparin-induced thrombocytopenia (HIT) [2]. The classic HIT is a progressive thrombotic syndrome that can result in both venous and arterial thrombosis and occurs 5–14 days after heparin exposure, suggesting an autoimmune reaction during this period. HIT is characterized by the presence of platelet-activating antibodies that recognize multimolecular complexes between the cationic PF4 and the anionic heparin, which leads to platelet activation and microparticle release, contributing to thrombosis. The removal of platelets via phagocytosis by splenic macrophages in an FcγR-dependent mechanism [17] or platelet consumption caused by thrombi formation can explain thrombocytopenia [2], and this disorder may also lead to bleeding in other places. There is another important question, namely, do platelet microparticles (PMPs) play a role in VITT and thrombosis at unusual sites? PMPs are smaller in size than platelets. They bear a heterogeneous and condense set of receptors, repertoire of which depends on the physiological platelet status during PMP shading post platelet activation. Their smaller dimensions enable them to diffuse more quickly in the less controlled manner than platelets and allow PMPs to reach sites not easily accessible to platelets. The coagulation abilities of activated platelets and PMPs are very similar despite the approximately 100-fold difference in their surface area. Therefore, it can be concluded that the specific procoagulant activity of the PMP membranes is approximately 50- to 100-fold higher than that of activated platelets. Most likely, this occurs because phosphatidylserine and membrane proteins participating in the binding of coagulation factors are concentrated on PMPs during the shedding process [18,19].

Other triggers that can cause prothrombotic events similar to HIT without exposure to heparin are pentosan polysulfate [20], the anti-angiogenic agent PI-88 [21], hyper sulfated chondroitin sulfate [21], viral and bacterial infections [22,23], and knee-replacement surgery [24,25]. Such a prothrombotic syndrome is termed autoimmune or spontaneous heparin-induced thrombocytopenia [14,26]. Autoimmune heparin-induced thrombocytopenia differs from classic heparin-induced thrombocytopenia, in that it causes unusually severe thrombocytopenia, an increased frequency of disseminated intravascular coagulation, and atypical thrombotic events.

According to Greinacher et al. [2], VITT was linked to IgG antibodies that recognize PF4 and activate platelets through their Fc receptors. Free DNA can cause PF4-reactive antibody development in Ad vector vaccines that form complexes with PF4 [27] or a strong inflammatory response to vaccination that results in the production of anti-PF4 autoantibodies [2].

The highly positively charged PF4 binds to many negatively charged polyanions such as heparin forming large highly immunogenic multimolecular immune complexes. Ad/PF4, anti-PF4/PF4, or other immune complexes as well as non-immune complexes have access to platelets through a large array of specific receptors for RNA and DNA viruses as well as other biomolecules such as the IgG-specific receptor FcγRIIa, which is the only receptor on platelets to recognize the constant fragment of IgG and enables it to bind to IgG-immune complexes [28–30]. This does not only cause platelet activation and thrombocytopenia, but leads to severe complications if linked with additional etiological factors [31]. Free DNA and/or RNA exposing multiple negatively charged phosphate groups might also form multimolecular complexes with PF4 as demonstrated by circular dichroism (CD) spectroscopy for heparin-induced conformational changes of PF4 [27]. Recently, some oligonucleotide-based drugs have been associated with platelet activation and mild to moderate reversible thrombocytopenia with a decline in number of platelets (<50,000 platelets/μl) depending on the sequences, dose concentration, and repetition [32]. Of note, as inflammation occurs in many VITT patients, DNA and histone release during inflammation or infection might stimulate coagulation, thrombosis, and thrombocytopenia, and has even caused organ damage in mice [33–35]. As there is a possibility that some vaccine-related DNA and/or RNA is released causing VITT, the exact mechanisms for VITT need to be further investigated.

Have VITT patients been tested for autoantibodies (i.e., autoantibodies that are directed against peptides and proteins that are citrullinated, anti-cyclic citrullinated peptide antibodies or anti-CCPs)? In the case of rheumatic arthritis (RA), anti-RA peptide autoantibodies could be detected up to 14 years before the onset of RA, showing that inflammatory diseases can remain asymptomatic for a long time [36]. The anti-vimentin/cardiolipin antibody is strongly associated with both arterial and venous thrombosis [37]. Human anti-vimentin antibodies can induce platelet activation in vitro [38]. The unusually high prevalence of thromboembolic events in COVID-19 patients involving both arterial and venous circulation and thrombosis has been associated with anti-phospholipid syndrome acquired through molecular mimicry and endothelial dysfunction [39,40]. Indeed, not only anti-phospholipid or anti-CCP antibodies but many other autoantibodies may be directly involved and/or indirectly be associated with thrombocytopenia/thrombosis [39]. In a randomly chosen COVID-19 (severely-ill) patient without any autoimmune disease (AID) history, many circulating autoantibodies [41,42] were found, which were not limited to the aforementioned species, but extended to phosphatidylserine/prothrombin (aPS/PT) autoantibodies also associated with higher prevalence of thrombotic events, and usually found in some carriers of anti-phospholipid antibodies [43]. Most interestingly, COVID-19 elicit high titers of anti-PF4 without pre-exposure to heparin, thus strengthening the hypothesis that SARS-CoV-2 can cause autoimmune-based coagulation disorders, particularly in severely ill patients with high levels of exacerbating cytokines [44,45]. Why is this seen in only certain patients and not in all severely ill COVID-19 patients?

Another question is what would be the common factor between COVID-19 patients and VITT? In addition to the above-mentioned AID autoantibodies, a substantial association between periodontal pathogen infections (*A. actinomycetemcomitans* and *P. gingivalis*) and natural circulating anti-PF4/H was described [46]. The infection by these pathogens plays an important role as primary immunogens stimulate the synthesis of anti-H (similar to bacterial polyanions glycosaminoglycans (GAGs)), also detected in sepsis patients [47] and complexed with PF4 can activate platelets [46,48]. Based on their binding affinity, anti-PF4/polyanion antibodies (from human patients) have been divided into three groups [49]. Only members of group-3 (with binding forces Z100pN) bind to PF4 alone in the absence of polyanions, then clustering the PF4-molecules forming antigenic complexes, which allow binding of polyanion-dependent anti-PF4/P-antibodies. As the resulting immunocomplexes could induce massive platelet activation in the absence of heparin, the question is whether the differences in binding affinity reflects the differences in anti-PF4 between individuals [49]? The risk for development of new thromboses may depend on FcγRIIA polymorphism , which affects the binding affinity to different human IgG subclasses [50] and molecules involved in FcγRIIA signaling [51], as has been shown for the risk of clinical HIT. Are the VITT patients currently or previously infected with these pathogens and/or do they have FcγRIIA polymorphisms? As previously reported, periodontal pathogens, particularly *A. actinomycetemcomitans* and *P. gingivalis* play a significant role in the induction of some AIDs [52]. Therefore, VITT patients should be tested for AIDs to help identifying the exact mechanism behind it. Additionally, as a precaution, individuals with autoimmunity predisposition should be evaluated before subjected to vaccinations.

The scenario of a potential accidental injection of Ad-based vaccines into the bloodstream has been investigated [53,54]. The innate responses may occur within minutes to hours, leading to blood pressure changes, thrombocytopenia, inflammation, and fever. Dysregulation of coagulation can spread to multiple organs and lead to disseminated intravascular coagulation (DIC). Activation of vascular endothelial cells by Ad vectors results in the release of ultra-large-molecular-weight multimers of the von Willebrand factor (vWF), a blood protein that is critical for platelet adhesion. The Ad-induced thrombocytopenia was found to be dependent on the vWF since vWF-knockout (KO) mice did not show thrombocytopenia when exposed to the virus [55]. Ad vectors

also activate platelets and induce exposure of the adhesion molecule P-selectin (as the platelets express the Coxsackie adenovirus receptor (CAR), although ChAdOx1 can use other receptors than CAR) and formation of platelet-leukocyte aggregates, ultimately causing thrombocytopenia and thus a risk for bleeding. Important cellular interactions occurring early after systemic Ad vector delivery involve vascular and hepatic endothelial cells, platelets, Kupffer cells, hepatocytes, and splenic macrophages (MFs) and DCs.

2. Risk factors

HIT is more common in female patients, particularly those who received unfractionated heparin during cardiac surgery and in patients who received heparin after surgery, especially cardiac and orthopedic procedures [56]. Most of the 39 individuals that developed thrombosis and thrombocytopenia 5–24 days after vaccination with the ChAdOx1 nCoV-19 vaccine were females younger than 50 years of age, some of whom were receiving estrogen-replacement therapy or oral contraceptives [56]. Moreover, bilateral superior ophthalmic vein thrombosis, ischemic stroke, and immune thrombocytopenia was reported in a 55-year-old woman after vaccination with the ChAdOx1 nCoV-19 vaccine [57]. Although anti-platelet IgGs were detected in this study, no anti-PF4 antibodies were discovered [57].

The platelet suspension immunofluorescence test and the monoclonal antibody-specific immobilization of platelet antigen assay were also positive, which on the one hand supports a diagnosis of secondary immune thrombocytopenia [57]. As already known, anti-phospholipid syndrome, thrombotic microangiopathy, viruses, such as influenza virus H3N2, Dengue virus, hepatitis B and C viruses, HIV, cytomegalovirus, hantaviruses, adenoviruseAds, and *H. pylori* (Table 2) are possible causes of thrombocytopenia [55,57]. These pathogens, through molecular mimicry, have previously been proposed to provide a classic mechanism responsible for the vaccine-associated immune thrombocytopenic purpura (ITP) [58]. Antibody-bound platelets and megakaryocytes undergo reticuloendothelial phagocytosis and direct lysis by cytotoxic T-cells leading to thrombocytopenia. Furthermore, ITPs have also been previously reported for several other vaccines, such as influenza, poliomyelitis, pneumococcal, hepatitis, Measles, Mumps, and Rubella (MMR), and rabies. The vaccine-mediated autoimmunity was proposed to be associated with both antigen and vaccine constituents, for instance, trace proteins from the culture media (such as yeast proteins), adjuvants, preservatives, or formulation carriers [10,58].

One of the possible molecular mechanisms of VITT is related to the capability of platelets to translate mRNA and synthesize proteins, facts known for over fifty years [59] and to the capability of some viruses, such as Dengue, influenza, and HIV to infect platelets. Based on these observations, Dr. Hamis Merchant, in his Rapid Response to the BMJ Research News on "Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots" [10] suggested that since RNA viruses can directly infect platelets, then the viral mRNA translation and spike protein synthesis within platelets can initiate an autoimmune response against platelets [10].

The observations that vaccine-associated thrombosis is more prevalent in women makes sense, as females are generally more exposed to the risk of thrombosis throughout their life. Examples of risk factors encountered frequently by women include oral contraceptive use, hormone replacement therapy, pregnancy, puerperium, and various obstetric complications [60,61]. Furthermore, genetic risk factors should be taken into account as well. Application of GWAS (genome-wide association study) demonstrated that several single nucleotide polymorphisms (SNPs) in the T-cell death-associated gene 8 (TDAG8) and one of the HLA class II alpha chain paralogues, HLA-DRA (which is expressed in autoimmune disease), were associated with HIT and formation of PF4/heparin antibodies in non-heparin treated patients [61]. Those SNPs can be genotyped in recipients of Ad-based COVID-19 vaccines to identify those with the most significant risk of thromboembolic complications and VITT. Similarly, it was previously found that high anti-PF4/heparin antibody levels were associated with a specific class II HLA haplotype (HLA-DRB1*03:01-DQB1*02:01), which is widely implicated in autoimmunity [62]. Of note, the exact mechanism behind the development of an anti-PF4/heparin response is still poorly understood, as neither heparin nor PF4 are foreign antigens to humans. The hypothesis is that exogenous heparin may alter intracellular PF4 processing within antigen-presenting cells, causing the presentation of aberrant PF4-derived peptides (neoantigens) to T-cells [63]. Human PF4 neoantigen presentation may be restricted to specific HLA molecules. It was also hypothesized that patients having specific class II HLA alleles are predisposed to increased anti-PF4/heparin antibodies after exposure to heparin [62]. More information on potential risk factors is needed to determine whether VITT could be associated with a person's genotype. In fact, many platelet inheritance factors are distributed in family-specific traits [64], which may have effects on VITT as reported in the case of the familial thrombocytopenia flare-up following the first dose of mRNA-1273 COVID-19 vaccine [65]. As with the highly variable probability of SARS-CoV-2 infection, different populations and individuals will likely respond uniquely to the SARS-CoV-2 vaccine, simply because the main viral antigen inducing pathophysiology associated with infection is the spike glycoprotein, which represents the main viral component in those vaccines that induce VITT, due at least in part to genetic variations. The genetic analysis revealed a list of SNPs and genes that can be used as biomarkers to predict the development of coagulation [65,66].

Table 2
Major etiological causes of secondary ITP.

	Secondary ITP	
Vaccines	Influenza, poliomyelitis, pneumococcal, MMR, HPV, and HBV	[58]
Infections	HIV, HCV, CMV, DV, HV, AdVs, EBV, *H. pylori*, and TB	[28,29,55,74]
Drugs	NSAIDS, antibiotics, and antivirals	[75]
Connective tissue disease	LES, Sjogren, and APLS	[76]
Autoimmune thyroiditis	Basedow's and Hashimoto's diseases	[77,78]
Immunodeficiencies	CVID, IgA deficiency, DiGeorge's syndrome	[79,80]
Neoplasia	LNH and solid tumors (paraneoplastic)	[81,82]
Lymphoproliferative disorders	ALPS	[83]

ITP: immune thrombocytopenic purpura; MMR: measles/mumps/rubella; HPV: human papillomavirus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; HCV: hepatitis C virus; CMV: cytomegalovirus; DV: Dengue virus; HV: Hantavirus; AdV: Adenovirus; EBV: Epstein-Barr virus; TB: tuberculosis; NSAIDs: non-steroidal anti-inflammatory drugs; LES: Lupus erythematosus; APLS: anti-phospholipid syndrome; CVID: common variable immunodeficiency; LNH: non-Hodgkin's lymphoma; ALPS: autoimmune lymphoproliferative syndrome.

3. Diagnosis is suggested by some reports

Generally, healthy individuals present acute atypical thrombosis, primarily involving unusual sites such as cerebral venous sinus thrombosis, thrombosis in the portal, splanchnic, or hepatic veins, pulmonary emboli, or acute arterial thrombosis [8] with concurrent thrombocytopenia 6 to 24 days after the administration of the first dose of the ChAdOx1 nCoV-19, Ad26.COV2·S or mRNA (Pfizer/BioNTech and Moderna) vaccines [7]. The detection of high levels of antibodies to PF4 by enzyme-linked immunosorbent assay (ELISA) is unrelated to the use of heparin therapy. D-dimer levels are much higher than would be expected in patients with acute venous thromboembolism [5]. The detection of high levels of antibodies to PF4 by ELISA is unrelated to the use of heparin therapy. Functional platelet HIT antibody tests can be positive [67]. Functional platelet HIT antibody assays are of higher specificity than the heparin-PF4 ELISA, where they determine the extent

to which these antibodies activate platelets in the presence of heparin, leading to aggregation [68]. However, lack of standardization may lead to laboratory-dependent differences in results [69,70]. Examples of functional platelet HIT antibody tests include [67]: 1) Serotonin release assay (SRA), which measures serotonin release from dense granules in platelets as a marker for platelet activation, 2) Latex immunoturbidimetric assay (LIA), which detects the presence of PF4 HIT antibodies based on their ability to competitively inhibit agglutination of HIT-like monoclonal antibodies bound to latex particles, and 3) P-selectin expression assay (PEA), which measures platelet surface P-selectin expression as a marker of platelet activation.

4. Treatment

The regimens for successful treatment of autoimmune HIT can be applied for VITT as well. This includes intravenous immunoglobulin (IVIG) and high-dose glucocorticoid injections [71,72]. Non-heparin anticoagulants, such as argatroban, danaparoid, fondaparinux, or direct oral anticoagulants, should be considered [16]. Platelet transfusions should be avoided because they can act as substrates for further antibody-mediated platelet activation and coagulopathy [5]. Furthermore, repurposed inhibitors of Bruton tyrosine kinase (BTK) have been suggested for the treatment of VITT, as they are expected to pleiotropically target multiple pathways downstream of the platelet Fc receptor FcγRIIA-mediated BTK activation, e.g. as demonstrated for the effective inhibition of platelet aggregation, dense granule secretion, P-selectin expression, and platelet-neutrophil aggregate formation stimulated by FcγRIIA cross-linking. Furthermore, CLEC-2- and GPIb-mediated platelet activation, interactions and activation of monocytes, and release of neutrophil extracellular traps, as encountered in HIT, could be attenuated by BTK inhibitors [73].

5. Conclusions

VITT is rare among vaccinated individuals, and the key mechanisms that cause it still need to be further investigated and acquired data analyzed. Accumulated data suggest that Ad-vector, DNA, and/or RNA vaccine molecules may interact with platelets and/or PF4. Furthermore, many cases have a thrombosis history and/or predisposition for thrombosis, specific haplotypes, and various internal factors, such as smoking and/or taking specific medications, including those that cause an autoimmune reaction. These observations clearly suggest that the VITT seems to be caused by both vaccines and host conditions.

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