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Review article

Coagulopathies after vaccination against SARS-CoV-2: The sole solution might lead to another problem

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Abstract

The common reported adverse impacts of COVID-19 vaccination include the injection site's local reaction followed by various non-specific flu-like symptoms. Nevertheless, uncommon cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) and cerebral venous sinus thrombosis (CVST) following viral vector vaccines (ChAdOx1 nCoV-19 vaccine, Ad26.COV2 vaccine) have been reported. This literature review was performed using PubMed and Google Scholar databases using appropriate keywords and their combinations: SARS-CoV-2, adenovirus, spike protein, thrombosis, thrombocytopenia, vaccine-induced immune thrombotic thrombocytopenia (VITT), NF-kappaB, adenoviral vector, platelet factor 4 (PF4), COVID-19 Vaccine, AstraZeneca COVID vaccine, ChAdOx1 nCoV-19 COVID vaccine, AZD1222 COVID vaccine, coagulopathy. The abstracts and titles of each article were assessed by authors for screening and inclusion English reports about post-vaccine CVST and VITT in humans were also collected. Some SARS-CoV-2 vaccines based on viral vector, mRNA, or inactivated SARS-CoV-2 virus have been accepted and are being pragmatic global. Nevertheless, the recent augmented statistics of normally very infrequent types of thrombosis associated with thrombocytopenia have been stated, predominantly in the context of the adenoviral vector vaccine ChAdOx1 nCoV-19 from Astra Zeneca. The numerical prevalence of these side effects seems to associate with this particular vaccine type, i.e., adenoviral vector-based vaccines, but the meticulous molecular mechanisms are still not clear. The present review summarizes the latest data and hypotheses for molecular and cellular mechanisms into one integrated hypothesis demonstrating that coagulopathies, including thromboses, thrombocytopenia, and other associated side effects, are correlated to an interaction of the two components in the COVID-19 vaccine.

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1. Introduction

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), first reported in Wuhan, China, at the end of 2019 has become the heaviest global pandemic since the Spanish flu from 1918–1920, with more than 562 million infected persons and more than 6.37 million deaths worldwide by 17 July 2022 and 6-digit infection rates daily (1). The COVID-19 (coronavirus disease) pandemic had an overwhelming effect on public health, social life, and economy worldwide (2). The development of vaccines has been indicated to be the

sole effective tool to deal with the situation. Indeed, vaccines prevent severe illness from SARS-COV-2 infection (3).

Thus far, two kinds of SARS-CoV-2 vaccines are developed. Messenger RNA (mRNA) vaccines including Pfizer/BioNTech's (BNT162b2) and Moderna's (mRNA-1273) and viral vector vaccine namely Oxford-AstraZeneca vaccine (AZD1222 (ChAdOx1)) and Johnson & Johnson COVID-19 vaccine (JNJ-78436735 (Ad26.COV2-S)) (4). Safety concerns have been raised concerning the vaccines since they have been utilized. The common adverse impacts post COVID-19 vaccination are composed of the injection site's local reaction followed by non-specific systemic symptoms namely headache, fatigue, myalgia, and fever. These symptoms might occur soon following vaccination and resolve in a short period(5, 6). Nevertheless, several rare cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) have been reported, chiefly with viral vector vaccines, patients with cerebral venous sinus thrombosis (CVST) are also included in these reports. In this review we discuss coagulation disorders following vaccination (5).

2. Methods

This literature review was performed using PubMed and Google Scholar using subsequent Keywords were utilized: SARS-CoV-2, adenovirus, spike protein, thrombosis, thrombocytopenia, vaccine-induced immune thrombotic thrombocytopenia (VITT), NF-kappaB, adenoviral vector, platelet factor 4 (PF4), COVID Vaccine, AstraZeneca COVID vaccine, ChAdOx1 nCoV-19 COVID vaccine, AZD1222 COVID vaccine, Janssen COVID vaccine, Johnson & Johnson COVID vaccine, Ad26.COV2 COVID vaccine, coagulopathy. The abstracts and titles of each article were assessed by authors for screening and inclusion. English reports about post-vaccine CVST and VITT in humans were also collected. It is deduced that vaccination may cause coagulation. However, further research is required to become certain about it.

3.1. COVID-19 vaccines and signals leading to coagulation

3.1.1. Superantigen Induce Procoagulant Activity

Among several uncommon side effects after anti-SARS-CoV-2 vaccination, a disease called multisystem inflammatory syndrome in children (MIS-C) which was found to be related to COVID-19 pandemic with some weeks delay after peaks in SARS-CoV-2 infection incidence and presence of SARS-CoV-2 reactive antibodies has sparked interest (7). It develops hyper inflammation, shock, continuous high fever and it can also causes numerous organ failure such as cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic symptoms in most of affected children. It strongly resembles the late, severe COVID-19 phase in adults. It is believed that MIS-C is a post infectious disease or an immune or autoimmune disease triggered by SARS-CoV-2 infection (8). MIS-C is to some extent reminiscent of toxic shock syndrome (TSS) found in severe cases following sepsis with Gram-positive bacteria such as staphylococcus (8) .It is worth noticing that TSS can be caused by various types of superantigens (SAgs) like viruses and bacteria. The determination of clotting time displayed that procoagulant activity in whole blood and in mononuclear cells were induced by enterotoxin A, B, and toxic shock syndrome toxin 1 from staphylococcus aureus (9). Procoagulant activity was dependent on the expression of tissue factor (TF) in monocytes. In other words, extrinsic coagulation pathway is activated by superantigens from staphylpcoccus aureus inducing the expression of TF in monocyte (10). Apart from that, during acute sepsis, activation of blood coagulation plays a vital pathophysiological role resulting in septic shock due to massive release of cytokines and activation of the coagulation system causing disseminated intravascular coagulation (DIC) and multiorgan dysfunction syndrome (11). Wide activation of T cells, cytokine storm and shock are caused by the antigen specificity of TCRs bypassing. It is depicted that COVID-19 patients with severe hyper inflammation status show TCR skewing consistent with superantigen activation. Overall, SARS-CoV-2 spike protein is capable of acting as a superantigen, with which the development of MIS-C and cytokine storm in adult COVID-19 patients are triggered (12).

3.1.2. Superantigens and NF-κB Pathway

Toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxins A and B induce the activation of NF-κB, which acts as a transcriptional enhancer by means of binding to sequences found in both the IL-1 beta and TNF-alpha promoters (13).The inhibitors of protein tyrosine kinase and protein kinase C downregulated the induction of

NF-κB DNA-binding proteins and NF-κB enhancer function, which indicates a role for these protein kinases in the induction of NF-κB by means of MHC class II ligands. Besides, proteasome inhibition reduced superantigen mediated T cell activation. PS-519, a powerful and selective proteasome inhibitor, was demonstrated to hinder NF-κB activation by means of blocking the degradation of its inhibitory protein IκB and reducing superantigen-mediated T cell activation in vitro and in vivo (14). Proliferation was inhibited in conjuction with the expression of very early (CD69), early (CD25), and late T cell (HLA-DR) activation molecules. Moreover, the inhibition of the NFκB pathway by two antioxidants, N-acetyl-cysteine (NAC) and pyrrolidine dithiocarbamate (PDTC), was demonstrated to dose-dependently inhibit staphylococcal enterotoxin stimulated (SE-stimulated) T-cell proliferation (by 98%), the production of chemokines and cytokines by means of PBMCs, and the expression of SE-induced cell surface activation markers (15).Indeed, NF-κB Pathway plays a role in normal T cell activation. Normal or physiological antigen stimulation of TCR signaling to NF-κB is necessary for T cell proliferation and differentiation of effector cells. Activation of a specific protein kinase C (PKC) isoform, protein kinase C theta (PKCθ), connects TCR proximal signaling events to distal events that finally result in NF-κB activation (16). It is worth noticing that PKCθ activation is also driven by engagement of the T cell costimulatory receptor CD28 by B7 ligands on antigen presenting cells and via intermediate steps resulting in the activation of IKKβ. IKKβ then phosphorylates IκBα, triggering its proteasomal degradation and enabling nuclear translocation of canonical NFκB heterodimers consisted of p65 (RELA) and p50 proteins. Once in the nucleus, the transcription of multiple genes involved in T cell survival, proliferation, and effector functions are governed by NF-κB. Indeed, nuclear factor-κB (NF-κB) is mainly implicated in atherosclerosis and its pathological complication in atherothrombotic diseases due to its transcriptional role in maintaining pro-survival and pro-inflammatory states in vascular and blood cells (15, 16).

3.1.3. SARS-CoV-2 Spike Protein Induces NF-κB

The pathogenesis of COVID-19 can involve over activation of the NF-κB pathway in which the spike (S) protein potently induces inflammatory cytokines and chemokines, namely IL-6, IL-1β, TNFα, CXCL1, CXCL2, and CCL2 yet not IFNs in human and mouse macrophages (17). No such inflammatory response was detected in response to membrane (M), envelope (E), or nucleocapsid (N) proteins. Inflammatory cytokines and chemokines were also produced by A549 human lung epithelial cells when stimulated with extracellular S protein (18). Epithelial cells expressing S protein intracellularly are non-inflammatory but trigger an inflammatory response in macrophages when cocultured. Biochemical studies indicated that the inflammation is triggered by S protein via NF-κB activation pathway in a MyD88-dependent manner. Furthermore, NF-κB activation pathway was abolished in TLR2-deficient macrophages (19). S1 interaction with the human ACE2 receptor and early activation of endoplasmic reticulum (ER) stress and associated unfolded protein response (UPR) and MAP kinase signaling pathways are required for CoV2-S1-induced NF-κB activation. Furthermore, in terms of effect of recombinant SARS-CoV-2 spike protein S1 on human peripheral blood mononuclear cells (PBMCs), PBMCs were stimulated with spike S1 protein resulting in a significant release of TNFα, IL-6, IL-1β, and IL-8 and this cytokine release was inhibited by pretreatment with dexamethasone (20). In addition, the NF-κB pathway was activated by S1 stimulation of PBMCs as indicated by phosphorylation of NF-κB p65, IκBα degradation, and elevated DNA binding of NF-κB p65 following stimulation with spike S1 protein. NF-κB activation was impeded by treatment of PBMCs with dexamethasone or the specific NF-κB inhibitor BAY11-7082 in this investigation (18, 21). Another study has shown that SARS-CoV-2 S protein bound to LPS. Spike protein in combination with low levels of LPS, increased NF-κB activation in monocytic THP-1 cells and cytokine responses in human blood and PBMC, respectively. The study depicted that the S protein modulated the aggregation condition of LPS, providing a potential molecular link between excessive inflammation during infection with SARS-CoV-2 and comorbidities involving enhanced levels of bacterial endotoxins (22). IL-6 and TNF productions are dependent on NF-κB, activated by IκB degradation. powerful NFκB activation is induced by SARS-CoV-2 S spike protein, showing strong similarity to data recorded for the SARS-CoV S protein (23). Similar to SARS-CoV-2, the clinical picture of severe acute respiratory syndrome (SARS) is characterized by an over activated immune response with lung lymphomononuclear cell infiltration and

proliferation that may account for tissue injury further than the direct impact of viral replication (24).

3.1.4. NF-κB Activation is Central role to Coagulation Event

Plasminogen activator inhibitor-1 (PAI-1) is the foremost inhibitor of plasminogen activation and likely plays critical roles in coronary thrombosis and arteriosclerosis (25). Tumor necrosis factor-alpha (TNFα) is one of widely known physiological regulators of PAI-1 expression and might contribute to increased plasma PAI-1 levels in sepsis and obesity(26). A 50 distal TNFα-responsive enhancer of the PAI-1 gene is located 15 kb upstream of the transcription start site including a conserved NF-κB-binding site that mediates the response to TNFα. This newly recognized site was entirely capable of binding NF-κB subunits p50 and p65, whereas the upregulation of the NF-κB inhibitor IkappaB prevents TNFα-induced activation of this enhancer element (27). In an investigation, monocyte NF-κB activation, monocyte TF expression, thrombin generation, and the procoagulant activity of blood in extracorporeal circulation were all obstructed by the proteasome inhibitor MG132, signifying that intravascular TF expression during extracorporeal circulation of blood is due to NF-κB-mediated activation of monocytes (possibly by complement) (28). Another investigation has revealed that C5a increased PAI-1 (both mRNA and protein level) in human monocyte-derived macrophages (29). Pertussis toxin or anti-C5aR/CD88 antibody totally abolished the impact of recombinant human C5a on PAI-1 induction, showing a role of the C5a receptor. Moreover, C5a induced NFκB binding and the increase in PAI-1 were entirely abolished by an NF-κB inhibitor, indicating that C5a upregulates PAI-1 in macrophages via NF-κB activation (30). Eventually, platelets are megakaryocyte-derived fragments lacking nuclei and used to maintain primary hemostasis by commencing blood clots on injured vascular endothelia. Pathologically, platelets go through the same physiological processes of activation, secretion, and aggregation with such pronouncedness that they orchestrate and make headway in terms of the progression of atherothrombotic diseases not merely through clot formation but also by forcing a pro-inflammatory state. Indeed, NF-κB has been involved in platelet survival and function (31).

3.1.5. JAK/STAT3 Activation Is Induced by SARS-CoV-2 Spike Protein Subunit S1

Parallel to the activation of the NF-κB pathway (or probably in consequence of the NF-κB-induced cytokines/chemokines as well), there is also a noticeable activation of Janus kinases/signal transducer and activator of transcription 3 (JAK/STAT3) pathway following SARS-CoV-2 infection(32). Cytokines which bind to type I (e.g., IL-6, G-CSF) and type II (e.g., IL-10) receptors, as well as multiple chemokines binding to G-protein coupled receptors, directly provoke the activation of JAK/STAT3 pathway, characterized by Tyr phosphorylation. Essentially, STAT3 activation was indicated to be involved in COVID-19 associated coagulopathy via enhancement of the expression of tissue factor and of PAI-1 (33). Various other cytokines, such as G-SCF or GM-CSF, and a diverse range of chemokines namely IL-8, MCP-1, MIP1α, and MIP1β found to be elevated in acute COVID-19 patients are also known to activate the JAK/SAT3 pathway. The elevated transcription of JAK/STAT3 activators, such as IL-6 and multiple chemokines (including IL-8, MCP-1, MIP1α, and MIP1β), found during acute respiratory viral infections, including also SARS-CoV-2, is mostly triggered also by NF-κB pathway activation. Essentially, a positive feedback loop of IL-6–JAK/STAT3 signaling with amplification of NF-κB activation was suggested to be involved in COVID-19 induced cytokine storm and mortality (34).

3.2. VITT

3.2.1. Pathophysiology of Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)

VITT is clinically similar to spontaneous autoimmune heparin-induced thrombocytopenia (HIT). Platelet-activating immunoglobulin G (IgG) antibodies causes HIT against platelet factor 4 (PF4) complexed with heparin. Then, this complex binds to the platelet FcRγIIA receptors and results in platelet activation and formation of platelet microparticles (35). These microparticles commence the formation of blood clots and induce a coagulation cascade, which consequently lessens platelet count and causes thrombocytopenia. In addition, the reticuloendothelial system, specifically the spleen, removes the antibody-coated platelets and aggravates thrombocytopenia (36). AstraZeneca COVID vaccine (ChAdOx1) and Johnson & Johnson (Ad26.COV2) vaccines contain replication-

incompetent adenoviral vectors; chimpanzee ChAdOx1 and human Ad26.COV2-S respectively (37). The spike glycoprotein on SARS-CoV-2 is encoded by these two factors. Interactions between the vaccine and platelets or PF4 could play a role in the pathogenesis of VITT due to the reason that the free DNA in the vaccines could bind to PF4 and trigger these PF4-reactive autoantibodies in the VITT setting (38).

3.2.2 Is VITT observed in all marketed adenovirus-vector vaccines?

There are presently four marketed adenovirus-vector vaccines against SARS-Cov-2 which make use of a different adenovirus vector (non-replicating chimpanzee adenovirus in ChAdOx1, Ad5 in CanSino Biologicals Ad5-nCoV and first Sputnik V dose, Ad26 in Johnson & Johnson/Janssen and in the booster Sputnik V dose) (39). No corresponding signals have appeared for Sputnik 5 or CanSino or even the since 2020 licensed adenoviral Vector vaccine Ad26. ZEBOV against Ebola virus disease for that situation. Nevertheless, there are no adequate safety data with regard to other adenovirus-vector vaccines utilized in COVID-19 prevention in light also of concerns of Ad-5 replication (40). Moreover, there is lack of detailed data on the adverse events of Sputnik V reported throughout the clinical trial. Despite a noticeable and increasing cumulative number of vaccinations, it would seem at first unlikely that the entity creates a class effect for all adenoviral vector vaccines (41). Differences among vaccines concerning the spike protein inserts and utilized adenoviral vector shells may theoretically have an impact on the risk of VITT/TTS manifestation. In addition, various adenovirus strains may bind to variable cellular receptors, and therefore may infect a different spectrum of host cells. In terms of influence of VITT on COVID-19 vaccination strategies, however uncommon, the severity of this potentially mortal complication which basically evaded detection during clinical testing deteriorated preexisting public skepticism not only towards these vaccines but also against COVID-19 vaccination in general (42). Current reports have demonstrated that the incidence of VITT/TTS may be in reality remarkably higher than previously presumed, and this may possibly further rise as awareness and understanding of the syndrome becomes further extensive among physicians. The estimated incidence of VITT alters between reports from 1 for every roughly 25,000 individuals vaccinated with ChAdOx1 to 1 for every more than 500,000 Ad26. COV2-S vaccinations (43)(**Table. 1**). These estimates are by all accounts lower than the fatality rates of SARS-Cov-2 infection, basically in all age groups, and certainly less likely than the rates of thromboses complicating actual SARS-CoV-2 infection, specifically those with a severe disease course. Individuals should be recommended to immediately seek medical attention in case that alarming clinical symptoms appear, particularly within the time frame that VITT/TTS would be expected to manifest after vaccination (44). Adenoviral vector vaccines utilize recombinant, non-replicative adenoviruses which act as shells for the carriage of the DNA strand that codes for the SARS-CoV-2 spike protein, which is essential for its pathogenicity (45). Upon intramuscular administration, recombinant viruses enter local cells expressing, among others, the Coxsackie-adenovirus receptor (CAR) by means of clathrin-mediated endocytosis, the carried episomal DNA enters the nucleus, is transcribed into mRNA coding for viral spike protein and is the translated in the endoplasmic reticulum (46). A few mechanisms implicating adenoviral vectors and/or other vaccine ingredients as triggers of prothrombotic states have been proposed:

1- In HIT, the pathogenic autoantibodies target PF4 complexes with heparin, which is chemically a polyanion itself. Moreover, the PF4-polyanion-autoantibody complexes activate platelets through their Fcγ-receptors resulting in an increased risk of thrombosis. In the case of VITT/TTS, the adenoviral DNA content or other currently unaccounted for polyanionic vaccine contents could bind to PF4, and therefore autoantibody production and subsequent platelet activation is induced , which would basically render VITT/TTS a subtype of HIT (47).

2. Coxsackie-adenovirus receptor (CAR) is expressed by platelets as well, so it can be hypothesized that megakaryocytes, their nucleated precursors may be susceptible to recombinant adenovirus infection. A subsequent SARS-CoV-2 spike protein expression could render platelets primary antibody targets or enhance thromboxane A2 production (48).

3. After intravenous administration, adenoviruses might bind to circulating platelets in a von Willebrand Factor- and P-selectin mediated fashion, causing their

Table 1. Report of thromboembolic events after vaccination with The Oxford–AstraZeneca COVID-19 vaccine

Number	*Authors*	*Time from vaccination (days)*	*Laboratory findings*	*Reference*
1	Scully et al.	11.7(Range: 6–19)	Platelet count: Mean: 48 (Range: 7–113) cells×10^9/l PF4 IgG Assay: Done in 10 cases, 9 Positive and 1 Negative D-Dimer: Positive in 13 cases and 3 cases not done.	(85)
2	Bayas et al.	10	Platelet count: 30 cells×10^9 /l PF4 IgG Assay: Negative	(86)
3	Castelli et al.	11	Platelet count: 20 cells×10^9 /l D-Dimer: Positive	(87)
4	Franchini et al.	7	Platelet count: 15 cells×10^9/l PF4 IgG Assay: Positive D-Dimer: Positive	(88)
5	Wolf et al.	6.3 (Range: 4–8)	Platelet count: 75.5 cells×10^9 /l (Range: 60–92) PF4 IgG Assay: Positive D-Dimer: Positive	(64)
6	Mehta et al	7.5 (Range: 6–9)	Platelet count: 24.5 cells×10^9 /l (Range: 19–30) PF4 IgG Assay: 1 Positive 1 unknown D-Dimer: 1 Positive 1 unknown	(89)
7	Blauenfeldt et al.	9	Platelet count: drops to 5 cells×10^9 /l PF4 IgG Assay: Positive D-Dimer: Positive	(90)
8	Schultz et al.	8.7 (Range: 7–10)	Platelet count: Mean: 31.2 (Range:19–70) cells×10^9 /l PF4 IgG Assay: Positive in all cases D-Dimer: Positive in all cases	(91)
9	D'Agostino et al.	12	Thrombocytopenia D-Dimer: Positive	(92)
10	Greinacher et al.	9.3 (Range: 5–16)	Platelet count: 27.3 cells×10^9 /l (Range: 8–75) PF4 IgG Assay: 7 Positive 2 unknown D-Dimer: Positive in all cases	(93)

activation and sequestration in the reticuloendothelial system.

4. In addition to platelets, anti-PF4 antibodies may also bind to and activate different other cell types, including neutrophils, monocytes (thus inducing the expression of tissue factor), as well as endothelial cell, therefore further promoting thrombotic manifestations (49).

5. Greinacher et al. have proposed that the Ethylenediaminetetraacetic acid (EDTA) included in the vaccine preparation might boost local vascular permeability in the injection site and cause the systematic dissemination of vaccine components which interact with preformed natural antibody, inducing a serum sickness-like disease. This inflammatory state may act as a co-signal to augment the antibody production of anti PF4-antibody-producing B-cells(49)**(Fig. 1).**

A probable diagnosis of VITT is confirmed with the demonstration of circulating PF4/polyanion antibodies (usually with high optical density readings) by enzyme-linked immunosorbent assay (ELISA), in the absence of prior heparin exposure (50). Unfortunately, the rapid immunoassays used for HIT screening (including latex-enhanced, lateral flow and particle gel immunoassays) particularly in non-tertiary centers, do not appear to be sensitive for the detection of PF4-polyanion-autoantibodies in VITT/TTS, and are consequently not useful in the diagnostic workup outside specialized departments In that case, readily available standard coagulation studies should be ordered awaiting further testing (51). A logical clinical suspicion of VITT even pending certain laboratory confirmation mandates the initiation of anticoagulation therapy. While there is no evidence for the notion that unfractionated or low molecular weight heparin (LMWH) may negatively influence the course of the syndrome, due to its similarities with HIT, the majority of societies advise in preference to the use of non-heparin anticoagulants. A short course of intravenous immunoglobulin (IVIG)

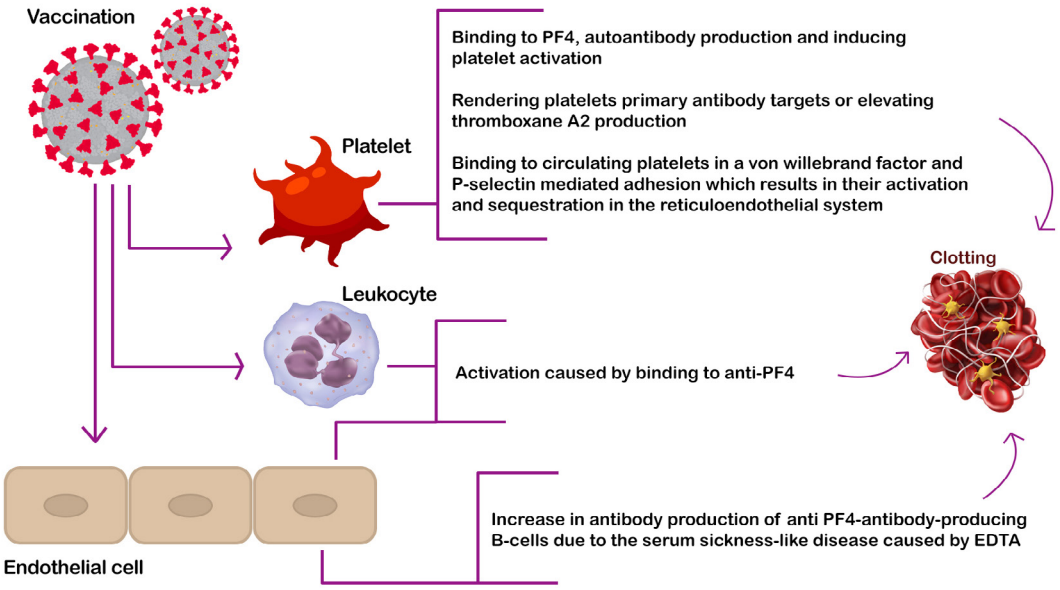

Figure 1. Pathophysiology of Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) after COVID-19 Vaccination

in the acute phase of the syndrome may impede platelet activation and lower thrombosis risk through the blockade of platelet surface Fcγ-receptors (52).

3.2.3. Coagulation approach after Vaccination

Thrombotic thrombocytopenia following vaccination is not a novel event in the history of vaccination. One of the first thrombotic thrombocytopenia was reported after influenza vaccination. H1N1, Rabies, and pneumococcal vaccination also have this report. Even though cerebral venous sinus thrombosis (CVST) was not reported in these patients, cases of CVST have been reported post-COVID-19 vaccines. Both AstraZeneca (chAdOx1) and Johnson & Johnson (Ad26.COV2) vaccination caused cases of VITT and CVST. The majority of patients with CVST associated with VITT were females. Symptom onset occurred within one week following the first dose (Range: 4-19) and headache was the most common presenting symptom in the patients with CVST (53). Malaise, vomiting, lethargy, loss of consciousness, blurred vision, hemiparesis, abdominal pain, and back pain were also reported as other symptoms in patient with concurrent portal vein thrombosis. Subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) were seen as consequences of CVST in the majority of patients. Pulmonary embolism, lower extremity deep venous thrombosis, splanchnic vein thrombosis, bilateral adrenal hemorrhage, portal vein thrombosis, , internal jugular vein thrombosis, iliofemoral vein thrombosis and Ischemic bowel infarct are other sites of thrombosis in the reported patients (43).

3.2.4. Diagnosis of VITT

In spite of the high mortality associated with VITT and CVST post COVID-19 vaccination, prompt recognition and early management will likely lead to better neurological outcomes. Essential diagnostic criteria of VITT include the subsequent items **(Fig. 2):**

1-The patient has been vaccinated with the Johnson & Johnson (Ad26.COV2) or AstraZeneca COVID (ChAdOx1) vaccines within the last 30 days (between 4 and 30 days).
2-Presence of moderate to severe thrombocytopenia. Nonetheless, in several cases, this thrombocytopenia might be mild, particularly in the beginning stages of VITT.
3- The presence of thrombosis frequently in the forms of CVST (Patients may present with headache) or splanchnic veins thrombosis (patients may present with abdominal or back pain (or both) and nausea and vomiting). Seldom does the arterial thrombosis occur.
4-Positive PF4 antibody "HIT" (heparin-induced thrombocytopenia) ELISA (51).

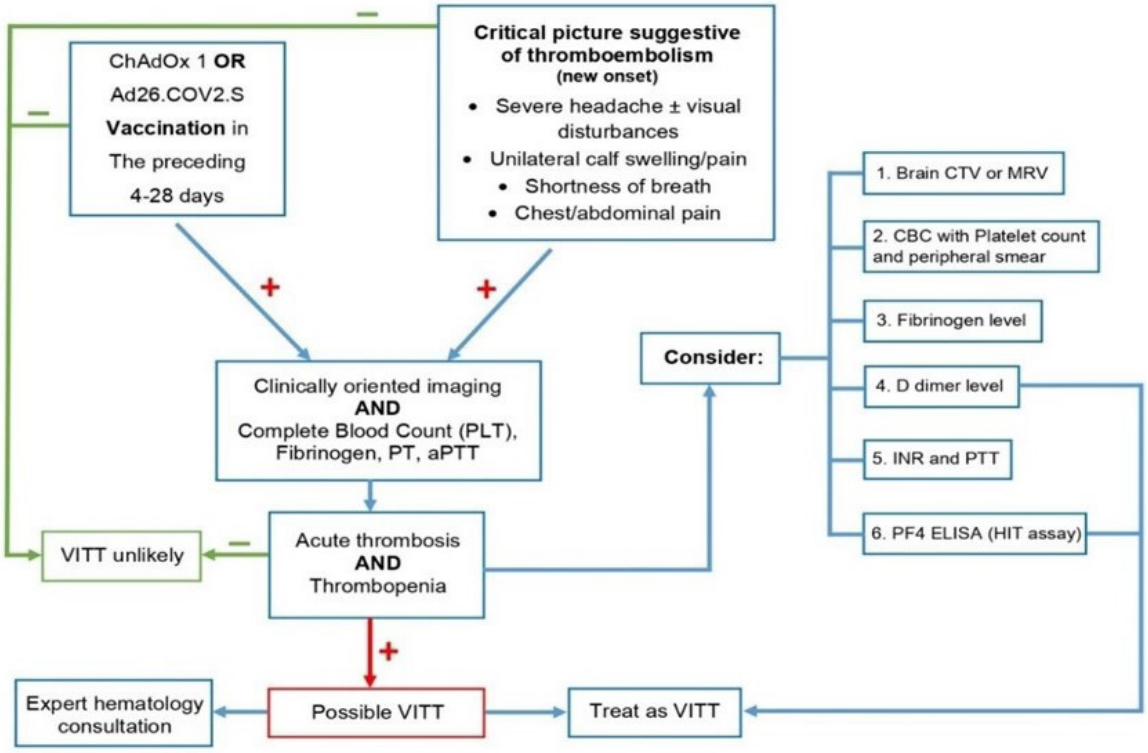

Figure 2. VITT detection algorithm in vaccinated patients

In spite of transient headaches being a common adverse effect of vaccination, if a patient has a continuing headache, petechiae, easy bruising, blurred vision, or bleeding following AstraZeneca COVID (ChAdOx1) or Johnson & Johnson, CVST after VITT should be regarded. If a patient presents with a normal platelet count and thrombosis following AstraZeneca COVID (ChAdOx1) or Johnson & Johnson (Ad26. COV2) vaccination, early stages of VITT should take into consideration (54). The aPTT is prolonged in multiple COVID-19 patients. It can be because of the presence of a lupus anticoagulant (LA) or antiphospholipid antibodies (aPL). Moreover, High levels of acute phase reactants such as C-reactive protein can also result in false positives by prolonging in vitro clotting times. Prolonged aPTT due to LA may require the use of the anti-factor Xa assay for monitoring heparin therapy. Other coagulation parameters in addition to the commonly evaluated laboratory parameters discussed above, enhanced coagulation factor VIII (FVIII) and von Willebrand factor (VWF) are common findings in hospitalized COVID-19 patients (55). Increased clot strength with contributions of both elevated fibrinogen and platelets are demonstrated by viscoelastic testing (thromboelastography, rotational thromboelastometry). Fibrinolysis is also suppressed. Furthermore, thrombin generation is normal to increased even in patients receiving prophylactic anticoagulation (56).

3.2.5. Bleeding in COVID-19

Bleeding is unusual in the setting of CAC, which has a predominantly prothrombotic phenotype. In an analysis of 400 COVID-19 hospitalized patients in Boston, Al-Samkari et al found a higher overall bleeding rate of 4.8%; major bleeding occurred in 2.3%, including 5.6% of critically ill patients, and was associated with a platelet count $<150 \times 10^9$/L at admission (57). Preliminary data from a multiplatform, randomized controlled trial found a 0.9% and 1.9% rate of major bleeding in noncritically ill participants on prophylactic or therapeutic anticoagulation, respectively. Among critically ill patients, however, major bleeding occurred in 3.1% on therapeutic anticoagulation and 2.4% on thromboprophylaxis (58). Among patients with COVID-19 ARDS treated with extracorporeal membrane oxygenation (ECMO), major bleeding occurs in >40%, including intracranial bleeding in up to 12%, which is significantly higher than the 2% to 6% bleeding rate reported in non-COVID-19 ECMO cohorts. DIC, shear stress-induced acquired von Willebrand syndrome, COVID-19-related endothelitis, and intensive anticoagulation are

implicated in severe bleeding on ECMO. The anticoagulation required for ECMO and the activation of coagulation from artificial surfaces might confound interpretation of coagulation studies. Careful interpretation is required to balance anticoagulation, bleeding, and thrombosis in patients receiving ECMO (59).

3.2.6. Platelet Factor 4 Role

Vaccine-induced thrombotic thrombocytopenia (VITT), as noticed in rare cases after vaccination with vaccines from AstraZeneca or Johnson & Johnson, was similar to heparin-induced thrombocytopenia (HIT). The hallmarks of HIT are specific antibodies for the heparin/platelet factor 4 (PF4) complex that cause thrombocytopenia and thrombosis through platelet activation. Platelet factor 4 (PF4 and CXCL4) released by activated platelets belongs to the chemokine family and has crucial functions in blood coagulation. PF4 represents a positively charged tetramer with a high binding affinity for heparin and other glycosaminoglycan (GAGs). Binding of the positively charged PF4 causes the neutralization of the negative charge of the heparan sulfate side chains of GAGs on the surface of platelets and endothelial cells, which paves the way for platelet aggregation and thrombus formation. In addition to blood coagulation, PF4 has extra activities, with increased PF4 expression found following trauma and in response to infection (60). When patients are exposed to heparin, heparin binds to PF4 and stimulates PF4 aggregation, forming ultra large and antigenic PF4–heparin complexes. A couple of patients develop antibodies against PF4–heparin complexes that cause heparin-induced thrombocytopenia (HIT). Anti-PF4–heparin antibodies are found in about half of patients after cardiac surgery and in more than 10% of surgical patients treated with heparin in comparison to 3–4% of healthy subjects. However, solely 5–30% of patients with antibodies against heparin develop HIT. Circulating PF4–heparin antibody complexes can bind to the FcγRIIA receptor on platelets and to various additional Fc receptor-bearing blood cells, including monocytes and neutrophils. Binding to FcγRIIA leads to platelet activation, resulting in the release of the contents of the cytoplasmic granules and procoagulant microparticles (61). The vascular endothelium can be activated by the activation of platelets and neutrophils by means of HIT antibodies. Importantly, Platelet activation after binding of HIT-related immune complexes to FcγRIIA and transactivation of monocytes and endothelial cell also increase the expression of phosphatidylserine (PS) and the binding of factor Xa to platelets, which results in the generation of thrombin andthrombotic vessel occlusions, e.g., venous thromboembolism (38, 62). Several studies have indicated that PF4 may have a significant role in bacterial defense, and HIT may merely be a misdirected antibacterial host defense mechanism. It has been shown that a cationic component can charge-associate with adenovirus particles, which carry a net negative surface charge and will facilitate attachment to the negatively charged cell membrane—an approach employed for boosting the gene transfer efficacy of adenoviral vectors. Similarly, adsorption of adenovirus coding for the beta-gal2 gene (Ad2 beta gal2) in the presence of various polycations, including polybrene, protamine, DEAE-dextran, or poly-Llysine, significantly increased transfection efficacy into different cell types (63). An investigation revealed that the surface of the ChAdOx1 viral capsid has strong electronegative potential. It is worth noticing that the ChAdOx1 hexon hypervariable regions (HVRs) are different from other adenoviruses. In terms of apical electrostatic surface potential, calculated on equilibrated hexon structures, ChAdOx1 has the most electronegative surface potential, which can be expected to affect the strength of incidental charge-based interactions with other molecules. Molecular simulations have suggested that this charge, together with shape complementarity, is a mechanism by which an oppositely charged protein, e.g., platelet factor 4 (PF4), may bind the vector surface (64).

3.2.7. Additive and Synergistic Effects of the S Protein and Adenoviral Vector

It has been recently demonstrated that the severe side effects noticed in rare cases may have to be attributed to adenoviral vaccines. Transcription of wild-type and codon-optimized spike open reading frames enables alternative splice events that bring about C-terminal truncated, soluble spike protein variants. Severe side effects may be initiated by these soluble spike variants when binding to ACE2-expressing endothelial cells in blood vessels(30). Analogous to the thromboembolic events caused by the spike protein encoded by the SARS-CoV-2 virus, the underlying disease mechanism has been called "Vaccine-Induced COVID-19

Mimicry" syndrome (VIC19M syndrome) vector-based vaccines. It was demonstrated that NF-κB mediates the leaky expression of Ad genes from the Ad vector and that the inhibition of NF-κB can suppress Ad gene expression and hepatotoxicity following application of Ad vectors (65). Activation of NF-κB by recombinant TNFα significantly increased the leaky expression of Ad genes, while Ad gene expression was suppressed by inhibitors of NF-κB or siRNA-mediated knockdown of NF-κB. An adenoviral vector encoding for the dominant-negative IκBα (Adv-CADNIκBα) mediated 70% suppression of the leaky expression of Ad genes in the liver. Essentially, Adv-CADNIκBα did not induce apparent hepatotoxicities. These results depict that the inhibition of NF-κB results in the suppression of adenoviral vector-mediated tissue damage by both suppression of inflammatory responses and reduction in the leaky expression of adenoviral genes. Altogether, these studies indicate that both SARS-CoV-2 spike protein AND adenoviral vectors activate the NF-κB pathway together with several additional signal transduction pathways, which can lead to additive and synergy (66).

3.3. Management of Patients after Vaccination

3.3.1. Management of COVID - 19 - associated coagulopathy (CAC)

Which laboratory parameters should be evaluated in CAC? There is inadequate evidence to recommend monitoring of coagulation markers such as D-dimer, platelet count, PT, and fibrinogen, since these are unlikely to have an impact on management in outpatients with COVID-19 (67). On the other hand, for inpatients patients, it is agreed with the interim recommendations from the International Society on Thrombosis and Hemostasis (ISTH) and the American Society of Hematology to sequentially monitor D-dimer levels, platelet count, PT, and fibrinogen since these help with risk stratification (68). Deteriorating of these parameters may warrant further aggressive critical care support and consideration of investigational therapies. D-dimer elevation is nonspecific and require not prompt imaging for venous thromboembolism (VTE) in the absence of clinical symptoms or signs of VTE. Nevertheless, increasing D-dimer in the setting of decreasing C-reactive protein might warrant screening for VTE (69).

3.3.2. Treatment of VITT

In suspected patients, the use of heparin should be prevented until VITT has been ruled out. Close collaboration among vascular neurologists, hematologists, and other consultants with relevant knowledge is the cornerstone of managing VITT-associated systemic thrombosis and CVST (70). In spite of very limited data on treatment strategies, administration of intravenous immunoglobulin (IVIG) (1 g/kg body weight) daily for two days has been recommended after PF4 antibodies have been sent. IVIG hinders antibody -mediated platelet clearance and may also down-regulate platelet activation by blocking platelet FcRγIIA receptors. Multiple experts recommended using high-dose glucocorticoids, which may improve the platelet count within days (71). Plasmapheresis could perhaps be another treatment option that could temporarily reduce pathologic antibodies and correct coagulopathy. Platelet transfusion should be prevented due to the risk of further antibody-mediated platelet activation and coagulopathy. Use of non-heparin anticoagulants, such as direct oral factor Xa inhibitors (Apixaban, Rivaroxaban), direct thrombin inhibitors (Argatroban, Bivalirudin), and Indirect (antithrombin-dependent) factor Xa inhibitors: Danaparoid, Fondaparinux, at therapeutic anticoagulant dosage might be considered. In severe thrombocytopenia (i.e., <20,000 per mm3) or low fibrinogen levels, dosing strategy might require alteration (72, 73). In critically ill patients, parenteral agents with a short half-life are preferred .Even in the presence of secondary ICH; anticoagulation should be used in CVST to avoid progressive thrombosis. Once there is full platelet count recovery, and no other contraindications, direct oral anticoagulants or vitamin K antagonists have been recommended for subacute/chronic management (74).

3.3.3. Role of Blood Product Transfusion

It has not been proven that blood component therapy to correct abnormal laboratory parameters develop outcomes in the absence of bleeding. In patients with bleeding or those requiring invasive procedures, we recommend transfusion of platelets to maintain a platelet count ≥50×10^9/L, cryoprecipitate if fibrinogen is <150mg/dL, and plasma for an international normalized ratio ≥1.8 following correcting fibrinogen. Four factor prothrombin complex concentrate (25 units/kg) may be utilized instead of plasma in patients

with severe coagulopathy and bleeding to prevent volume overload that can exacerbate respiratory status(75).

3.3.4. Anticoagulation Activity

As with other coagulopathies, treatment of the underlying condition is the sole definitive solution. Based on the association of D-dimer and other coagulation markers with severe disease, fatality, and thrombosis, at least prophylactic-dose anticoagulation is suggested in hospitalized patients with COVID-19 (76). Particularly, this recommendation is alike to that for other acutely ill inpatients. In the absence of important renal impairment, we suggest the use of low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) to prevent possible heparin resistance with UFH. If UFH is utilized, we encourage monitoring anti-factor Xa levels due to potential confounding of the aPTT due to enhanced FVIII and fibrinogen or LAs (77). In addition, anticoagulation recommendations may require to be modified for patients with severe thrombocytopenia, bleeding risk, and extremes of body weight. Early in the pandemic, there were reports of thrombosis regardless of standard thromboprophylaxis. According to these reports and extreme laboratory derangements, clinicians often escalated anticoagulation to intermediate or even therapeutic intensity (78). However, whether a higher intensity of anticoagulation lessens morbidity or mortality without an unacceptable increase in bleeding risk remains uncertain and is being evaluated in several trials. Pending the final results of multiple studies, the American Society of Hematology guideline panel recommends prophylactic over intermediate or therapeutic dosing in moderately and severely ill patients with COVID-19 without confirmed or suspected VTE. Higher-intensity anticoagulation may be preferred in moderately ill (non-ICU, stage 2) patients regarded as high thrombotic and low bleeding risk. Therapeutically dosed anticoagulation is appropriate for patients with preexisting indications including atrial fibrillation and mechanical heart valves and, if needed, to maintain extracorporeal circuits and vascular access devices (79).

3.3.5. COVID-19 Vaccines: Cytopenia, Bleeding, and Thrombosis

In spite of the fact that the COVID-19 vaccines have proven to be extremely safe and effective, cases of immune thrombocytopenia and bleeding, such as life-threatening hemorrhage, have been reported following exposure to the mRNA-based vaccines produced by Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2)(80). Luckily, most of these respond to immune thrombocytopenia-directed treatments including intravenous Ig and corticosteroids. Currently, rare cases of a vaccine-induced thrombotic thrombocytopenia (VITT) were reported after administration of the adenoviral vector vaccines (ChAdOx1 nCoV-19 and Ad26.COV2.S) (81). The estimated incidence is 1 case per 100,000 exposures with a slight female preponderance, and it occurs more frequently in younger (<55-60 years) individuals .VITT is associated thrombocytopenia and thrombosis, specifically at unusual sites namely the cerebral or splanchnic circulations, along with high levels of platelet-activating IgG antibodies that recognize platelet factor 4 (PF4) in the absence of heparin. Patients with VITT often have a consumptive coagulopathy with enhanced D-dimer and hyperfibrinogenemia. VITT is associated with high mortality, with cerebral hemorrhage as the leading cause of death. Treatment with a nonheparin anticoagulant and intravenous Ig is recommended, with platelet transfusions reserved for bleeding. These hematologic should not get in the way of vaccination due to being highly rare (82).

4. Conclusion

Inflammation, intravascular coagulation activation, and microvascular thrombosis result in coagulation derangements in COVID-19. Enhanced D-dimer and fibrinogen levels are the most common finding and are predictive of adverse consequences, including the requirement for crucial care and mortality. On the contrary to DIC, thrombocytopenia is rare, and the PT/aPTT are generally normal or minimally prolonged (83). APTT prolongation due to aPL is indicated by several patients. Bleeding, while rare, might occur in critically ill patients developing a consumptive coagulopathy and those on ECMO. Health care providers should be aware of clinical presentations, pathophysiology, diagnostic criteria, and management strategies of CVST related to VITT post-COVID-19 vaccination. In spite of being extremely uncommon, this phenomenon is serious and possibly fatal. Promote diagnosis and rapid

initiation of the appropriate treatment may help to provide patients with a better neurological outcome. The results of ongoing trials assessing the effect of higher-intensity anticoagulation on COVID-19 outcomes are eagerly awaited. Until then, standard thromboprophylaxis should be received by all hospitalized patients (84).

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Author contributions

M.S., S.H. Conceptualization, Methodology. M.S. and S.H. collected the data. M.S. supervised the project. M.P. wrote the initial manuscript. A.D. reviewed the final version before submission. All authors discussed the results and contributed to the final manuscript.

Data availability

the authors declare that data supporting the findings of this study are available within the article.

Conflicts of interest

The author(s) stated no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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