Thrombotic Thrombocytopenia Syndrome

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The thrombotic thrombocytopenia syndrome (TTS), a complication of COVID-19 vaccines, involves thrombosis (often cerebral venous sinus thrombosis) and thrombocytopenia with occasional pulmonary embolism and arterial ischemia. TTS appears to mostly affect females aged between 20 and 50 years old, with no predisposing risk factors conclusively identified so far. Cases are characterized by thrombocytopenia, higher levels of D-dimers than commonly observed in venous thromboembolic events, inexplicably low fibrinogen levels and worsening thrombosis.

Keywords: COVID-19 ; COVID-19 vaccine ; disseminated intravascular coagulation ; heparin induced thrombocytopenia ; platelet factor 4 ; thrombosis ; thrombotic thrombo-cytopenic purpura ; vaccine induced thrombocytopenia and thrombosis

1. Introduction

A new deadly virus of the coronavirus family was first identified in December 2019 and named SARS-2-CoV-2; this virus caused severe acute respiratory syndrome and is now known as COVID-19. Patients presented with variable symptoms, ranging from asymptomatic carriers to life-threatening/changing consequences. Several vaccines have been developed and are currently being used to reduce disease incidence and mortality in many countries. Lately, rare but life-threatening events such as thrombosis with thrombocytopenia syndrome (TTS) (also called VITT—vaccine induced thrombocytopenia and thrombosis) have been reported with some COVID-19 vaccines. Recent reviews of TTS following COVID-19 vaccinations have not included clinical management guidelines [1][2]. To this end, this entry summarizes the available data on the pathophysiology of COVID-19 and thrombosis, the different types of vaccines used to prevent COVID-19, the proposed mechanisms of TTS and some clinical management recommendations.

2. Possible Pathophysiology of TTS

Antibody-mediated thrombotic thrombocytopenia during COVID-19 is presumed to be an autoimmune reaction induced by SARS-CoV-2. The high incidence of thrombotic thromboembolic events during severe COVID-19 results in the frequent administration of heparin in affected patients [3]. HITT is a possible cause when thrombocytopenia is associated with thrombosis in this setting [4]. Several studies report the presence of anti-PF4/heparin antibodies in COVID-19 patients, these antibodies can also be found without any history of heparin administration [5]. Furthermore, these antibodies do not always activate platelets in the presence of heparin/PF4 complexes [6], although they can do so in presence of PF4 alone [7], suggesting that their production is likely unrelated to HIT [8]. Related to this notion is that IgG antibodies in the serum of severe cases of COVID-19 infections induce platelet apoptosis and procoagulant activity via FcγRIIA (CD32) receptor-dependent mechanisms [9]. The antigenic specificity of these antibodies is unclear, although it is likely that at least some of them are directed against PF4.

The model we support is based on the hyperactivation of platelets during COVID-19, which results in the release of PF4 into the circulation [10]. Circulating PF4 forms complexes with endogenous polyanionic proteoglycans released by damaged endothelial cells. Syndecan-1 and endocan are potential proteoglycans candidates as their serum levels are increased in severely ill COVID-19 patients in association with other markers of endothelial injury [11]. Complexes formed between PF4 and endothelial cell-derived polyanionic proteoglycans can then stimulate extra follicular B cells that produce anti-PF4 antibodies, as suggested by previous reports that autoimmune responses elicited by extra follicular B cells may be involved in the pathophysiology of severe COVID-19 [12].

A recent study by Kowarz and colleagues suggested a different slicing mechanism for spike open reading frame in adeno vector vaccines, which results in soluble spike variants that can initiate severe side effects when binding to ACE2-expressing vascular endothelial cells. They compared this phenomenon to thromboembolic events caused by spike protein encoded by the SARS-CoV-2 virus and termed this possible mechanism as the “Vaccine-Induced COVID-19 Mimicry” syndrome (VIC19M syndrome) [13].

Anti-phospholipid antibodies could also additionally contribute to platelet activation, as suggested by increases in anti-SARS-CoV-2 antibodies in other viral diseases [14]. The rare prothrombotic thrombocytopenic events following vaccination with Vaxzevria (~1 in 100 000 recipients) has a clinical presentation similar to HIT, suggesting that a vaccine-induced autoimmune response to PF4 may be plausible. Supporting this hypothesis is a recent study identifying platelet-activating anti-PF4 antibodies in the sera of patients suffering from unusual thrombotic events associated with thrombocytopenia within 4 to 16 days after receiving Vaxzevria [15]. The progression of this possible vaccine-induced anti-PF4 autoimmune response could be related to mechanisms similar to those for prothrombotic thrombocytopenia induced by the SARS-CoV-2 virus itself. Other possible mechanisms include adenoviral vector entry in megakaryocytes and the subsequent expression of spike protein on platelet surfaces and also direct platelet activation by the vector [16].

3. Thrombocytopenia following Vaccine Administration in Children

Thrombocytopenia is an adverse event associated with vaccine administration and can limit vaccine use due to several factors such as uncertainly about which vaccines are likely causative triggers, its incidence and severity, the risk of chronic disease and the possibility of recurrences after additional doses of the same vaccine. Vaccine-related thrombocytopenia is considered to be of immune origin because antibodies can be detected on platelets in about 79% of cases, making it a part of secondary ITPs in the subgroup of drug-induced ITPs. Thrombocytopenia following vaccine administration depends on the development of autoantibodies that cross-react with naturally present antigenic targets on platelets [17]. A comprehensive review on vaccine administrations and very rare development of ITP in children concluded that it can occur after the administration of vaccines. The only vaccine that is currently known to cause ITP is the mumps, measles and rubella (MMR) vaccine, but again the incidence of ITP is significantly lower than caused by mumps, measles and rubella, which are the diseases for which the vaccine provides 99% protection. Thus, ITP, regardless of its association with vaccination, should not limit the use of MMR vaccines, and a careful risk-benefit analysis performed particularly in children with persistent or chronic ITP should be performed. It is possible that newer technologies such as reverse vaccinology could prepare protein vaccines with a lower risk of causing ITP [18].

The role of adenoviral vectors in the development of thrombocytopenia has been described early in the pandemic. Adenoviral vectors remain ideal candidates as vaccine carriers and in cancer gene therapy due to their ability to effectively activate CD8+ T cells [19]. Early innate immune responses related to adenoviral vectors are associated with the activation of vascular endothelial cells, resulting in the release of ultra-large-molecular-weight multimers of the von Willebrand factor, a blood protein that is critical for platelet adhesion. This also activates platelets and induces the exposure of the adhesion molecule P-selectin and formation of platelet-leukocyte aggregates, ultimately causing thrombocytopenia and, thus, a risk for bleeding [20].

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