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Editorials

# COVID-19 vaccine-induced immune thrombotic thrombocytopenia: An emerging cause of splanchnic vein thrombosis

Between December 2020 and March 2021, the European Medicines Agency (EMA) approved 4 vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on rigorous randomized, blinded, controlled trials, including the ChAdOx1 nCoV-19 vaccine (Aztra-Zeneca), a recombinant chimpanzee adenoviral vector encoding the spike protein of SARS-CoV-2 [1]; however, towards end of February 2021, a significant number of venous thromboses (VTE) in unusual sites (cerebral venous-sinus thrombosis [CVST], and splanchnic vein thrombosis [SVT]) in combination with thrombocytopenia were observed in individuals that received the Aztra Zeneca coronavirus disease 2019 (COVID-19) vaccine; which on March 15, 2021, prompted the temporary suspension of the administration of such vaccination by the EMA in several countries, including Austria, Germany, France, United Kingdom and Norway [2,3]. After a careful safety assessment by the EMA pharmacovigilance assessment risk committee, evaluating benefits versus risks of the Aztra Zeneca COVID-19 vaccine, it was decided to resume vaccination campaigns by March 19, 2021 [3].

Notably, as of April 4th, 2021, a total of 169 cases of CVST and 53 cases of SVT were reported among 34 million people had been vaccinated in the European Union by that date [2]. Recently, Greinacher and colleagues described in detail the clinical and laboratory profiles of 11 patients from Germany and Austria in which thrombotic thrombocytopenia developed after the administration of the Aztra Zeneca ChAdOx1 nCoV-19 vaccine. Of the 11 patients, 9 were women, with a median age of 36 years (range of 22–49 years). Investigators also analyzed laboratory characteristics of 28 additional patients, in which there was a high clinical suspicion of ChAdOx1 nCoV-19 vaccine-induced thrombotic events. From all, nine out of 11 patients had CVST, three had SVT, and 4 had pulmonary embolism, some of these patients had thromboses in different vascular territories found at the same time (e.g., CVST and SVT simultaneously); of these, 6 patients died [4]. All patients presented with concomitant thrombocytopenia (median nadir of platelet count of 20,000 $\times$ mm$^3$; range from 9000 to 107,000) and none of the patients had received any form of heparin before onset of symptoms. All the 28 additional patients included in the analysis tested positive for the platelet-factor 4 (PF-4)-heparin antibodies for both, ELISA, and the platelet-activation assays. Interestingly, the three patients who had SVT, also developed concomitantly CSVT, two cases were fatal, and one patient is recovering [4]. Symptom onset started approximately between 4–16 days post Aztra Zeneca COVID-19 vaccine administration. Investigators found that these thrombotic thrombocytopenic syndromes shared striking similarities with severe heparin-induced thrombocytopenia (HIT), a well-known hypercoagulable disorder caused by platelet-activating antibodies that recognize multimolecular complexes like those formed by PF-4 and anionic heparin, triggering prothrombotic events, with the exception that the above-described patients never were exposed to heparin, a variant known as autoimmune HIT [5,6].

Greinacher and colleagues recommended a detailed diagnostic and therapeutic algorithm for these thrombotic thrombocytopenic syndromes, considering the administration of high doses of intravenous immunoglobulin (IVIG), with the aim of inhibiting platelet activation, increasing platelet count, and ameliorating hypercoagulability. It is also recommended to use non-heparin anticoagulants to treat HIT, like direct oral anticoagulants ([DOACs] e.g., rivaroxaban, apixaban, edoxaban), direct thrombin inhibitors (e.g., argatroban, bivalirudin, dabigatran), or indirect Xa inhibitors (e.g., danaparoid or fondaparinux). Finally, authors proposed to name this new entity ***Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)*** [4].

Schultz et al. from Oslo University Hospital recently described five cases in health care workers of CVST and thrombocytopenia 7–10 days after receiving the ChAdOx1 nCoV-19 vaccine among 130,000 people vaccinated [7]. All patients showed high levels of PF-4/heparin polyanionic antibodies, without previous exposure to heparin. They concluded that VITT represents a new rare but potentially serious thrombotic phenomenon among otherwise healthy young adults, indicating that VITT may be more frequent than expected, and recommending a thorough assessment of benefits versus risks analysis, whether to decide if the Aztra Zeneca COVID-19 vaccine may trigger such devastating serious adverse events in selected population [7].

Several international societies, including the *International Society for Thrombosis and Haemostasis (ISTH)* have recently published their guidance for the diagnosis and management of VITT, which currently represents a “rare entity/phenomenon”, but can affect patients of all ages and both sexes [8–10].

We recommend that clinicians be familiarized and be extremely alert and raise awareness among other colleagues regarding the clinical and laboratory features that may trigger a clinical concern for VITT, having an exceptionally low threshold for further investigations in these patients since they could present with non-specific signs and symptoms of VTE in unusual sites like CVST or

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SVT. Within the setting of previous exposure to the Aztra Zeneca ChAdOx1 nCoV-19 vaccine, we suggest the following steps:

a) In the event of significant post-vaccination symptoms like severe abdominal pain, nausea/vomiting, melena or hematochezia, persistent high fevers, especially for > 2 days, further investigations should be performed, intentionally looking for unusual sites of venous thrombosis like SVT.
b) Complete blood cell count with peripheral blood smear, D-dimer levels, coagulation profile, fibrinogen, and if clinically indicated, pertinent imaging studies such as venous compression ultrasound, or contrast-enhanced computed tomography of the abdomen should be performed to objectively document VTE or thrombosis of unusual sites.
c) If venous thrombosis (e.g., CVST or SVT) and thrombocytopenia (platelet count < 150,000 $\times$ mm$^3$) are confirmed, immediate consultation with an expert in clinical adult thrombosis/hematology, to further guide diagnostic and therapeutic approach, including more specific testing for HIT and VITT [11,12]. In this regard, the involvement of a VTE rapid response multidisciplinary team may be a suitable option, if such team is available.
d) If the initial screening test of PF-4/heparin antibodies by ELISA is positive, then a classical heparin-induced platelet activation (HIPA) assay or a serotonin release assay (SRA) should be performed as a functional confirmatory test for VITT.
e) If the diagnosis of VITT is made, consider high doses of IVIG for 1–2 days, non-heparin anticoagulants, and avoid platelet transfusions unless active bleeding is present; once thrombocytopenia has resolved (platelet count > 150,000 $\times$ mm$^3$), consider switching to either DOACs or vitamin K antagonists for at least 6 months, with a close follow-up in a designated venous thrombosis/anticoagulation multidisciplinary clinic.

In comparison to VITT, the development of arterial and venous thromboembolic complications from COVID-19 per se, range between 6% and up to 28%, depending how ill patients are while being hospitalized [13,14]. VITT represents an extremely rare entity but which can be quite severe and worrisome for clinicians, and perhaps, not that "infrequent".

As of April 12, 2021 the United States (US) health authorities recommended a pause in the use of Johnson & Johnson's (Janssen) COVID-19 vaccine after 6.8 million doses had been administered in the US, to investigate the occurrence of VITT cases in six women between the ages of 18 and 48 years who got the vaccine and developed symptoms of CVST between six- and thirteen-days post-vaccination, one of whom died [15].

We will definitively continue to be updated and "tuned-up" while further research in critical areas like etiopathogenesis, and emerging therapies for VITT unfolds in this new fascinating but poorly understood arena of clinical thrombosis. Clinicians and researchers should continue to pay special attention not only to the Aztra Zeneca ChAdOx1 nCoV-19 vaccine, but also to other COVID-19 vaccine manufacturers as well.

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