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Letter to the Editor

Potential role of macrophage activation in mediating thrombotic complications associated with the different vaccines against COVID-19

Dear Editor,

The paper by Fanni et al[1] is a very interesting article reporting a case of VITT syndrome characterized by severe thrombosis and thrombocytopenia with fatal outcome developing after the first dose of ChAdOx1 nCoV-19 vaccine. Alongside the case report, the article also describes in a very complete and exhaustive manner the diagnostic approach, the laboratory and the histological findings, as well as the potential pathogenetic mechanism and possible management of this severe thromboembolic disease. Therefore, this manuscript may help readers develop an appropriate clinical, diagnostic, and therapeutic approach of this rare, but sometimes fatal condition, especially in absence of a prompt recognition and correct treatment.

Identification of the pathogenetic mechanisms involved is a crucial point for determining the actual risk and establishing the best management of vaccine-associated thrombosis. The currently available literature mostly hypothesizes a vaccine-induced immune-thrombotic thrombocytopenia (VITT) that mimics heparin-induced thrombocytopenia (HIT). HIT is an autoimmune condition where antibodies counter to platelet factor 4-polyanion complexes (PF4), a cytokine released from the alpha-granules by the activated platelets, induce a massive platelet activation via the Fc receptor. This shifts thrombocytes to a hypercoagulable state, causing the release of additional PF4 and the promotion of both arterial and venous thrombosis[2]. The case report by Fanni et al[1] correctly reached a diagnosis of VITT. However, we would highlight that the induction of macrophage-mediated inflammatory events following vaccination in contributing to the thrombotic complications could not be excluded. It can be hypothesized that the antigen introduced with the vaccine, once recognized by cells of the immune system, induces cell-mediated and innate immune responses characterized by macrophage activation. This is similar to what occurs after viral antigen exposure during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which is the etiological cause of COVID-19. In this regard, it is noteworthy that it has recently been reported that the spike glycoprotein (S-protein), the primary SARS-CoV-2 vaccine antigen, is able to selectively and potently initiate inflammasome activation and cytokine secretion by human macrophages[3].

During the early phases of the immune response, macrophages react by inducing the release of interferon (IFN), which aims to limit the virus replication. Further, macrophages through the synthesis of IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) regulate the functions of CD4+ T cells by stimulating the synthesis of interleukin (IL)-2 meanwhile enhancing the expression of the IL-2 receptor, mainly on cytotoxic CD8+ T cells[4]. Nevertheless, persistent and elevated release of proinflammatory cytokines and reactive oxygen species (ROS) by activated macrophages determine a nonspecific inflammatory response, which leads to immunopathology with associated thrombotic disorders. M1-polarized macrophages are the key cells involved in these events[4].

M1-polarized macrophages are the main producers of IL-6 and ROS. The contribution of IL-6 in determining thrombocytosis with related increased levels of thromboplastin and acute phase proteins fibrinogen and C-reactive protein has been widely and clearly demon-

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strated in ovarian cancer[4]. Moreover, proinflammatory cytokines, IL-6 in particular, are also able to stimulate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, that is connected with activation of the apoptotic pathway in endothelial cells by inducing mitochondrial injury and endoplasmic reticulum stress[5]. Meanwhile, ROS strongly contribute to tissue damage and endothelial alterations, thus triggering the pathogenesis of thrombosis. In particular, ROS can inactivate endothelium-derived nitric oxide, stimulate cell-signaling, and induce protein alterations, which are events contributing to the initiation and progression of endothelial damage, thereby favoring the activation of thrombosis-related pathogenesis[5,6]. Moreover, activation of proinflammatory M1-polarized macrophages is characterized by the induction of HIF-1 signaling. This enhances the NF-κB pathway-mediated inflammatory response that in turn increase complement-mediated endothelial injury[6].

Endothelial damage resulting from the above mechanisms triggers the activation of platelets through the collagen receptor glycoprotein VI (GPVI) and activates the tissue factor (TF)-dependent synthesis of thrombin via the extrinsic pathway of coagulation factor VII. The increased generation of thrombin leads to the deposition of fibrin with the following development of coagulopathy at systemic levels. Endothelial injury is also related with disruption of the glycocalyx, a layer that coats the endothelial surface and modulates thrombus generation, vascular permeability, and inflammation, thereby inducing the synthesis of adhesion factors that recruit platelets and leukocytes into the endothelium[5].

Another factor associated with inflammatory response is macrophage stimulating 1 (Mst1). Mst1 can stimulate mitochondria-dependent endothelial cell death by inhibiting mitophagy and is a main inducer of venous endothelial cell apoptosis[5].

The above noted events have been well described during the clinical course of COVID-19[7]. Their occurrence supports the association between hypercoagulability/severe thrombotic events and elevated levels of fibrinogen, C-reactive protein, IL-6, ferritin, and D-dimer in patients with severe COVID-19.

Consistent with these hypotheses and in accordance with similarities observed in severe and complicated cases of COVID 19, Fanni et al[1] report that the occurrence of VITT is associated with increased levels of D-dimer and low hemoglobin levels. In this context, the low levels of platelets and decreased fibrinogen that characterize the evolution of VITT may more likely be the manifestation of the final steps of a thrombotic complication. This is in line with what has been already reported for COVID-19-related coagulopathy[6,7]. The assessment of proinflammatory markers as C-reactive protein could also show similarities with severe COVID-19, as observed by other authors in a case of extensive thrombosis associated with mRNA vaccine[8].

The exact pathogenesis of the thromboembolic events that may develop after the administration of mRNA vaccines remains to be definitively established and is likely multifactorial[9]. In this regard, it is important to carry out additional studies aimed to assess and define the dynamics of immune responses after vaccination against SARS-COV-2 and to determine the extent and phenotype of macrophage activation and their potential role in contributing to thrombotic complications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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