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Letter to the Editor

Vaccine-induced thrombotic thrombocytopenia, a rare but severe case of friendly fire in the battle against COVID-19 pandemic: What pathogenesis?

ARTICLE INFO

Abbreviations
CVT
cerebral venous (sinus) thrombosis
HIT
heparin-induced thrombocytopenia
PF4
platelet factor 4

Dear Editor,

We have read with great interest two recent contributions to the *Clinical Insights* section of the *Journal* concerning reports of thromboembolic complications associated with the administration of the COVID-19 vaccine by Astra Zeneca [1,2]. Since its initial outbreak in December 2019, Coronavirus disease 2019 (COVID-19) has become a rampant pandemic responsible for more than 140 million confirmed cases and more than 3 million deaths as of the end of April 2021. At such a pivotal time, rapid, worldwide vaccination against the SARS-CoV-2 virus to achieve herd immunity has become the most pressing issue for combat the global threat of the virus. Currently, four vaccines have been approved either by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA): two messenger RNA-based vaccines, namely BNT162b2 (produced by Pfizer-BioNTech) and mRNA-173 (produced by Moderna), and two recombinant adenovirus-associated vector vaccines, ChAdOx1 nCoV-19 (Astra-Zeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen). Although these vaccines are highly efficacious in protecting against SARS-CoV-2 infection, there have been some reports of severe thrombosis in cerebral veins and in other atypical sites after immunization with the ChAdOx1 nCoV-19 vaccine, some of which have been fatal [3]. The seminal study by Greinacher et al. [3] showed for instance the occurrence of thrombotic thrombocytopenic syndromes (mainly CVT* and splanchnic venous thrombosis) in 11 patients after 5–16 days ChAdOx1-nCov-19 vaccination. Hence, this particular type of thrombosis with thrombocytopenia has been defined as vaccine-induced thrombotic thrombocytopenia (VITT) or, as correctly proposed by M. Cattaneo, thrombosis with thrombocytopenia syndrome (TTS)[1]. The pathogenesis of this thrombotic syndrome was attributed by most authors to the presence of platelet-activating antibodies against PF4-polyanions, mimicking those found in the heparin-induced thrombocytopenia (HIT) syndrome, where PF4 is bound to heparin. However, as most patients suffering from VITT/TTS were not previously exposed to heparins, the genesis of the anti-PF4 autoantibodies is still controversial. Thus, the fundamental issue to be addressed concerns the cause responsible for the enhanced secretion of PF4 associated with ChAdOx1-nCov-19 vaccine administration. Based on known mechanisms employed by adenoviruses and coxsackieviruses to attack and enter the host cells [4], a plausible interpretation to our opinion can be put forward. Adenoviruses and coxsackieviruses interact in fact with coxsackie-adenovirus-receptors (CAR) and adhesion molecules (CD62) on platelets, endothelial cells, and other various cell types in the brain, heart, and intestine [4,5]. This could be the same for ChAdOx1 as well. Stone et al., showed in fact that the delivery of the recombinant adenovirus-based vectors (serotype 5, Ad5) used for therapy, caused platelet activation and sequestering, followed by their entrapment in the liver with final capture by Kupffer cells [6]. Moreover, Ad5 interacts also with the platelet adhesion molecule CD62 (P-selectin), mediating the interaction of activated platelets and endothelial cells with leukocytes [6]. The platelet adhesion to endothelial cells and their activation may also be one of the causes of severe thrombocytopenia observed in these cases. This biological phenomenon is also crucial in the process of thrombus formation and growth. Greinacher et al. observed in fact a strong activation of platelets by ChAdOx1-nCov-19 but interpreted this phenomenon as a mere *in-vitro* artifact [3]. Instead, a plausible interpretation is that ChAdOx1nCov-19 particles, after vaccination and consequent possible viremia, can directly reach different cell types. Among these cells there are also platelets and endothelial cells [5], which can be activated, via CAR and CD62 binding, releasing PF4 and polyphosphates, contained in the α- and dense platelet granules, respectively [7]. PF4-polyphosphates-Ig immunocomplexes bind to FcγRIIA on the surface of platelets and thus cross-link these receptors, inducing platelet activation and perpetuating over time a platelet activation/consumption and prothrombotic state even without heparin [8]. Moreover, polyphosphates contained in the dense granules of platelets are able to induce autoactivation of FXII and trigger the contact phase-dependent coagulation cascade [9]. M. Cattaneoreported in fact that both the intravenous infusion of immunoglobulins (IVIg) at high doses (2 gr/Kg body weight over 2 to 5 days) and the potent thrombin inhibitor argatroban are efficient agents to inhibit the two fundamental steps responsible for triggering TTS, that is platelet activation (FcγRIIA ligation by PF4-polyanions-IgG complex) and

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