Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

American Journal of Emergency Medicine 57 (2022) 156–157

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

The conundrum of thrombosis with thrombocytopenia syndrome following COVID-19 vaccines

In the very important paper published in Am J Emerg Med [1], the authors presented the thrombosis with thrombocytopenia syndrome associated with the vector COVID-19 vaccines, which affects mainly female individuals, younger than 55 years of age, with mortality approximately 40%. They described the symptomatology, laboratory evaluation, management and treatment, especially in the emergency department and emphasized that the thrombosis involves atypical locations such as the cerebral venous sinus vasculature where there is restriction of the passage of blood into the cerebrospinal fluid due to the blood–brain barrier. Moreover, the delayed appearance of thrombosis which can occur 5–24 days after vaccination and is not dependent to heparin exposure and the pathophysiology of these events that are not completely understood have correctly emphasized. The arising questions, therefore, include: why this syndrome occurs in the absence of heparin administration, involves atypical locations, occurs in 2 specific COVID-19 vaccines, affects young middle-aged women and has delayed appearance? Is there any common pathway that connects all these 5 conditions? Thrombocytopenia with thrombosis and especially serious cerebral venous sinus thrombosis, in the absence of external heparin administration, is indeed rare manifestations of both ChAdOx1 nCov-19 and Ad26.COV2·S vector vaccines [2]. In such cases, high levels of PF4-polyanion complexes are present as has been emphasized by the authors. The PF4 is a protein present in the a-granules of platelets and can quickly bind to either exogenous or endogenous heparin. The latter belongs to endogenous glycosaminoglycans which also include heparan sulphate, and dermatan sulphate, that when released into the bloodstream can cause severe bleeding [3]. A recent study demonstrated that increased levels of anti-PF4 antibody isotypes, endogenous glycosaminoglycans, and inflammatory biomarkers were associated with the pulmonary embolism severity and mortality [4]. Indeed, the pair of PF4/heparin acts as an autoantigen and induces anti-PF4/heparin antibodies of IgG class [5]. The triad PF4-heparin-IgG antibody complexes can cause thrombosis via activation of the specific low-affinity IgG (FcγRIIa) receptors on the platelet surface [5]. The extensive thrombosis increases the consumption of platelets leading to thrombocytopenia [6]. Platelet surface, however, disposes also high affinity IgE (FcεRI) and low affinity IgE (FcεRII) receptors that play an important role in the type I allergic inflammation and can promote hypersensitivity reactions, a fact that is not so well known to physicians [7,8]. Moreover, the platelet surface contains receptors for histamine, platelet-activating factor, thromboxan, thrombin, adenosine diphosphate that also promote hypersensitivity reactions associated with thrombosis [9]. Upon their activation, platelets secrete pro-inflammatory pro-thrombotic, adhesive, and chemotactic mediators that propagate, amplify and sustain the thrombotic process [10]. The authors correctly described the therapy of this condition with intravenous immunoglobulin, anticoagulation, and avoidance of heparin and platelet transfusion. Since platelet surface brings hypersensitivity receptors, steroid administration seems beneficial. The delayed appearance of reactions after vaccination is not new. Such reactions have been associated with vaccines containing antimicrobial agents and ingredients, such as thimerosal and aluminum and withJapanese encephalitis and rabies vaccines [5] These reactions are antibodyindependent, cell-mediated, stemming from over stimulation of T cells and monocytes/macrophages and cytokine's release that further cause inflammation, cell death, and tissue damage. Several pathophysiological explanations have been postulated and include vaccine-induced immune thrombotic thrombocytopenia, pro-thrombotic conditions, age, sex, anatomical and dysfunctional variants of the venous system, impaired protein homeostasis-systems and hypersensitivity reactions to vaccine components. Indeed, both vector ChAdOx1 nCov-19 and Ad26.COV2·S vaccines dispose excipients that could be potential antigens such as polysorbate 80 (PS80). PS80 can induce systemic reactions including IgE immediate reactions as well as non-immunologic anaphylactoid reactions but also local reactions such as thrombus formation, pain and erythema. PS80 can penetrate the blood–brain barrier, enhance membrane permeability, and facilitate the passage of drugs from the blood to the brain and in cerebral venous sinuses, an action that is used in oncology [11]. However, creams, ointments, lotions, cosmetics and dental materials, that are usually used by women and young individuals, contain PS80, whereas 1–5.4% of the general population has been sensitized to cosmetics or dental materials [12]. Indeed, there are, already suggestions of alternative excipients if vaccine component-induced hypersensitivity is confirmed by systematic future investigations [13]. Hypersensitivity to such excipients constitutes risk to patients with allergy to PS80. Safe COVID-19 vaccines could be offered to most patients, but according to new recommendations susceptible patients will await new vaccines containing different excipients [14]. Cerebral venous sinus thrombosis, pulmonary artery emboli, myocardial infarction and thrombotic events after COVID-19 vaccination are very rare and the benefits of vaccination should be taken into account and continue to be recommended to all those who are eligible.

Disclosures

The authors disclosed no relevant relationships.

Ethical approval

NA.

Informed consent

NA.

https://doi.org/10.1016/j.ajem.2022.04.019

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare no competing interests.

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