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"Portal vein thrombosis occurring after the first dose of mRNA SARS-CoV-2 vaccine in a patient with antiphospholipid syndrome"

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Dear Editor,

With the implementation of a global vaccination plan, the year 2021 began with the hope of definitively conquering the coronavirus disease 2019 (COVID-19) pandemic. The European Medicines Agency (EMA) has approved four vaccines, two of which are based on mRNA technology (BNT162b2 and mRNA-1273) and two of which employ an adenovirus vector (ChAdOx1-S and Ad26.COV2) [1]. The EMA Pharmacovigilance Risk Assessment Committee (PRAC) has recently assessed the safety profile of ChAdOx1-S following many reports of blood clotting events emerging days to weeks after the vaccine's first or second injection [2]. Following the report of six cases of thrombocytopenia and cerebral venous sinus thrombosis in female recipients aged 18–48 years, the Food and Drug Administration (FDA) suspended the use of the AD26.COV2 vaccine in the United States (US) in April 2021 [3]. This type of vaccine-induced immune thrombotic thrombocytopenia (VITT), also called thrombotic thrombocytopenia (TTS), implies an immunological reaction that mimics heparin-induced thrombocytopenia (HIT) [4]. SARS-CoV-2 infection is linked to an increase in venous thromboembolic (VTE) events, most likely because of a thrombotic state caused by inflammation and immune-mediated thrombosis [5]. More recently, some rare cases of classical VTE have been observed in citizens who received the mRNA-based vaccine (BNT162b2/Comirnaty/Pfizer/BioNTech) [6–8]. However, the link between COVID-19 vaccinations and thrombotic events remains unknown, while an immune-mediated mechanism analogous to what occurs in antiphospholipid syndrome (APS) could be a possibility. Furthermore, the majority of those who developed severe coagulation disorders after being vaccinated were young women, who are also the APS target population [9,10].

A 68-year-old woman presented to the emergency department (ED) complaining of abdominal pain, in the epigastrium and in the right hypochondrium. She had a mild fever and a slight increase of CRP, without any obvious site of infection and no history of trauma. She received the first dose of mRNA SARS-CoV-2 vaccine (BNT162b2/Comirnaty/Pfizer/BioNTech) subcutaneously, without any reported clinical problem 14 days before presentation. Her past medical history included obesity (first degree, with body mass index 30,1 kg/m^2), asthma, hypothyreosis, and irritable bowel syndrome (IBS-D). She had a miscarriage many years ago, early in pregnancy (before week 10). She had no history of thrombosis or abortions in the past, as well as preexisting autoimmune diseases. She had 3 normal pregnancies without complications afterward. She did not smoke. The physical examination was unremarkable. The complete blood count, the comprehensive metabolic panel, and the coagulation profile was unremarkable. D-dimer test was not performed. A Color-Doppler ultrasound revealed thrombosis of the portal vein. Evaluation with chest-abdomen-pelvis Computer Tomography Scan (CT) was negative for malignancy and liver cirrhosis. Thrombophilia screening was negative. Notably, IgG Beta-2 glycoprotein I antibodies were elevated (28 U/ml), and lupus anticoagulant was positive. Anti-cardiolipin antibodies was negative. Repeated positivity of lupus anticoagulant and IgG Beta-2 glycoprotein I antibodies, 12 weeks after first abnormal blood tests, confirmed the diagnosis of Antiphospholipid Syndrome (APS). The patient is being treated with Warfarin. Repeated Color-Doppler ultrasound revealed resolution of thrombosis, 3 months later.

To my knowledge, this is the first reported case of manifestation of APS in the form of portal vein thrombosis after the first dose of mRNA vaccine (BNT162b2/Comirnaty/Pfizer/BioNTech). It is supposed that pre-existent antiphospholipid antibodies (aPLs) might predispose to this complication, acting as the first trigger, although this is not determined a priori. Given the clinical resemblance between thrombotic events following COVID-19 vaccination and APS, researchers from Italy provided a pathogenic theory for this rare adverse event that involves a pre-existent or a de novo aPL positivity. While adenoviral vector-based vaccines may induce the synthesis of aPLs due to a molecular mimicry mechanism, the mRNA-based vaccines may instead trigger a more complex pathway, characterized by activation of Toll-like receptor (TLR), generation of a Type I Interferon (IFN) response, NETosis and the direct initiation of the coagulation cascade. Disruption of the physiological cross-talk occurring between platelets and endothelial cells drives these cells toward a pro-inflammatory and pro-coagulant phenotype [11].

The fast development of currently available COVID-19 vaccines may create certain considerations about potential long-term safety issues, but still, the intervention's advantages in stopping the spread of the COVID-19 pandemic appear to outweigh the risks associated with a longer-term

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characterization of the pharmacological profile of these vaccines. To determinate the degree of this potential side effect which, while extremely low, it is required a longer follow-up and a larger diffusion of SARS-CoV-2 vaccines in the population. In addition, side effects occurring in a minority of people belonging to specific populations (like aPL-positive subjects) may be underestimated.

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Informed consent

The author obtained informed consent from the patient involved in this report.

Declaration of competing interest

None declared.

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Nikolaos Melas
Gastroenterology and Hepatology Department, Karlstad Central Hospital, Rosenborgsgatan 9, 652 30, Karlstad, Sweden
E-mail address: nikolaos.e.melas@gmail.com.