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Case Report

Multiple sites of thrombosis without thrombocytopenia after a second dose of Pfizer-BioNTech COVID-19 vaccine

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Abstract

In the current international scientific panorama, rare cases of venous thrombotic complications following mRNA vaccine administration have been reported, consisting mainly of cerebral sinus thromboses and acute venous thromboembolism. The present paper describes the case of a 75-year-old woman in good health who developed cerebral venous thrombosis, deep venous thrombosis, and bilateral pulmonary emboli after receiving a second dose of Pfizer-BioNTech COVID-19 vaccine. A series of laboratory tests performed during hospitalization yielded interesting results, allowing us to exclude thrombophilic risk factors and to certify the absence of thrombocytopenia in the patient. Although COVID-19 vaccination is the most important tool in stopping the pandemic, pharmacovigilance is crucial for detecting potential multisystem thrombotic events, even for mRNA vaccines.

Keywords

COVID-19 infection, Pfizer-BioNTech vaccine, venous thrombosis, thromboembolism, thrombocytopenia, computed tomography

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Introduction

In rare cases, the Johnson & Johnson/Janssen and AstraZeneca COVID-19 vaccinations may cause vaccine-induced thrombotic thrombocytopenia (VITT),[1] a condition characterized by simultaneous acute thrombosis and thrombocytopenia. The condition is similar to heparin-induced thrombocytopenia. Given the extremely low case count, specific risk factors for VITT are yet to be determined, though onset seems to occur between 5 and 28 days post-vaccination. The rare risk of blood clots associated with the DNA vaccine is now well documented, but very recently, concerns have begun to emerge about the mRNA COVID-19 vaccine.[2] A recent study[3] investigated the occurrence of venous thromboembolism (VTE) in three women following administration of the Moderna vaccination at the same healthcare system. None of them showed thrombocytopenia. Here, we present a case of multiple sites of thrombosis without thrombocytopenia after a second dose of Pfizer-BioNTech COVID-19 vaccine.

Case presentation

We present the case of a 75-year-old woman in good health, with the exception of mild arterial hypertension, for which she was being treated with antihypertensive drugs. On entering the Emergency Medicine Unit, the patient presented

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with acute onset of nonfluent aphasia and code stroke protocol was followed. The subject's past medical history was negative, except for the administration of a second dose of Pfizer-BioNTech COVID-19 vaccine 10 days before symptom onset. The patient tested negative for COVID-19 infection.

In fact, 2 days after receiving the second dose, the patient began to experience a persistent and drug-resistant headache, and focal neurological symptoms appeared approximately 9 days later. In the emergency room, a computed tomography (CT) scan of the head was performed, which detected intraparenchymal hemorrhage in the left occipital lobe associated with perilesional vasogenic edema and further hemorrhagic lesions in the ipsilateral subcortical temporo-occipital site, with a round morphology.

The neurological physical examination confirmed nonfluent aphasia, but there were no sensory-motor deficits in the upper or lower limbs. After approximately 12 h, a brain CT scan was performed, which showed a significant deterioration, with numerical and dimensional increases in the hemorrhagic components of the temporal, occipital, and left parietal lobes, plus marked signs of perilesional edema. The CT image was also characterized by widespread hypovisualization of the cortical folds in the left hemispheric area due to the presence of edema, together with marked compression phenomena affecting the anterior and posterior horn and the trine of the left ventricular system. In the left frontoparietal region, there was a subdural hematoma (SDH) with a maximum thickness of 3 mm. A recommended computed tomography angiography (CTA) showed evidence of extensive opacification defects affecting the left transverse sinus, the left sigmoid sinus, and the lower portion of the petrous part of the left internal jugular vein, compatible with acute cerebral venous thrombosis (CVT) (Figure 1). In addition, a focal filling defect of similar significance was also found in the right transverse sinus.

The patient was hospitalized in the Neurology Unit, where specific therapy was prescribed (antiepileptic, antiedema, and anticoagulant therapy). Magnetic resonance imaging (MRI) of the brain revealed an extensive left temporo-parieto-occipital edema, corresponding to an extensive area of intraparenchymal bleeding, and confirming evidence of thrombosis of the left transverse and sigmoid sinuses of the proximal tract of the left internal jugular.

In the days that followed, the patient underwent a comprehensive series of laboratory and instrumental examinations, aimed at finding the etiology of cerebral thrombosis. Routine laboratory tests consisted of a complete blood count, coagulation screening including factors II and V Leiden, checks for the presence of neoplastic markers, and measurements of homocysteine, ferritin, beta-2-microglobulin, and immunoglobin levels. There was an increase in D-dimer levels (6175 ng/mL and 2885 ng/mL on the 4th and 9th day of hospitalization, respectively), while the remaining parameters were within normal range, including the platelet count (Table 1).

A total body CT excluded neoplastic lesions, but a pulmonary thromboembolism was found in both lower lobes with filling defects. For this reason, a venous Doppler examination of the lower limbs was carried out, with evidence of voluminous deep venous thrombosis (DVT) of a peroneal vessel of the left lower limb, extending to the distal lower third of the leg up to the tibial-peroneal trunk.

The patient was discharged after 15 days of recovery. Two weeks after discharge, another brain CT showed complete resorption of the hemorrhagic areas, and a CTA showed post-embolic rehabilitation of the petrous tract of the internal jugular vein and persisting stable filling defects from subtotal thrombosis affecting the transverse and

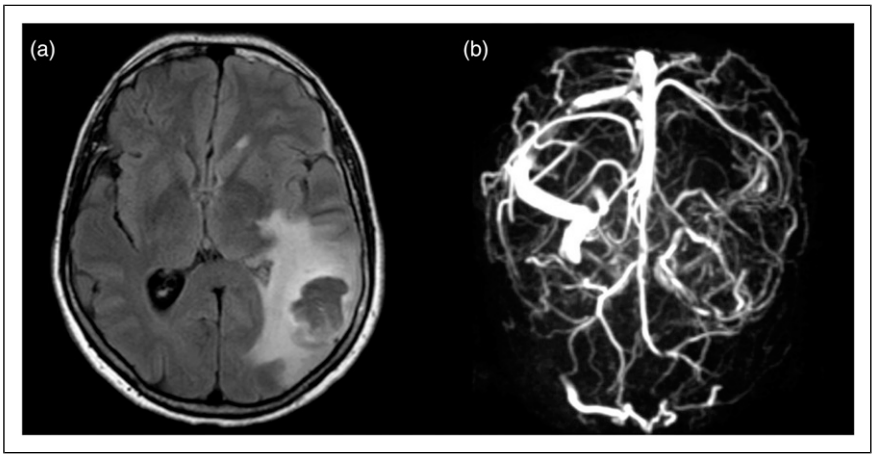

Figure 1. MR (a) and Angio-MR (b) during hospitalization. (a) Large areas of left temporo-parieto-occipital bleeding, with right midline shift. (b) Acute thrombosis of the left transverse and sigmoid sinuses.

Table 1. Routine laboratory tests performed during hospitalization.

	18/05/2021	20/05/21	21/05/21	22/05/21	24/05/21	27/05/21	31/05/21
Leukocytes (thousand/mm3)	7.6	15.2	13.1	8.7	7.9	6.7	4.9
Erythrocytes (million/mm^3)	4.23	4.20	4.22	4.2	4.34	4.11	3.95
Hemoglobin (gr/dl)	13.1	12.9	12.7	12.8	13.4	12.4	12.0
Hematocrit (%)	38.7	37.4	37.8	37.8	38.3	37.7	36.2
Platelets (thousand/mm^3)	256	246	205	209	212	235	270
I.N.R.	0.96	/	/	/	1.10	1.08	1.05
PTT RATIO	0.80	/	/	/	0.86	0.81	0.91
Fibrinogen (mg/dl)	328	/	/	/	273	370	384
Homocysteine	/	/	/	7.6 mL	/	/	/
D-dimer	/	/	/	6175 ng/mL	3124 ng/mL	2885 ng/mL	/
Factor V Leiden mutation	/	/	/	Absent	/	/	/
Prothrombin G20210A (Factor II mutation)	/	/	/	Absent	/	/	/
IgG anticardiolipin antibodies	/	/	/	Negative	/	/	/
IgM anticardiolipin antibodies	/	/	/	Negative	/	/	/

sigmoid sinus. In addition, a Doppler examination of the lower limbs showed complete resolution of the venous thrombosis. The patient's therapy was changed from subcutaneous enoxaparin to warfarin, adjusted to obtain a correct PT/INR range. The patient underwent CT and CTA approximately 2 months after admission, observing left temporo-parieto-occipital poromalacic areas; there were always filling defects from subtotal thrombosis. About 6 months after admission, there were extensive left temporo-parieto-occipital poromalacic areas, complete thrombosis of the left transverse sinus, partial thrombosis of the left sigmoid and petrosal sinuses, and partial thrombosis in the jugular foramen of the left internal jugular vein (Figure 2).

Discussion

In this report, we present a case of multiple thrombosis (cerebral, pulmonary, and lower limbs) occurring after a second dose of Pfizer-BioNTech COVID-19 vaccine. Although the risk of thrombosis following COVID-19 infection and the potential thrombotic risks following AstraZeneca and Janssen COVID-19 vaccinations were documented at the outset, cases of thrombosis have only been reported after Pfizer-BioNTech and Moderna vaccines in a later period.[4,5] Studies have shown that reported thrombotic events have been more prevalent in the <65 years age group among AstraZeneca vaccine recipients compared to Moderna or Pfizer.[6]

A possible explanation for the mechanism of thrombosis related to the mRNA COVID-19 vaccine is that general procoagulant and proinflammatory effects are associated with immune responses to nucleic acid. For mRNA vaccines, nucleic acid is recognized by pattern-recognition receptors such as toll-like receptors (TLRs) and retinoic acid-inducible gene I protein (RIG-I), and this potentially induces inflammatory reactions.[7]

Thrombocytopenia can occur after any kind of vaccine. However, previous investigations have not found an increased incidence of thrombocytopenia after exposure to BioNTech compared to a matched control.[8] There have been conflicting results regarding the increased prevalence of thrombocytopenia.[9]

Thrombosis is believed to complicate most suspected VITT cases, but it may not always present with thrombocytopenia.[10] The peculiarity of our case is that multiple sites of thrombosis were detected even in the absence of thrombocytopenia, which therefore ruled out VITT. Anti-PF4 antibodies were not tested (at that time, this specific test was not available in our hospital). However, in this case, the platelet count was perfectly normal; therefore, there was no strong indication to investigate PF4 antibodies, assuming that their presence could have suggested a diagnosis of VITT, which does not concern the specific case. The patient had not reported and showed no signs of ongoing COVID-19 infection and had no other risk factors for developing acute systemic thrombosis. In previous research, cases of venous thrombosis were reported following a COVID-19 vaccination despite normal platelet counts and negative PF4 antibodies, thus supporting the thesis that VITT is not the only cause of VTE after the administration of a COVID-19 vaccine.[11]

To investigate the causal association between COVID-19 vaccination and the occurrence of a multisystem thrombosis, we considered vaccination administration as being a primary cause of symptoms arising within 10 days, using a similar methodology to previous authors[12] who followed the basic framework of the World Health Organization (WHO). In particular, to confirm a causal relationship, other causal mechanisms were excluded, including possible pre-existing or predisposing conditions of the subject and the quality of the vaccine. Although it is impossible to establish the exact process that

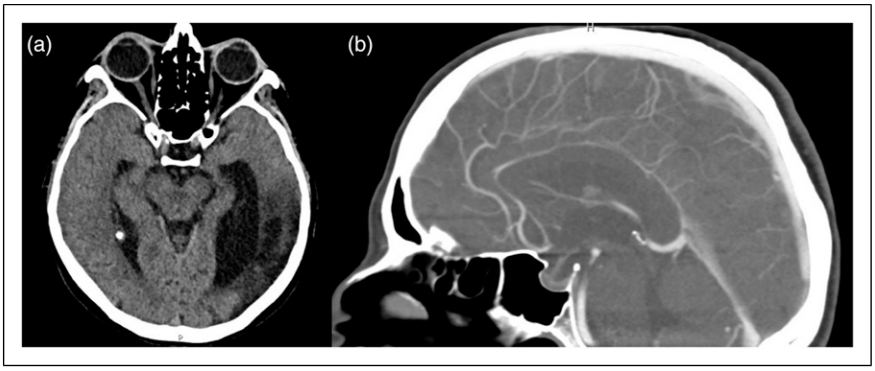

Figure 2. CT (a) and CT angiography (b) 6 months after discharge. (a) Left temporo-parieto-occipital poromalacic areas. (b) Complete thrombosis of the left transverse sinus and partial thrombosis of the left sigmoid and petrosal sinuses.

led to multisite venous thrombosis, the timing of onset indicates a concrete correlation with the COVID-19 vaccine itself, as many scientific contributions have already documented.[13]

The similarity between the COVID-19 virus and COVID-19 vaccines has been discussed in the literature.[14] As the virus has a high thrombogenic effect, the same thrombogenicity can occur after COVID-19 vaccination. Although the cause of this has not been established, observers have reported an association between elevated factor V activity and VTE.[15] Furthermore, a series of vascular events can be triggered by the spike proteins generated by mRNA vaccines, thereby leading to endothelial dysfunction and activation of a clotting mechanism.[16] Therefore, given the normal platelet count of the hospitalized patient in our report, it would be reasonable to investigate all possible cellular stress conditions that could be triggered by the vaccine and act on the vascular endothelium, which in normal conditions prevents hypercoagulability (by releasing antithrombotic and anti-inflammatory factors, thus maintaining a certain level of blood fluidity).[17] It is known that the platelet surface contains receptors for histamine, the platelet activating factor, thromboxane, thrombin, and adenosine diphosphate which also promote hypersensitivity reactions associated with thrombosis.[18] Although human platelets activated via IgE and FcεRI play an important role in the type I allergic inflammation[19] which can promote hypersensitivity reactions and a prothrombotic state, signs of an initial post-vaccine allergic reaction usually occur within minutes of administration or hours, except for limited cases of delayed hypersensitivity reactions after a few days.[20] In our case, the woman had a negative allergy history of any kind and the symptoms appeared after several days; in particular, focal neurological symptoms appeared about 9 days later, without clinical features suggesting an allergic adverse reaction.

Conclusions

Although COVID-19 vaccination is key to stopping the pandemic, ongoing pharmacovigilance is crucial to monitor potential side effects, thereby ensuring complete and accurate communication between vaccinator and patient. It is imperative to obtain a vaccination history in patients presenting symptoms of thrombosis with no other obvious predisposing factors.

Authors' note

Francesco Ottavio Logullo is now affiliated to Neurological Unit of the Azienda Ospedaliera Ospedali Riuniti Marche Nord, Pesaro, Italy.

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