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Letter to the Editors-in-Chief

Vaccine-induced immune thrombocytopenia and thrombosis after mRNA-1273 booster vaccination

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Vaccine-induced thrombosis with thrombocytopenia (VITT) is a rare complication of vaccination against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and has mainly been reported after adenovirus vector SARS-CoV-2 vaccines [1,2]. For the ChAdOx1 nCoV-19 vaccine (AstraZeneca), it has been proposed that components of this vaccine can bind platelet factor 4 (PF4) after which these aggregates can stimulate PF4 antibody production, resulting in the platelet activation that is seen in VITT [3,4]. Reports of VITT caused by messenger-RNA (mRNA) SARS-CoV-2 vaccines are scarce, and occurrences of VITT after a mRNA SARS-CoV-2 booster vaccination have not yet been described.

We report an 83-year-old woman previously known with hypertension and a transient ischemic attack for which she used a platelet aggregation inhibitor (clopidogrel) who presented to our hospital with dyspnea and retrosternal pain since one day. She received an mRNA-1273 SARS-CoV-2 booster vaccination (Moderna) 20 days prior to symptom onset. Eight months prior to the mRNA-1273 booster, this patient had been vaccinated twice with a BNT162b2 SARS-CoV-2 vaccine (Pfizer/BioNTech) without complications. Blood tests showed a thrombocytopenia ($48*10^9$/mL, $339*10^9$/mL five months earlier) and high D-dimers (>6.8 mg/l). Chest computed tomography angiography revealed large pulmonary emboli, almost completely occluding the right pulmonary artery branches. Pseudothrombocytopenia was ruled out and the patient was admitted to the Intensive Care department for hemodynamic and respiratory monitoring. Treatment with therapeutic dose low-molecular weight heparin (LMWH, twice daily 7500 IU subcutaneous) was initiated as well as nasal oxygen support.

Three days after admission, a further decline in platelets ($20*10^9$/L) was observed and a platelet transfusion was given to safely continue therapeutic anticoagulation, leading to a modest increase of platelet count (Fig. 1). Although deemed unlikely as it was not described previously, a mRNA-1273 SARS-CoV-2 booster-associated VITT was considered. Hence LMWH was switched to therapeutic subcutaneous danaparoid three days after admission and blood samples were collected for VITT diagnostics. An anti-platelet factor-4 (PF4) ELISA was performed, in which the presence of PF4 antibodies was measured using microtiter plate wells coated with 100 μl of 3 μg/ml PF4 (Chromatec) and was positive. Additionally, a modified heparin induced platelet activation assay, using platelet suspensions from four healthy donors as described by Greinacher et al. [5] showed strong positive platelet activation after 5 min with PF4 only, after 20 min with only buffer and after 15 min with low dose (0.2 IU) unfractionated heparin. Platelet activation was completely inhibited with high dose heparin (100 IU) or a FcγRIIa specific monoclonal antibody (IV.3) (Table 1). Based on these results, the diagnosis VITT was made and intravenous immunoglobulins (IVIg, Nanogam, 1 g/kg for two days) were given. Danaparoid was also switched to apixaban 10 mg bid for 7 days followed by 5 mg bid to achieve more stable therapeutic anticoagulant therapy. Platelet count normalized three days after IVIg initiation and the patient's condition improved. The patient was discharged from the hospital 20 days after admission. No longitudinal follow-up of PF4 levels was performed.

This patient met all the case definition criteria for a confirmed VITT, as proposed by Pavord et al. [6]. Additionally, presence of thrombocytopenia prior to initiation of LMWH without previous exposure to heparin support that the combination of thrombocytopenia and thrombosis in our patient are more compatible with VITT than heparin induced thrombocytopenia. To date, there are only two reports of suspected VITT after a mRNA-1273 vaccination (containing 100 μg of mRNA) [7,8]. These patients presented with thrombocytopenia and brain infarctions seven days after the first mRNA-1273 vaccination [8] and with thrombocytopenia and large bilateral pulmonary emboli ten days after receiving a second mRNA-1273 vaccination [7]. Both patients were treated with IVIG and plasmapheresis but died 20- [8] and 12-days [7] after hospital admission.

To the best of our knowledge, this is the first report of a patient with VITT after a mRNA-1273 booster vaccine (50 μg of mRNA). The mRNA-1273 SARS-CoV-2 vaccine has been demonstrated to be safe and highly effective against severe disease caused by SARS-CoV-2 [9]. The probable vaccine-induced thrombotic complication that we describe here likely is an extremely rare side-effect of the mRNA-1273 vaccine and possibly of vaccination in general. However, in patients with thrombosis and thrombocytopenia after an mRNA-1273 (booster) vaccination, it is of utmost importance to promptly initiate diagnostics for VITT and adequate immuno-neutralizing and anticoagulant treatment to improve

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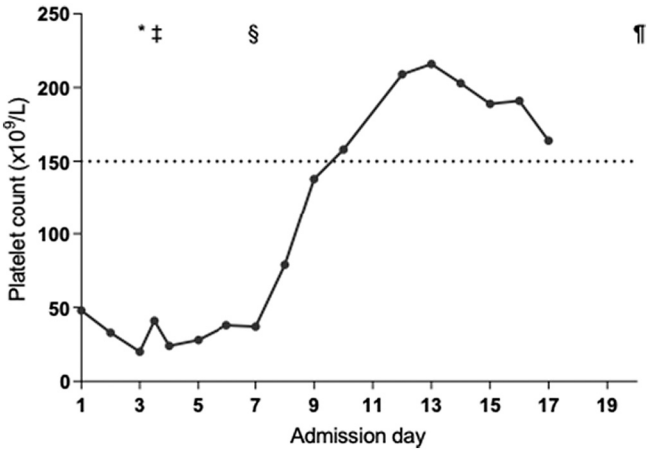

Fig. 1. Platelet levels during hospital admission. The dotted line indicates the lower limit of a normal thrombocyte count. * Platelet transfusion, ‡ Switch LMWH to danaparoid, § Start IVIg and switch danaparoid to apixaban, ¶ Discharge from hospital, LMWH low-molecular-weight heparin, IVIg intravenous immunoglobulins.

Table 1
Results from hematological, radiological, and additional tests.

Hematology	Result (normal)
Hemoglobulin at admission, mmol/L	7.0 (7.5–10)
Leukocyte count at admission, *10^9/L	11.0 (4.3–10)
Platelet count, nadir, *10^9/L	20 (150–350)
D-dimer at admission, mg/L	>6.8 (<0.5)
Fibrinogen at admission, g/L	2.8 (2.0–4.0)
Prothrombin time peak, seconds	13 (8–11)
Activated partial thromboplastin time peak, seconds	37 (20−30)
VITT diagnostic tests	
PF4 IgG ELISA, optical density	2.2 (<1.0)
Platelet activation assay, platelet activation time in minutes:	
	5 (<45)
- Serum + PF4	15 (>45)
- Serum + buffer	20 (>45)
- Serum +0.2 IU heparin	>45 (>45)
- Serum +100 IU heparin	>45 (>45)
- Serum + FcγRIIa blocking	
Additional tests	
Lupus anticoagulant	Absent
Anticardiolipin IgM	5.0 (<20)
Anticardiolipin IgG	<3 (<20)
SARS-CoV-2 PCR	Negative
Radiology	
Chest X-ray	Possible infiltrate right lower pulmonary lobe
Chest CTa	Large pulmonary embolisms in the right pulmonary arteries and right and left lower pulmonary lobe
Transthoracic echocardiography	Dilation of the right atrium and ventricle with non-diluted left ventricle

patient outcome.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] P. Bhuyan, J. Medin, H.G. da Silva, M. Yadavalli, N.K. Shankar, H. Mullerova, et al., Very rare thrombosis with thrombocytopenia after second AZD1222 dose: a global safety database analysis, Lancet 398 (2021) 577–578.
[2] I. See, J.R. Su, A. Lale, E.J. Woo, A.Y. Guh, T.T. Shimabukuro, et al., US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021, JAMA - J. Am. Med. Assoc. 325 (24) (2021 Jun 22) 2448–2456.
[3] A. Greinacher, K. Selleng, R. Palankar, J. Wesche, S. Handtke, M. Wolff, et al., Insights in ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia, Blood 138 (22) (2021 Dec 2) 2256–2268.
[4] M. Scully, D. Singh, R. Lown, A. Poles, T. Solomon, M. Levi, et al., Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination, N. Engl. J. Med. 384 (23) (2021 Jun 10) 2202–2211.
[5] A. Greinacher, T. Thiele, T.E. Warkentin, K. Weisser, P.A. Kyrle, S. Eichinger, Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination, N. Engl. J. Med. 384 (22) (2021 Jun 3) 2092–2101.
[6] S. Pavord, M. Scully, B.J. Hunt, W. Lester, C. Bagot, B. Craven, et al., Clinical features of vaccine-induced immune thrombocytopenia and thrombosis, N. Engl. J. Med. 385 (18) (2021 Oct) 1680–1689.
[7] S. Sangli, A. Virani, N. Cheronis, B. Vannatter, C. Minich, S. Noronha, et al., Thrombosis with thrombocytopenia after the messenger rna-1273 vaccine, Ann. Intern. Med. 174 (2021) 1480–1482. American College of Physicians.
[8] P.H. Su, Y.C. Yu, W.H. Chen, H.C. Lin, Y.T. Chen, M.H. Cheng, et al., Case report: vaccine-induced immune thrombotic thrombocytopenia in a pancreatic cancer patient after vaccination with messenger RNA−1273, Front. Med. 1 (2021 Nov) 8.
[9] L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, et al., Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine, N. Engl. J. Med. 384 (5) (2021 Feb 4) 403–416.

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