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Case Report

Vaccine-induced massive pulmonary embolism and thrombocytopenia following a single dose of Janssen Ad26.COV2.S vaccination

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ABSTRACT

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has emerged as a rare side effect of adenoviral vector-based vaccines against coronavirus disease 2019 (COVID-19), and is most frequently reported after use of the Vaxzevria (AstraZeneca) vaccine. This report describes a case of severe thrombocytopenia associated with massive pulmonary embolism and portal vein thrombosis occurring 13 days after the administration of the single-dose adenoviral vector-based vaccine Ad26.COV2.S (Janssen Vaccines). Based on early clinical suspicion, the patient quickly received treatment with corticosteroids and intravenous immunoglobulin, followed by a rapid increase in platelet count that allowed timely administration of full-dose anticoagulation. Treatment with intravenous immunoglobulin, however, could mask the ability of anti-platelet factor 4-heparin antibodies to bind and activate platelets in the presence of heparin, leading to false-negative results on the immunoassay functional test. Therefore, if VITT is suspected, blood samples for diagnostic confirmation should be collected prior to any treatment to improve diagnostic performance.

Case report

A 68-year-old man presented to the emergency department with swelling of the left leg with subacute pain, associated with weakness, dizziness and progressive dyspnoea. His medical history included hypertension and an euthyroid nodular goitre; personal history of thrombosis was negative. Molecular test for SARS-CoV-2 nucleic acid (polymerase chain reaction) was negative and anti-Spike immunoglobulin G was 316 AU/mL. Vaccination for coronavirus disease 2019 (COVID-19) with a single dose of Ad26.COV2.S vaccine (Janssen Vaccines, Leiden, The Netherlands) was reported 13 days previously. He denied any previous exposure to anticoagulants, including heparins.

The patient was slightly dyspnoic and tachypnoic in room air with peripheral oxygen desaturation and his left leg was swollen and painful. The remaining examination was unremarkable. A point-of-care ultrasound evaluation revealed left femoropopliteal deep vein thrombosis and no signs of right heart overload/dysfunction. Total-body contrast-enhanced computed tomography showed massive bilateral pulmonary artery embolism and a right intrahepatic portal thrombosis (Figure 1). Laboratory tests revealed severe thrombocytopenia (platelet count 7,000/μL), markedly elevated D-dimer (32,533 ng/L), and increased serum lactate dehydrogenase (LDH) and C-reactive protein. Fibrinogen, prothrombin and activated partial thromboplastin time were all within normal ranges (Table 1).

Vaccine-induced immune thrombocytopenia (VITT) was suspected. Therefore, high-dose parenteral corticosteroids (methylprednisolone 80 mg IV daily) and intravenous immunoglobulin (IVIg) (1 g/kg/day for 2 days) were started immediately. An inferior caval vein filter (IVF) was implanted.

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Table 1
Laboratory characteristics of the case patient.

Laboratory analysis	Reference value	Day 1	Day 4	Discharge
Haemoglobin (g/dL)	13.5–18.0	12.2	10.2	11.3
Platelet count (per mm^3)	140,000–440,000	7,000	24,000	230,000
Leukocytes (per mm^3)	4,500–10,800	5,540	5,540	8,420
Partial thromboplastin time (s)	22–32	25	28	22
International normalized ratio	0.85–1.20	1.08	1.33	1.05
Thrombin time (s)	70–120	86	61	91
Fibrinogen (mg/dL)	160–420	217	58	350
D-dimer (mg/L)	0–350	32,533	ND	ND
Aspartate aminotransferase (U/L)	0–41	46	33	16
Alanine aminotransferase (U/L)	3–63	60	56	32
γ-Glutamyltransferase (U/L)	0–55	108	112	ND
Lactate dehydrogenase (U/L)	0–248	302	195	ND
C-reactive protein (mg/dL)	0–0.8	5.5	ND	ND

High-titre antibodies to platelet factor 4 (PF4)–polyanion complexes were identified (optical density 2.21, negative <0.4) by enzyme-linked immunosorbent assay (ELISA; Lifecodes PF4-Immucor-USA), whereas the rapid immunological chemiluminescence assay (HemosIL AcuStar HIT-IgG, Werfen-Bedford-USA) was negative, in agreement with the known pattern of VITT-associated anti-PF4-antibody positivity. A heparin-induced platelet aggregation assay was also performed but resulted negative. Serological tests for human immunodeficiency virus, hepatitis B and C viruses, TORCH screen, lupus anticoagulant, anticardiolipin and anti β_2-glycoprotein antibodies were all negative. Blood levels of C and S proteins, and C3 and C4 complement fractions were within normal ranges.

Reduced-dose parenteral anticoagulation with fondaparinux was started on day 4, when platelet count reached 20,000/mm^3, and direct oral anticoagulation was started on day 6 when platelet count exceeded 50,000/mm^3. On day 16, a Doppler ultrasound showed recanalization of lower limb proximal veins, but IVF retrieval was postponed due to the presence of thrombosis of the caval vein filter. The patient was eventually discharged in good clinical condition under direct anticoagulants; levels of platelets, fibrinogen and LDH had returned to normal ranges.

This report describes a case of severe thrombocytopenia and venous thromboembolism occurring 13 days after administration of the single-dose Janssen COVID-19 vaccine. To the best of the authors' knowledge, this is the first case of VITT associated with the Ad26.COV2.S vaccine described in Italy.

On 4 April 2021, the European Medicines Agency Safety Committee provided a systematic assessment of thromboembolic events associated with thrombocytopenia following administration of the ChAdOx1 nCoV-19 viral vector-based vaccine (Vaxzevria, AstraZeneca, University of Oxford, and Serum Institute of India). In total, 169 cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis were reported to EudraVigilance, leading to the conclusion that a causal relationship between vaccination with Vaxzevria and thromboembolic events with thrombocytopenia was at least a reasonable possibility. Later, given that six cases of CVST with thrombocytopenia were also identified in the USA among recipients of approximately 7 million doses of the Janssen vaccine, the US Food and Drug Administration and the Centers for Disease Control and Prevention suggested temporary pausing of the administration of Janssen vaccine to allow further investigation (US Food and Drug Administration, 2021).

VITT has been mainly reported among females aged <55 years, and between 4 and 16 days after receiving adenoviral vector-based vaccines, although exceptions exist, such as cases observed in males, in subjects up to 77 years old, and occurring from 2 to 28 days after vaccination (Gresele et al., 2021a). Its pathogenesis is still unclear and under investigation, but many reports highlight similarities with autoimmune heparin-induced thrombocytopenia (HIT), tracking a continuum between different platelet-activating anti-PF4/heparin disorders. Autoimmune HIT is a form of HIT without any previous exposure to heparin. Possible roles of the adenoviral vector platform and/or of free nucleic acids in development of the autoimmune response have been suggested (Gresele et al., 2021a). McGonagle et al. (2021) suggested that local tissue microtrauma following vaccine inoculation brings adenoviral DNA into contact with PF4, thus increasing anti-PF4 autoantibody production in susceptible subjects. Other hypotheses related the syndrome to the adenoviral vector platform carrying a message from an RNA virus, with consequent random splicing of the DNA message producing unwanted circulating soluble Spike protein (Gresele et al., 2021a).

Venous thrombosis in VITT typically occurs in unusual sites, including cerebral, splanchnic (splenic, portal, mesenteric, adrenal) and ophthalmic veins. Anticoagulation is a cornerstone of HIT-related thrombosis but is prevented by severe thrombocytopenia and disseminated intravascular coagulation. Full-dose anticoagulants should be administered as soon as possible in patients with VITT, provided that concurrent thrombocytopenia is corrected (Gresele et al., 2021b). To this end, administration of IVIg, or plasma exchange in severe/refractory cases, is critical to interrupt the immune-mediated mechanisms causing VITT, and to obtain a fast increase in platelet count that, in turn, allows full-dose anticoagulants to be administered safely in a timely manner (Gresele et al., 2021b). In the case patient, a fast satisfactory response to treatment with high-dose corticosteroids and IVIg was obtained in terms of platelet count, allowing full-dose anticoagulation to be applied with resolution of the acute clinical picture. Despite the paucity of data on optimal anticoagulant treatment of VITT, principles of guidance are based on the use of non-heparin-based anticoagulants (e.g. fondaparinux, argatroban), and switching to direct oral anticoagulants when the platelet count reaches 50,000/mm^3 (International Society on Thrombosis and Haemostasis, 2021).

Two positive assays are conventionally required to confirm suspected VITT: a quantitative ELISA assay, which detects and quantifies anti-PF4 antibodies; and a functional assay, which assesses the ability of anti-PF4-heparin antibodies to bind and activate platelets in the presence of heparin. However, the simultaneous administration of IVIg could mask their functional ability to activate platelets (Bourguignon et al., 2021). This may also be of importance because if VITT is suspected, as it was in the study case, blood samples for diagnostic confirmation should be collected prior to any treatment to improve diagnostic performance. When treatment has to be started as soon as possible and immunoassay tests are not rapidly available, D-dimer levels may guide clinical management (Zazzeron et al., 2021).

Many questions related to VITT remain unanswered: (1) What are the viral-vector vaccine components responsible for VITT? (2) What are the molecular mechanisms behind the heterogeneity of results of anti-PF4 functional assays? (3) Is it possible to screen for populations susceptible to VITT? (4) Do vaccinated people with VITT develop more severe symptoms after re-exposure to severe acute respiratory syndrome coronavirus-2? Further studies are needed to answer these important and urgent questions.

Conflict of interest statement

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Author contributions

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