Journal of Thrombosis and Thrombolysis (2022) 53:954–958
https://doi.org/10.1007/s11239-021-02604-2

Eltrombopag for refractory vaccine-induced immune thrombotic thrombocytopenia

Giorgio Maraziti[1] · **Cecilia Becattini**[1]

Accepted: 31 October 2021 / Published online: 19 November 2021

Abstract
Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a life-threatening complication described after administration of recombinant adenoviral vector encoding the spike protein antigen of Severe Acute Respiratory Syndrome CoronaVirus-2. The syndrome is characterized by platelet consumption and thrombosis. High levels of antibodies to platelet factor 4 (PF4)–polyanion complexes were identified in many patients with VITT by enzyme-linked immunosorbent assay (ELISA). A 64-year-old woman presented with thrombocytopenia, right renal vein thrombosis with renal infarction, right intra-right atrium and intra-right ventricle thrombosis and pulmonary embolism after ChAdOx1-S vaccine administration. ELISA for antibodies to PF4–polyanion complexes tested positive, while functional tests were not. Thrombocytopenia was refractory to intravenous immunoglobulins and corticosteroids. Eltrombopag was introduced and platelet gradually rose to normal values. VITT is a novel complication yet to be understood. The clinical case we reported highlights the difficulties in the management of this disorder and discloses a new potential therapy in refractory conditions.

Keywords SARS-CoV-2 · COVID-19 · Vaccines · Thrombosis · Thrombocytopenia

Highlights

- Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a severe complication described after the administration of recombinant adenoviral vector encoding the spike protein antigen of Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2).
- We describe a case of VITT associated with ChAdOx1-S vaccine in a 64-year-old woman presenting with thrombocytopenia, right renal vein thrombosis with renal infarction, intra-right atrial and intra-right ventricular thrombosis and pulmonary embolism.
- Thrombocytopenia was refractory to intravenous immunoglobulins and corticosteroid therapy. After the introduction of eltrombopag, platelet count gradually rose to normal values without complications.
- VITT is a potentially life-threatening complication due to vaccine administration yet to be understood. Eltrombopag may be a new potential therapy in refractory conditions.

Brief communication

Pandemic caused by Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) moved the development of highly effective vaccines to obtain infection control and potentially reduce related mortality. Initial trials on efficacy and safety of vaccines included tens of thousands of individuals and reported no major safety warnings. As for nowadays, after global vaccination, rates of serious adverse effects remained remarkably low. [1] From February 2021 independent reports detailed a life-threatening syndrome characterized by thrombosis, mainly in atypical locations, and thrombocytopenia occurring in healthy individuals within weeks from vaccination with the adenoviral-based ChAdOx1-S vaccine. [2–4] Subsequently, a similar syndrome was described with Ad26.COV2.S, a recombinant chimpanzee adenoviral vector vaccine. [5, 6] Many of these described events led to death, some due to ischemic brain

✉ Giorgio Maraziti
marazitigiorgio@gmail.com

[1] Internal and Cardiovascular Medicine—Stroke Unit, University of Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy

injury, other to superimposed haemorrhage, or both conditions, often despite anticoagulation.

This new syndrome, sharing similar findings with autoimmune heparin-induced thrombocytopenia (HIT), was named vaccine-induced immune thrombotic thrombocytopenia (VITT). [7] In fact, as for HIT, high levels of antibodies to platelet factor 4 (PF4)–polyanion complexes were identified in many patients with VITT by enzyme-linked immunosorbent assay (ELISA), as well by assays based on platelet activation, which, when tested, was enhanced by the addition of PF4. [2–6, 8] In contrast to HIT, the binding of antibodies to PF4 occurred in the absence of heparin. However, conflicting data have been reported on rates of positivity in functional platelet assays, in particular in standard platelet activation assays for the detection of HIT antibodies [9].

Intravenous immunoglobulins (IVIG) and high-dose glucocorticoids have been suggested to improve platelet count within days [2]. Although the condition of several patients apparently improved when they were given low-molecular-weight heparin, choosing non-heparin antithrombotic agents as in the case of HIT is generally preferred.

Immune thrombocytopenia (ITP) is another autoimmune platelet disorder that was reported in association with the two messenger RNA (mRNA)-based anti-SARS-CoV-2 vaccines. [10] It is characterized by an abnormally low number of circulating platelets which promotes purpura, petechiae and bleeding episodes, whose seriousness depends on the location. The first line of treatment consists, as for VITT, mainly in corticosteroid and IVIG therapy. [11–13] For the second line of therapy, eltrombopag, an agonist of the so-called TPO receptor (TPO-R), was found to be effective, safe and well-tolerated and it is being increasingly used for ITP patients instead of other treatments or more aggressive procedures like splenectomy. [14–18]

We report a case of VITT associated with ChAdOx1-S vaccine, refractory to corticosteroid and IVIG therapy, with a successful response after eltrombopag therapy introduction.

A 64-year-old woman presented to the emergency department with headache 21 days after vaccination with ChAdOx1 nCoV-19. She was on chronic treatment for systemic arterial hypertension and had pacemaker implantation due to advanced atrial-ventricular block two years before. At emergency department admission, moderate thrombocytopenia (56,000/mm^3) was diagnosed that was not present on a recent blood count performed one month before vaccination (175,000/mm^3) (Fig. 1). Due to elevated blood pressure values, she received a diagnosis of uncontrolled hypertension and was discharged. The patient returned to the emergency department 22 days later for right flank pain. Computed Tomography (CT) showed right renal vein thrombosis with renal infarction, bilateral pulmonary embolism, and right intra-right atrial and intra-right ventricular thrombosis. Transoesophageal echocardiography (TEE) confirmed the presence of thrombi of the right atrial and ventricular pacemaker catheters (Fig. 2).

Blood count showed moderate thrombocytopenia (54,000/mm^3), and she tested positive for antibodies to PF4–polyanion complexes identified by ELISA with negative functional tests. The patient had evidence of disseminated intravascular coagulation, including elevated d-dimer levels, low fibrinogen levels and a mildly increased

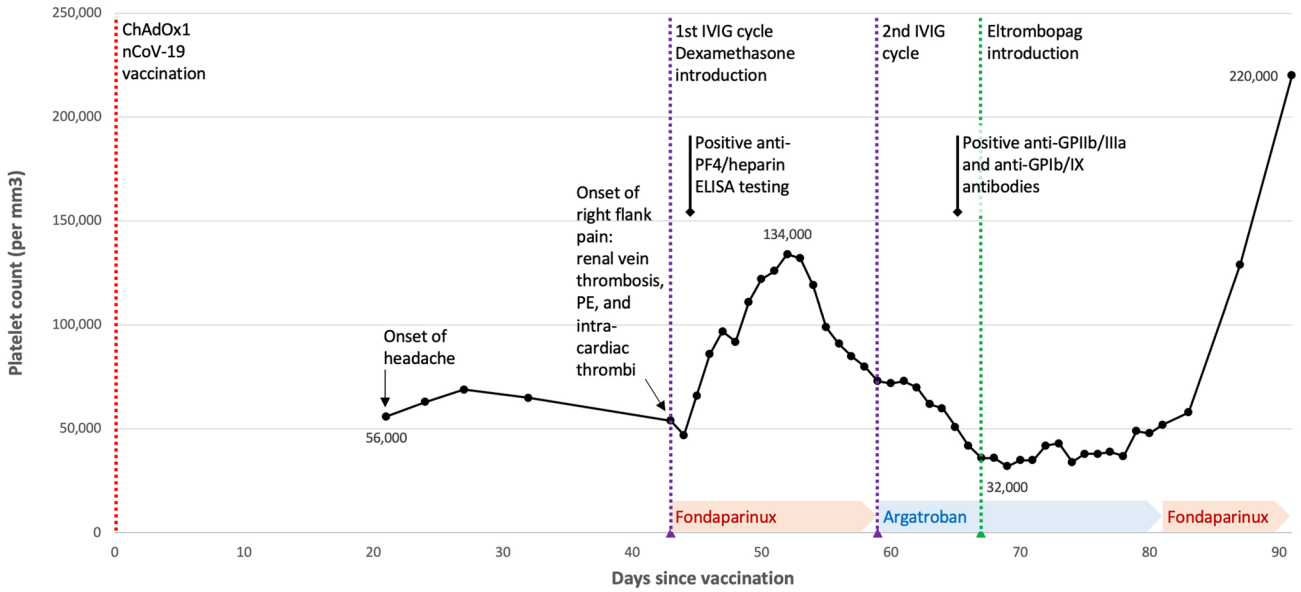

Fig. 1 Longitudinal platelet count variation and administered treatments. *PE* pulmonary embolism; *IVIG* intravenous immunoglobulins; *PF4* platelet factor 4; *ELISA* enzyme-linked immunosorbent assay

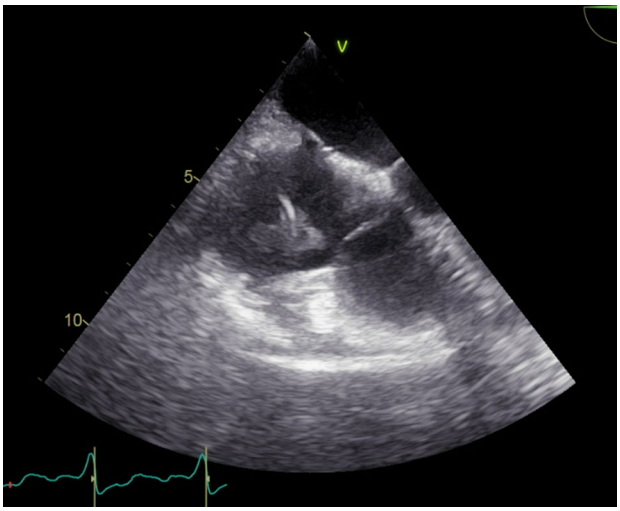

Fig. 2 Thrombosis on pacemakers catheters in the right heart sections

international normalized ratio. No other relevant laboratory tests were positive, including tests for thrombophilia, antinuclear antibodies, extractable nuclear antigen, ADAMTS13 levels, lupus anticoagulant and anticardiolipin antibodies.

The patient was treated with dexamethasone (40 mg per day), IVIG (1 g/kg for 4 days) and fondaparinux (5 mg per day then 7.5 mg per day) with a good response in terms of platelet count (up to 134,000/mm^3). Due to recurrence of thrombocytopenia at day 12 after IVIG, at a platelet count of 59,000/mm^3 a second cycle of IVIG was administered (1 g/kg for 4 days), and fondaparinux was substituted with argatroban by continuous infusion. A second CT scan showed a reduction of the filling defects in the pulmonary arteries and the right renal vein. Persistence of the intra-right atrial and intra-right ventricular thrombi was observed at a control TEE. The patient was then transferred to our Department.

At arrival in our Department, the patient had good general clinical conditions and in the absence of bleeding complications or new thromboembolic events. The platelet count was 51,000/mm^3 and progressively decreased during the following days. Therapy with methylprednisolone 1 g per day was administered for two days, but it was halted as soon as two blood cultures tested positive for Methicillin-resistant Staphylococcus aureus (MRSA). Antibiotic therapy with daptomycin 700 mg per day was introduced. In addition, a urine culture tested positive for Escherichia coli (colony-forming units > 100,000/ml) that was treated with ciprofloxacin 750 mg per day. A third TEE confirmed the persistence of thrombi adherent to pacemaker catheters in the right atrium and ventricle in the absence of valvular vegetations. At this stage, anti-GPIIb/IIIa and anti-GPIb/IX antiplatelet antibodies were tested and found transiently positive. ELISA test for antibodies to PF4–polyanion complexes was repeated with positive results, while functional tests were constantly negative. Due to the persistent decrease of platelet count (up to 32.000/mm^3) and the need to ensure adequate levels for optimal anticoagulation, therapy with eltrombopag was introduced (50 mg per day and then 75 mg per day).

In the following days, platelet count remained initially stable and then started to increase gradually. At about two weeks after the introduction of eltrombopag, the platelet count reached 52,000/mm^3. Argatroban was withdrawn and substituted with fondaparinux (up to 5 mg per day). Dexamethasone dosage reduction was started. The patient opted for an outpatient follow-up and was discharged 18 days from admission. At 19 days from eltrombopag introduction, platelet count was 120,000/mm^3, so fondaparinux was increased at 7.5 mg per day. Subsequent control at 24 days from introduction showed a platelet count of 220,000/mm^3.

Our reported clinical case has some unclear aspects. Despite a positive test for antibodies to PF4–polyanion complexes identified by ELISA, patient serum obtained before IVIG administration showed negative reaction patterns on functional HIT assay. Nevertheless, other studies on VITT reported low rates of positivity for these tests. [9] At some point, we hypothesized that the persistence of thrombocytopenia could be related to an unrecognized infection. However, thrombocytopenia didn't regress after targeted antibiotic therapy for E. coli urinary tract infection and MRSA blood culture positivity. Besides, after IVIG treatment, we found a positivity of anti-GPIIb/IIIa and anti-GPIb/IX antiplatelet antibodies. This finding was confusing in this particular clinical context, and one explanation might be a false-positive result after the recent administration of IVIG therapy. This test was repeated after a week from discharge with a negative result. Although the complexity of the case and laboratory results, diagnosis of VITT was considered more likely in relation to the recent vaccination and due to the severe thrombotic manifestations in the absence of haemorrhagic events. Finally, concerning the potential risk of thrombosis with eltrombopag, we considered that this occurrence could be balanced by ensuring optimal anticoagulant therapy through the achievement of adequate platelet counts. In fact, data about determinants of thromboembolic risk associated with TPO-R agonist's therapy are lacking, but no thromboembolic events were reported in the major trials that studied eltrombopag in ITP while few of these complications were described in the long-term treatment [14–17, 19, 20]. On the other hand, VITT was found to be a life-threatening condition for which proper anticoagulant therapy is needed, especially in a case with a high thromboembolic burden. [2–4]

The prompt global administration of vaccines against SARS-CoV-2 has inevitably resulted in reducing the spreading of the infection. However, reports of adverse events potentially associated with vaccine administration have

been released. [1] In particular, VITT has been reported as a severe complication of recombinant adenoviral vectors encoding the spike protein antigen of SARS-CoV-2. [2, 3, 5, 9] This syndrome is characterized by a combination of clinical and laboratory features, while its pathogenesis and optimal management are still unclear. Currently, several VITT treatment guidelines recommend the administration of IVIG and/or high-dose glucocorticoids to improve the platelet count within days, contemplating plasma exchange and mechanical thrombectomy as second-line therapies. [21–23]

Successful use of eltrombopag to treat refractory VITT, as described in our patient, is a novel finding. Since patients with VITT can have severe thrombocytopenia that potentially impedes optimal anticoagulation, early administration of eltrombopag in cases refractory to first-line therapy may be an important adjunct therapy for their management instead of other treatments or more aggressive procedures. Results from clinical trials and clinical practice in the clinical context of ITP suggest that this drug is effective, well-tolerated and substantially safe to restore platelet counts.

The clinical case we reported highlights the difficulties in the diagnosis and management of VITT and disclosed a new potential therapy in refractory conditions.

Acknowledgements None.

Authors' contributions GM was responsible for conceiving the idea and drafting of the manuscript. CB was responsible for drafting and critical revision of the manuscript. Both authors contributed to literature search and in the approval of final manuscript.

Funding None.

Data availability All data of the clinical case are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Conflict of interest All authors declare absence of any real or potential conflicts of interest related to this case.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication Informed consent for publication of data was obtained from the patient.

References

1. WHO Coronavirus (COVID-19) Dashboard. Geneva: World Health Organization (https://covid19.who.int/).
2. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S (2021) Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 384:2092–2101
3. Schultz NH, Sørvoll IH, Michelsen AE et al (2021) Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 384:2124–2130
4. Scully M, Singh D, Lown R et al (2021) Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 384:2202–2211
5. Centers for Disease Control and Prevention Emergency Preparedness and Response. Johnson & Johnson/Janssen COVID-19 vaccine and thrombosis with thrombocytopenia syndrome (TTS): update for clinicians. https://emergency.cdc.gov/coca/calls/2021/callinfo_0427
6. Sadoff J, Davis K, Douoguih M (2021) Thrombotic thrombocytopenia after Ad26.COV2.S vaccination—response from the manufacturer. N Engl J Med. 384(20):1965–1966
7. Greinacher A, Selleng K, Warkentin TE (2017) Autoimmune heparin- induced thrombocytopenia. J Thromb Haemost 15:2099–2114
8. Pavord S, Scully M, Hunt BJ et al (2021) Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. N Engl J Med. https://doi.org/10.1056/NEJMoa2109908
9. See I, Su JR, Lale A et al (2021) US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26COV2S vaccination, March 2 to April. JAMA. 325(24):2448–2456
10. Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N (2021) Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccine. https://doi.org/10.1016/j.vaccine.2021.04.054
11. Lambert MP, Gernsheimer TB (2017) Clinical updates in adult immune thrombocytopenia. Blood 129:2829–2835
12. Matschke J, Müller-Beissenhirtz H, Novotny J et al (2016) A Randomized trial of daily prednisoneversus pulsed dexamethasone in treatment-naïve adult patients with immune thrombocytopenia: EIS 2002 study. Acta Haematol 136:101–107
13. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA, American Society of Hematology (2011) The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 117:4190–4207
14. Bussel JB, Cheng G, Saleh MN et al (2007) Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 357:2237–2247
15. Bussel J, Provan D, Shamsi T et al (2009) Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet 373:641–648
16. Cheng G, Saleh MN, Marcher C et al (2011) Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 377:393–402
17. Bussel JB, Saleh MN, Vasey SY, Mayer B, Arning M, Stone NL (2013) Repeated short-term use of eltrombopag in patients with chronic immune thrombocytopenia (ITP). Br J Haematol 160:538–546
18. Saleh MN, Bussel JB, Cheng G et al (2013) EXTEND Study Group. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood 121:537–545
19. Wong RSM, Saleh MN, Khelif A et al (2017) Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood. 130(23):2527–2536
20. Swan D, Newland A, Rodegheiro F, Thachil J (2021) Thrombosis in immune thrombocytopenia - current status and future perspectives. Br J Haematol 194(5):822–834

21. COVID-19 rapid guideline: vaccine-induced immune thrombocytopenia and thrombosis (VITT). London: National Institute for Health and Care Excellence (NICE); 2021 Jul 29. PMID: 34406720
22. Vaccine-induced thrombotic Thrombocytopenia (VITT) and COVID-19 Vaccines: WHAT Cardiovascular clinicians need to know. American College of Cardiology. (2021, June 8), https://www.acc.org/latest-in-cardiology/articles/2021/04/01/01/42/vaccine-induced-thrombotic-thrombocytopenia-vitt-and-covid-19-vaccines
23. Furie KL, Cushman M, Elkind MSV, Lyden PD, Saposnik G, American Heart Association/American Stroke Association Stroke Council Leadership (2021) Diagnosis and management of cerebral venous sinus thrombosis with vaccine-induced immune thrombotic thrombocytopenia. Stroke. 52(7):2478–2482