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CASE REPORT

Refractory vaccine-induced immune thrombotic thrombocytopenia (VITT) managed with delayed therapeutic plasma exchange (TPE)

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Abstract

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a newly described hematologic disorder, which presents as acute thrombocytopenia and thrombosis after administration of the ChAdOx1 nCov-19 (AstraZeneca) and Ad26.COV2.S (Johnson & Johnson) adenovirus-based vaccines against COVID-19. Due to positive assays for antibodies against platelet factor 4 (PF4), VITT is managed similarly to autoimmune heparin-induced thrombocytopenia (HIT) with intravenous immunoglobulin (IVIG) and non-heparin anticoagulation. We describe a case of VITT in a 50-year-old man with antecedent alcoholic cirrhosis who presented with platelets of $7 \times 10^3/\mu L$ and portal vein thrombosis 21 days following administration of the Ad26.COV2.S COVID-19 vaccine. The patient developed progressive thrombosis and persistent severe thrombocytopenia despite IVIG, rituximab and high-dose steroids and had persistent anti-PF4 antibodies over 30 days after his initial presentation. As such, delayed therapeutic plasma exchange (TPE) was pursued on day 32 of admission as salvage therapy, with a sustained improvement in his platelet count. Our case serves as proof-of-concept of the efficacy of TPE in VITT.

KEYWORDS

coronavirus, platelet factor, thrombocytopenia, thrombosis, vaccines

1 | INTRODUCTION

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a newly described prothrombotic state identified in a small subset of patients following administration of the ChAdOx1 nCov-19 (AstraZeneca)[1-3] and Ad26.COV2.S (Johnson & Johnson)[4,5] adenovirus-based vaccines against COVID-19, with a case report of possible VITT after the messenger RNA-1273 (Moderna) vaccine.[6] Most patients affected by VITT present within 30 days of vaccination with acute thrombocytopenia and thrombosis, including unusual thromboses such as cerebral sinus venous thrombosis and splanchnic thrombosis, in addition to extremely high D-dimer levels.[7]

In early case series of VITT, nearly all patients exhibited strongly positive enzyme-linked immunosorbent assays

Abbreviations: COVID-19, Coronavirus Disease 2019; CT, computed tomography; ELISA, enzyme-linked immunosorbent assays; HIPA, heparin-induced platelet aggregation assay; HIT, heparin-induced thrombocytopenia; IVIG, intravenous immunoglobulin; PEA, PF4-dependent p-selectin expression assay; PF4, platelet factor 4; SRA, serotonin release assay; TIPS, transjugular intrahepatic portosystemic shunt; TPE, therapeutic plasma exchange; VITT, vaccine-induced immune thrombotic thrombocytopenia.

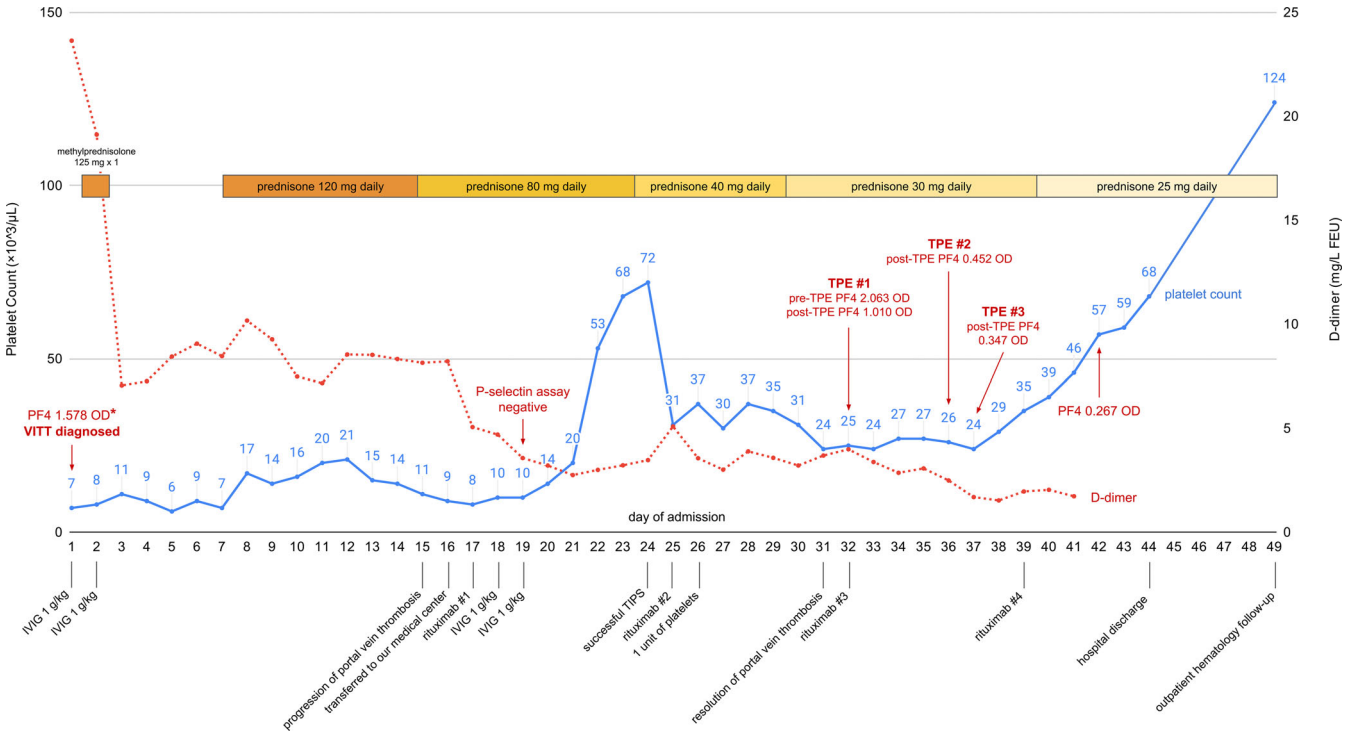

FIGURE 1 Platelet and D-dimer trend over the patient's hospital course, including all VITT testing and treatments. PF4 indicates anti-PF4/polyanion antibody ELISA testing. The asterisk indicates PF4/polyanion antibody ELISA testing performed at the outside hospital with an IgG-specific assay, whereas assays performed at our institution were performed with a polyspecific IgG/IgA/IgM assay; as such, the optical density (OD) cannot be compared between these assays

(ELISA) for antibodies against platelet factor 4 (PF4).[1-3] Given the combination of thrombosis, thrombocytopenia, and PF4 ELISA positivity in VITT patients, the disease resembles autoimmune heparin-induced thrombocytopenia (HIT).[8] As such, the management of VITT currently mirrors the treatment paradigm of autoimmune HIT, with empiric initiation of non-heparin anticoagulation as well as intravenous immunoglobulin (IVIG).[9-12] Some consensus guidelines discuss that therapeutic plasma exchange (TPE) may be utilized for severe VITT, although the role of TPE in HIT is controversial.[10,13]

We present a case of VITT associated with the Ad26.COV2.S vaccine that was refractory to multiple doses of IVIG, rituximab and high-dose steroids, and which was successfully managed with delayed TPE over 30 days after initial presentation. This case serves as a proof-of-concept that TPE may be used to remove anti-PF4 antibodies from the plasma compartment to improve the platelet count in refractory disease.

2 | CASE REPORT

A 50-year-old man with alcoholic cirrhosis and obesity presented to a local hospital with 1 week of abdominal pain and distention, fatigue, and dark urine. In the emergency department, initial laboratory testing revealed platelets of $7 \times 10^3/\mu L$, white blood cell count $9.5 \times 10^3/\mu L$, hemoglobin 15.7 g/dL, INR 2.0, creatinine 1.1 mg/dL, total bilirubin 2.2 mg/dL, AST 235 U/L, and ALT 198 U/L. D-dimer was elevated at 23.64 mg/L FEU (upper limit of normal 0.49 mg/L FEU) and fibrinogen was normal at 211 mg/dL. Computed tomography (CT) imaging revealed cirrhotic liver disease and possible thrombi in the portal and hepatic veins. He did not have recent heparin exposure. His baseline platelet count was 113-161 $\times 10^3/\mu L$ in the 6 months prior to admission. He had received the single-dose Ad26.COV2.S COVID-19 vaccine 21 days prior to presentation. Abdominal ultrasonography confirmed complete thrombosis of the right portal vein and partial thrombus in the main portal vein. IgG-specific PF4/polyanion antibody ELISA testing (LIFECODES, Immucor) was positive at 1.578 OD. The patient was formally diagnosed with VITT and began treatment with therapeutic argatroban and IVIG 1 g/kg on the day of presentation.

The patient's platelet trend, D-dimer trend, and VITT treatments over his hospital course are depicted in Figure 1. The patient initially received IVIG 1 g/kg daily for 2 days by ideal body weight and methylprednisolone

125 mg on the first day. Due to persistent thrombocytopenia, oral prednisone was initiated on day 7 with a prolonged taper, with a transient increase in his platelet count to 21 $\times$ 10^3/μL by day 12. Repeat abdominal Doppler ultrasound on day 15 revealed progression of his portal vein thrombosis despite therapeutic argatroban.

On day 16, the patient was transferred to our medical center and was switched to intravenous bivalirudin due to worsening liver dysfunction. ADAMTS13 testing confirmed normal activity. Due to worsening thrombocytopenia to 9 $\times$ 10^3/μL, the patient received rituximab 375 mg/m2 on day 17, followed by two additional doses of IVIG 1 g/kg. A PF4-dependent P-selectin expression assay (PEA, Versiti, Inc.) was performed on day 19 and was negative, with 8% activity with 30 mcg of PF4 and 0% activity with 30 mcg of PF4 and 100 U of heparin. The patient had a transient response to IVIG, with a maximum platelet count of 72 $\times$ 10^3/μL on day 24. On day 24, the patient underwent a transjugular intrahepatic portosystemic shunt (TIPS) procedure, with successful recanalization of the portal vein.

As shown in Figure 1, the patient's platelet count continued to downtrend after day 24. A single unit of platelets was given on day 26 and was ineffective in producing a platelet increment on a post-transfusion complete blood count, subsequently reaching a nadir of 24 $\times$ 10^3/μL on day 31. Repeat abdominal CT on day 31 demonstrated an intact TIPS with complete resolution of the portal vein thrombosis. With no other apparent causes of persistent thrombocytopenia, refractory VITT was considered and a repeat anti-PF4/polyanion ELISA (polyspecific IgG/IgA/IgM, LIFECODES, Immucor) on day 32 was positive at 2.063 OD. The decision was made to pursue TPE, which was performed using the Spectra Optia (TerumoBCT) instrument via internal jugular dialysis catheter. In each TPE, 6.0 L of plasma (equivalent to ~1.1 times total plasma volume) was exchanged using 100% donor plasma as replacement fluid.

After the first TPE on day 32, PF4 ELISA was reduced to 1.010 OD. Given persistent thrombocytopenia, the decision was made to pursue serial TPE until the PF4 became negative. As shown in Figure 1, the PF4 decreased to 0.452 OD after the second TPE on day 36, and then decreased to negative at 0.347 OD after the third TPE on day 37.

The patient's platelet count improved after three TPE procedures, with a platelet count rising to 57 $\times$ 10^3/μL by day 42 (Figure 1). Repeat PF4 ELISA on day 42 continued to be negative at 0.267 OD. The patient's clinical status continued to improve and he was switched to subcutaneous fondaparinux and discharged from the hospital on day 44 with a platelet count of 68 $\times$ 10^3/μL. At outpatient hematology follow-up on day 49 after presentation, the patient's platelet count had recovered to his baseline of 124 $\times$ 10^3/μL. The platelet count was sustained at 109 $\times$ 10^3/μL on day 56 and 105 $\times$ 10^3/μL on day 63 after presentation.

3 | DISCUSSION

VITT is a novel and rare hematologic disease associated with specific adenovirus-based COVID-19 vaccines, namely the ChAdOx1 nCov-19 (AstraZeneca)[1-3] and Ad26.COV2.S (Johnson & Johnson)[4,5] vaccines, with emerging reports of possible VITT after the messenger RNA-1273 (Moderna) vaccine.[6] The pathophysiology of VITT is favored to mimic that of autoimmune HIT,[2,8] although the exact mechanism and optimal management of VITT is currently unknown. In this case, typical therapies for HIT were unsuccessful in halting progressive thrombosis and thrombocytopenia, necessitating TPE as salvage therapy.

Despite immediate initiation of IVIG, argatroban and high-dose steroids as recommended by consensus guidelines,[9,10] the patient developed progressive portal vein thrombosis and persistent severe thrombocytopenia <30 $\times$ 10^3/μL, with a persistently positive PF4 ELISA on day 32 suggestive of refractory VITT. The finding of a negative PEA on day 19 of admission was initially reassuring for resolution of VITT, as confirmatory testing using functional platelet activation assays are frequently positive in VITT.[1-3,14] In retrospect, the negative PEA assay at day 19 may have been due to temporary effects of initial IVIG and steroid treatment on circulating functional antibodies. Additionally, we cannot rule out that the patient always had a VITT anti-PF4 autoantibody that was undetectable by PEA; occasional VITT cases with negative functional studies have been previously described.[15] As shown in Figure 1, three TPE procedures were sufficient to revert the PF4 ELISA to negativity and to increase the platelet count. Further, the D-dimer level, which significantly decreased with initial therapy but had been relatively stable and elevated since day 19, also rapidly decreased with TPE. D-dimer levels have been described as a potential biomarker for resolution of VITT, as normalization of the platelet count is not necessarily reliable.[16] It is plausible in this case that platelet recovery was due to a combination of TPE, effects of weekly rituximab, and post-TIPS normalization of portal pressures. However, the temporal association with the apparent TPE-dependent decrease in the PF4 ELISA with each subsequent TPE procedure does suggest a meaningful contribution of TPE to platelet recovery.

TPE has been proposed as a potential salvage therapy for VITT for the removal of pathogenic anti-PF4

antibodies,[17] and initial case reports described the use of TPE in VITT associated with the ChAdOx1 nCoV-19 vaccine[18] as well as the mRNA-1273 vaccine,[6] although patients in both of these cases were critically-ill at the time of TPE and subsequently died. Further descriptions of the role of TPE in VITT include a landmark case series of three patients with VITT due to the ChAdOx1 nCoV-19 vaccine, in which all patients immediately received IVIG, non-heparin anticoagulation, and steroids, as was done in our case.[16] However, all three patients began salvage TPE within the first 6 days of admission, and all experienced a gradual but sustained increase in the platelet count; further, all three patients survived. Unlike our case, PF4 ELISAs did not become negative after TPE in this case series; this may be due to the extensive administration of rituximab, IVIG and steroids prior to TPE in our case, the use of a different PF4 assay or timing of PF4 assessment relative to TPE, or a currently-unknown difference in the response of VITT to TPE between different vaccines. A larger cohort of 220 patients with presumed VITT due to the ChAdOx1 nCoV-19 vaccine described a mortality rate of 22% due to VITT, although survival was 90% for the 17 patients in the cohort who received TPE, most of whom had more severe disease presentations.[7]

Given the delayed use of TPE with our patient, this case is proof-of-concept that TPE can be safe and effective in the setting of refractoriness to IVIG and high-dose steroids, which are often initiated early and simultaneously in the disease course. Further, our case demonstrates the efficacy of TPE in VITT associated with the Ad26.COV2.S vaccine. Based on our experience and other emerging reports, in patients with documented VITT, there should be a low threshold for initiation of TPE if refractory thrombocytopenia or progressive thrombosis is present after 5 days of other typical therapies for HIT, or sooner in more severe presentations with extensive thromboses or a platelet count $<30 \times 10^3/\mu L$.[7,10,16]

CONFLICT OF INTEREST

G. D. W. receives honoraria from Diagnostica Stago (Parsippany, NJ). The other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Ajay Major conceptualized and wrote the manuscript, performed data analysis and interpretation, and provided final approval of the manuscript. Timothy Carll performed data analysis and interpretation, provided critical revision of the intellectual content, and provided final approval of the manuscript. Clarence W. Chan performed data analysis and interpretation, provided critical revision of the intellectual content, and provided final approval of the manuscript. Chancey Christenson performed data analysis and interpretation, provided critical revision of the intellectual content, and provided final approval of the manuscript. Fatima Aldarweesh performed data analysis and interpretation, provided critical revision of the intellectual content, and provided final approval of the manuscript. Geoffrey D. Wool performed data analysis and interpretation, provided critical revision of the intellectual content, and provided final approval of the manuscript. Kenneth S. Cohen performed data analysis and interpretation, provided critical revision of the intellectual content, and provided final approval of the manuscript.

DATA AVAILABILITY STATEMENT

The authors declare that data supporting the findings of this study are available within the article.

INFORMED CONSENT

Informed consent for the publication of this case report was obtained from the patient.

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