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SHORT COMMUNICATION

A case series of vaccine-induced thrombotic thrombocytopenia in a London teaching hospital

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The ChAdOx1 nCoV-19 vaccine has been associated with increased risk of thrombosis. Understanding of the management of these rare events is evolving, and currently recommended treatments include human normal immunoglobulin and nonheparin anticoagulation such as direct oral anticoagulants. Our report describes three consecutive patients presenting to a London teaching hospital with vaccine-induced thrombotic thrombocytopenia (VITT), also referred to as vaccine-induced prothrombotic immune thrombocytopenia. The patients ranged in age from 40 to 54 years and two had no known previous medical comorbidities. Two patients had cerebral venous sinus thrombosis and one had a deep vein thrombosis. Two were treated with anticoagulation, one with oral rivaroxaban and the other with an intravenous argotraban infusion that was later converted to oral apixaban. One patient received three doses of human normal immunoglobulin and 5 days of therapeutic plasma exchange. This case series may be used to improve understanding of the clinical course and management of VITT.

KEYWORDS
anticoagulants, drug utilisation, evidence-based medicine, vaccines, virology

1 | INTRODUCTION

The ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca) is a replication-deficient chimpanzee adenovirus vector vaccine with a recombinant spike protein of the SARS-CoV-2 virus.[1] Internationally, it is the most widely approved vaccine against coronavirus disease 2019 (Covid-19).[2] In March 2021, the European Medicines Agency announced findings of a rare thrombotic syndrome temporally associated with the vaccine, termed vaccine-induced immune thrombotic thrombocytopenia (VITT) or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). The report described 18 cases of cerebral venous sinus thrombosis and seven cases of thrombosis at multiple sites.[3,4] Based on reports submitted to the UK medicines regulator after approximately 24.7 million first doses of the ChAdOx1 nCoV-19 vaccine, the incidence of VITT has since been estimated at 14.8 per million first or unknown doses.[5] During the initial phase 3 trial of the vaccine, one case of cerebral venous sinus thrombosis was noted in a 25-year-old man with no past medical history or regular medications.[6] The pathogenesis of these thrombotic events is still under investigation but involves IgG antibodies that adhere to **platelet factor 4 (PF4)**, resulting in activation of the coagulation cascade.[7] Reports of these clots have led to vaccine administration being paused in some countries, and a withdrawal or caution against use in younger age groups in other countries.[8,9] Understanding of the pathogenesis and management of these blood clots is crucial in the ongoing roll out of the Covid-19 vaccine programme.

Interim guidance from the Expert Haematology Panel states that suspected cases of VITT in the United Kingdom should be reported to the Expert Haematology Panel and Public Health England.[10] Furthermore, all cases of thrombosis and thrombocytopenia that occur within 30 days of COVID-19 vaccination should be reported to the

Principle investigators are Dipender Gill and Isabella Watts. This study did not perform any intervention on human subjects and, as such, no Principal Investigator Statement is required.

Medicines and Healthcare Products Regulatory Agency (MHRA) via the Yellow Card system.[11] Recommended initial investigations include a full blood count and blood film to confirm true thrombocytopenia and a coagulation screen to include both fibrinogen and D-dimer measurements. If these tests are suggestive of VITT, testing to identify antibodies to PF4 to confirm the diagnosis and imaging to confirm thrombosis should be performed. Treatment strategies include anticoagulation with a nonheparin agent, correction of low fibrinogen with cryoprecipitate, consideration of intravenous normal human immunoglobulin (IVIG), steroids, and plasma exchange. The proposed mechanism for the effect of IVIG in VITT is thought to be similar to its effects in heparin-induced thrombocytopenia, where IVIG competitively inhibits the IgG antibodies that adhere to PF4, reducing platelet consumption and activation of the coagulation cascade.[12,13]

In this short report, we describe a series of consecutive patients who presented to a London teaching hospital with thrombosis after receiving a ChAdOx1 nCoV-19 vaccine, all with confirmed anti-PF4 antibodies. We describe their clinical presentation, investigations, and management to contribute to the collective understanding of this condition and its treatment.

What is already known about this subject

- Vaccination with the ChAdOx1 nCoV-19 vaccine has been associated with pathological thrombosis, including cerebral venous sinus thrombosis.
- Strategies to treat these rare events are being investigated and include the use of nonheparin anticoagulation and human normal immunoglobulin.
- Treatment guidelines are still evolving.

What this study adds

- Our study describes the presentation, management and clinical course of three consecutive cases of vaccine-induced prothrombotic immune thrombocytopenia (VITT) following the ChAdOx1 nCoV-19 vaccine.
- The cases included both cerebral venous sinus thrombosis and deep vein thrombosis, and management varied between patients.
- On presentation all patients had low platelet count, raised D-dimer measurement and were anti-PF4-antibody positive.
- These observations may be used to gain insight into the pathophysiology and optimal management of VITT.

2 | METHODS

Data were extracted from hospital electronic records and associated primary care records on 12 July 2021. Included patients presented to St George's Hospital between 1 March 2021 and 12 July 2021 with documented VITT, subsequently confirmed by imaging and presence of anti-PF4 antibodies. Informed consent for use of anonymised data for publication was obtained from the patient if possible, or if not, their next of kin. This work was undertaken as part of an audit to evaluate adherence to currently available expert consensus recommendations on management of VITT.[10] Approval was granted from the hospital audit department, with audit registration number AUDI001000.

Data were obtained from the clinical information system and electronic prescribing system, from the date of admission to either date of discharge or 12 July 2021, whichever was earlier. Data collection was performed by one author (I.W.) and double-checked by a second (D.G.).

3 | RESULTS

3.1 | Three patients with VITT were identified

Patient 1: A 49-year-old man who had his first ChAdOx1 nCoV-19 vaccine dose on 20 April 2021 (day 0). He had no known past medical history and was not taking any regular medications. He developed symptoms of a headache on day 7. On day 13, he awoke with vomiting and attended his local hospital. On presentation, he had new-onset atrial fibrillation and shortly after admission his Glasgow Coma Scale score decreased to 5/15 (subcomponent scores for eye response 1/4, verbal response 1/5, motor response 3/6). Rapid sequence induction of anaesthesia and endotracheal intubation were performed. A computerised tomography (CT) scan of his head showed a subarachnoid haemorrhage with extensive intraventricular extension of blood and early features of hydrocephalus (Figure 1). He was transferred to our centre for specialist neurosurgical management. Blood tests showed a platelet count of 8×10^9/L and D-dimer of >6000 ng/mL. A repeat CT scan later in the day showed extension of the bleed, with tonsillar herniation. CT venography showed left transverse sinus and sigmoid sinus thrombosis. Sadly the patient died on day 14 before the planned treatment with human normal immunoglobulin was started.

Patient 2: This 54-year-old woman had her first ChAdOx1 nCoV-19 vaccine dose on 11 March 2021 (day 0). She had a past medical history of hypertension, for which she was taking oral amlodipine 5 mg daily. On day 6 she developed a headache that lasted for 10 days, and was associated with one spell of vomiting. She then developed symptoms of swelling and pain in her right calf on day 16 and presented to hospital on day 19 with right leg swelling. Her initial platelet count was 90×10^9/L and D-dimer was 4205 ng/mL. An occlusive thrombus in the right popliteal vein was

identified on ultrasonography (Figure 2). She had no known risk factors for deep vein thrombosis. She was managed in ambulatory care with oral rivaroxaban, prescribed initially for at least 3 months (since extended to 6 months following review in the haematology outpatient clinic). After her initial management with anticoagulation she had a magnetic resonance imaging (MRI) scan and venogram of her head, which were both normal.

Patient 3: This 40-year-old woman had the ChAdOx1 nCoV-19 vaccine on 25 May 2021 (day 0). She had no comorbidities and was not on any prior medication. On day 2, she developed headache. On day 14, she presented to hospital with headache and seizures. The initial platelet count was 45×10^9/L and D-dimer was >6000 ng/mL. Acute superior sagittal and cortical vein thrombosis was identified on CT venography (Figure 3). In the emergency department, levetiracetam 2.8 g IV was administered for seizure management. Cryoprecipitate (2 pools), methylprednisolone (1 g IV) and human normal immunoglobulin (70 g IV, 1 g/kg, based on initially estimated body weight 70 kg) were administered on admission for clinically suspected VITT.

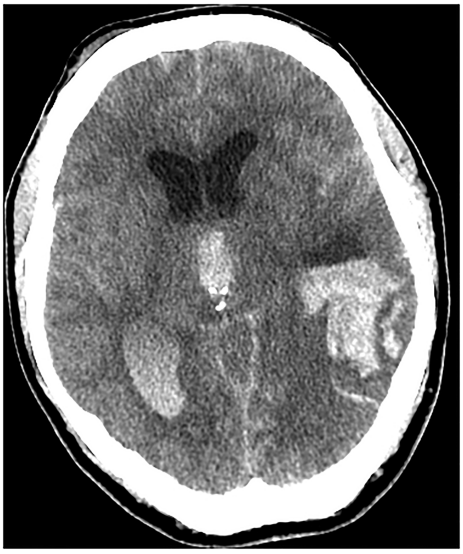

FIGURE 1 Admission CT head, patient 1

She was admitted to the neurointensive care unit for continued observation and management. There was evidence of further seizure

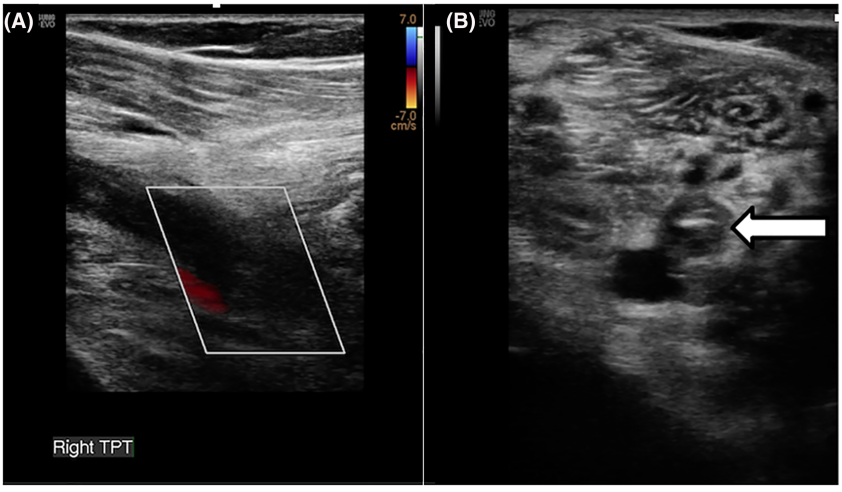

FIGURE 2 Imaging from patient 2. A, Doppler ultrasound image showing a longitudinal section through the right popliteal vein, with no blood flow demonstrated. B, Transverse section showing echogenic material in the vein

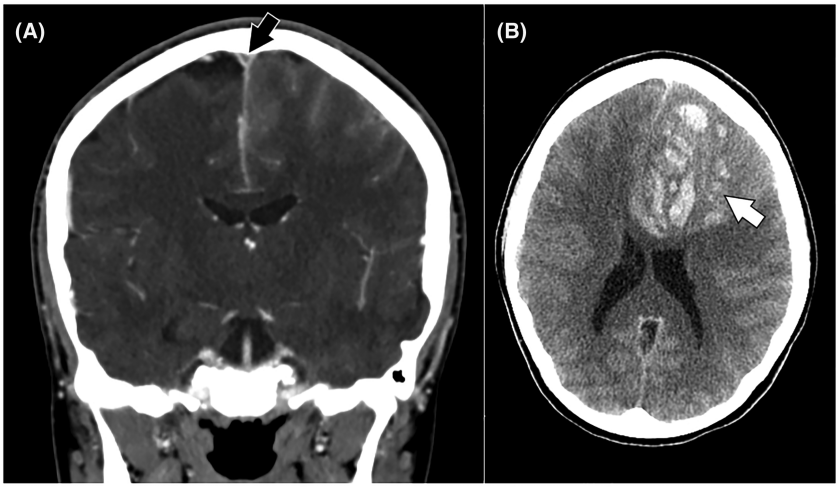

FIGURE 3 Imaging from patient 3. (A) A coronal section from the admission CT venogram, with a filling defect ("empty delta sign") seen in the superior sagittal sinus (black arrow). An axial section from the unenhanced CT scan performed approximately 6 hours later (B) shows venous haemorrhage in the left frontal lobe (white arrow), with marked mass effect

activity and continued fluctuation of her consciousness level. Antiepileptic treatment was intensified with the addition of sodium valproate 1.2 g twice daily. A second CT scan of her head demonstrated left intra-cerebral haemorrhage related to the venous thrombosis, with significant mass effect (Figure 3). A bifrontal decompressive craniectomy was performed and an intracranial pressure transducer was inserted. Cryoprecipitate and platelets were administered intraoperatively, targeting a fibrinogen concentration of >1.5 g/L and platelet count of >100 × 10^9/L, respectively. Due to the aggressive disease course, therapeutic plasma exchange was started postoperatively. An approximately equal ratio of human albumin solution 5% and human plasma (Octapas) was used as replacement fluid. This was repeated daily for five sessions. Following this, a second dose of human normal immunoglobulin was administered (70 g IV, 1 g/kg). Argatroban was started 24 hours post-operatively for anticoagulation. It was infused intravenously at a rate of 0.6–1 μg/kg/min, titrated to achieve a target activated partial thromboplastin time ratio of 1.5.

After 17 days of invasive ventilation, she was extubated. On day 36 she was deemed to be sufficiently stable for the argatroban infusion to be switched to apixaban 5 mg orally 12-hourly. She was subsequently transferred to the stroke unit on day 40. A third dose of human normal immunoglobulin was administered on day 44 (50 g IV, based on an accurate body weight), completing two effective doses with an interval of approximately 3 weeks, as it was considered that the first dose would have been removed by plasma exchange and anti-PF4 antibodies remained detectable. She was transferred to her local hospital for continued rehabilitation on day 52. At this time, she had severe left hemiparesis, and receptive and expressive dysphasia, and required seizure prophylaxis with sodium valproate 1.2 g twice daily and levitaracetam 1.5 g twice daily.

TABLE 1 Anti-PF4 antibody tests (in optical density units) and admission blood film comments

Patient	Anti-PF4 testing on admission (normal <0.400)	Blood film comments from admission
1	2.16	Genuine marked thrombocytopenia with few large platelet clumps noted. Toxic vacuolation on some neutrophils and mild left-shifted neutrophils to band form and reactive lymphocytes. No blast and red cell fragments noted.
2	2.84	Platelets appear reduced on blood film. Occasional large forms seen.
3	1.88	Genuine thrombocytopenia confirmed. No platelet clumps/fibrin strands seen. No red blood cell fragments. Normal white blood cell morphology noted.

3.2 | Investigations

Patients 1 and 3 had D-dimer levels >6000 ng/mL on admission, with the D-dimer of patient 2 initially recorded as 4205 ng/mL. The D-dimer values were higher in patients 1 and 3, both of whom experienced cerebral venous thrombosis, whilst patient 2 had a deep vein thrombosis. All patients had positive testing for anti-PF4 (Table 1).

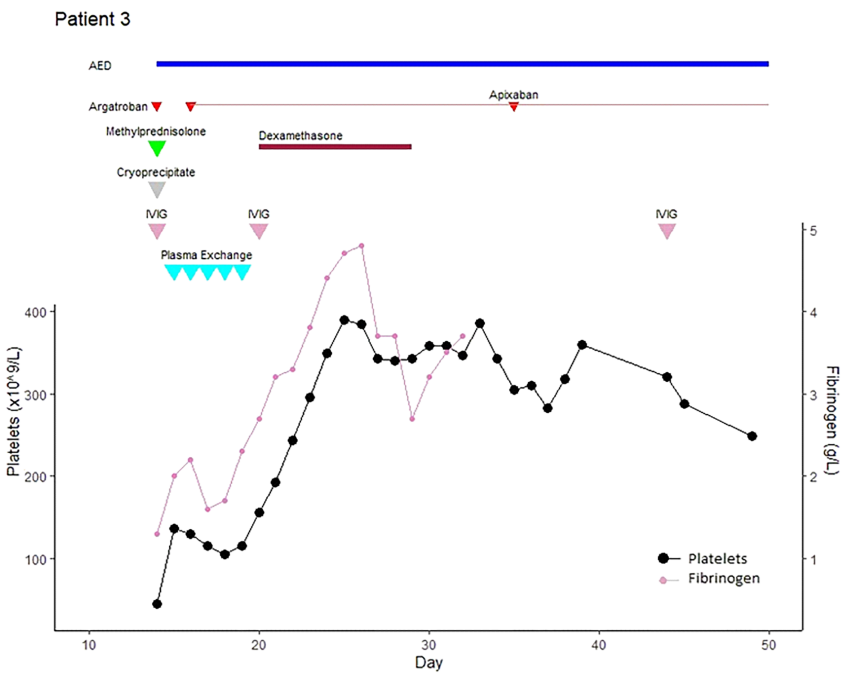

FIGURE 4 Platelet count, fibrinogen levels and treatments in patient 3 over the hospital admission

All patients had thrombocytopenia at baseline, confirmed on blood film microscopy (Table 1). In patient 1, who died shortly after admission, the baseline platelet count was 8×10^9/L. In patient 2, the platelet count was initially 90×10^9/L. The platelet counts of patient 3, in relation to relevant therapeutic interventions, are presented in Figure 4.

4 | DISCUSSION

Our case series adds to the growing body of literature discussing VITT.[12–15] Early studies observed cases occurring primarily in women under 40 years of age.[7,14,16] Our series describes VITT affecting two women and one man, somewhat older than the initial cases reported elsewhere. Whilst it was supposed that there may be a link between age and risk of VITT, this was not supported by a recent analysis performed by Public Health England that reviewed all the cases of VITT reported up to 26 May 2021.[17] At this time 348 suspected cases of VITT had been reported to the MHRA. The vaccine-related blood clots were not strongly linked to sex, and it was felt that the female preponderance in the earlier cohorts may have been due to a higher vaccine uptake in women at that time.

Our patients all presented within 3 weeks of vaccination and typically reported initial symptoms within 1 week of vaccination. This is in keeping with a recent study in the United States where patients presented with VITT 1–2 weeks post vaccination.[14] In an analysis of cases reported to the MHRA up to 26 May 2021, all cases of VITT occurred after the first dose of the vaccine and there were no reported cases after the second dose.[17] The implications of this are uncertain, as people affected by VITT after a first dose are unlikely to be re-challenged with a second dose. However, since the initial data was gathered by the MHRA, there have been data to support that risk of VITT after a second dose of the vaccine may not be any greater than that observed in the general unvaccinated population.[18]

The patients in our series received different treatments related to the nature and timing of their presentations. Two of the patients presented with bleeding associated with thrombosis. Patient 1 had major intracranial haemorrhage and died, patient 3 had a bleed after VITT diagnosis that resulted in major disability. Therefore, it is diagnostically important to be aware of patients presenting with bleeding post vaccination and consider VITT in these cases, rather than just in cases of thrombosis. Since anticoagulation is a core management strategy in VITT, this presents a difficult risk-benefit decision and further research is needed to determine optimal management.

Patient 3 had the longest duration of hospital stay, requiring three IVIG infusions and plasma exchange. This management is consistent with the rapid guidance from the Expert Haematology Panel which states repeated IVIG can be considered in cases of VITT, and that patients should be followed up after discharge and given further IVIG in the case of recurrently falling platelet counts or a rising D-dimer. Our patient had no relapse of these features but was given a repeat dose of IVIG due to the severity of her initial presentation and the persistence of anti-PF4 antibodies. The guidance also suggests that in cases refractory to IVIG, rituximab (a monoclonal antibody that targets CD20 protein on B cells) can be considered.[10] Our patient also had five sessions of plasma exchange, and a recent study indicated that in patients not responsive to IVIG, plasma exchange was effective in treating vaccine-induced thromboses.[19] Interestingly, IVIG was not offered in the management of patient 2. Whilst her presentation was less severe than the other cases, guidelines suggest that IVIG could have been considered to help reduce any disease progression. Despite the lack of IVIG her clinical course has remained good and she has had no further events of thrombosis.

Similar to other reports from the United States and Europe, all our patients had positive tests for heparin-induced thrombocytopenia antibodies and no historical exposure to heparin. The pathogenesis of vaccine induction of these antibodies is unclear, but it has been observed that VITT is almost exclusively associated with SARS-CoV-2 vaccines that use an adenovirus vector: ChAdOx1 nCoV-19 (platformed on a replication-deficient chimpanzee adenovirus, Oxford/AstraZeneca) and Ad26.COV2.S (replication-deficient human adenovirus 26, Janssen).[20,21] The Sputnik V vaccine (Gamaleya Research Institute) also uses an adenoviral vector and has not had any reported cases of VITT that we could identify.[22] Another vaccine using the adenoviral vector is the Ad5-nCOV (CanSino Biological Inc/Beijing Institute of Biotechnology), which has not yet been linked to pathological thrombosis. No increased risk of thrombosis has yet been reported with the use of the mRNA-platformed vaccines; however, these have been associated with rare reports of immune thrombocytopenia.[23] Acute thrombocytopenia has also previously been noted in animal trials with adenovirus vectored vaccines.[24–26] Case reports have similarly linked systemic adenovirus infection to a thrombotic thrombocytopenic picture.[27,28] Possible mechanisms for this include the development of antibodies against PF4 and direct interaction between the adenoviral vector and platelets. A recent report has found that the antibodies of patients with VITT bind to PF4 within the heparin-binding site.[29]

COVID-19 is itself a prothrombotic disease and thrombocytopenia is also frequently observed, with several putative explanations.[30] Therefore, another potential mechanism is cross-reactivity of the anti-SARS-Cov2 spike protein antibodies with PF4.[31] However, this does not explain the apparent difference in rate of VITT between different vaccine platforms, which all employ the SARS-CoV-2 spike protein as the antigenic target.

Our case series has several limitations. There are only three patients, so broad inferences about ongoing management strategies cannot be made. Patient 1 was transferred from a district hospital, and investigation results prior to the transfer were not available to us. Additionally, some laboratory investigations were not performed in all patients. We collected data retrospectively, and some relevant information was not available. Despite these limitations, this series adds to the collective body of evidence on the presentation, clinical course and management of this rare condition.

5 | CONCLUSION

In our three VITT cases, one patient died, one was managed in ambulatory care and the third is recovering in hospital, with life-changing

neurological impairment. Where immunomodulatory treatments (immunoglobulin and therapeutic plasma exchange) were employed in one case, this was followed by an improvement in platelet count. Likewise, use of nonheparin anticoagulants in two cases was followed by amelioration of the prothrombotic process. This aligns with reports from other centres. Through sharing of experiences of this rare complication, understanding and management can be optimised.

ETHICS APPROVAL

St George's Hospital audit registration number AUDI001000.

PATIENT CONSENT

Signed consent from the patient or their next-of-kin was obtained for anonymised data to be published in this report.

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COMPETING INTERESTS

D.G. is employed part-time by Novo Nordisk outside of the submitted work.

AUTHOR CONTRIBUTION

D.G. and I.W. contributed to the conception and design of the work. I.W. collected data from patient records, which was independently reviewed by D.G. I.W., D.S., A.W.H. and D.G. drafted the manuscript. All authors interpreted the data, critically revised the manuscript and provided final approval of the version to be submitted.

DATA AVAILABILITY STATEMENT

Anonymised data is available on reasonable request to the corresponding author.

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