

Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination: a single UK centre experience

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SUMMARY

We report clinical findings of three patients presenting with thrombosis and thrombocytopenia 10–16 days following the first dose of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2. All patients presented to a major university teaching hospital in the UK over a 5-day period and were found to have high-titre antibodies against platelet factor 4 (PF4) without previous exposure to heparin. All three patients presented with extensive venous thrombosis, significant thrombocytopenia, elevated D-dimer and borderline low fibrinogen. Two had fatal intracerebral haemorrhage secondary to cavernous venous sinus thrombosis and one had PE. Reference laboratory testing of serum demonstrated anti-PF4 antibodies in all three patients. The clinical and laboratory findings confirmed vaccine-induced thrombotic thrombocytopenia (VITT) which was poorly described at the time of presentation. We were able to manage successfully one patient with PE with intravenous immunoglobulin and corticosteroids.

BACKGROUND

Following regulatory approval by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in December 2020, the UK was one of the first countries worldwide to introduce large-scale non-trial vaccination with ChAdOx1 nCoV-19 for adults over 18 years of age to prevent COVID-19.¹ ChAdOx1 nCoV-19 is a recombinant adenoviral vector encoding the spike protein of SARS-CoV-2. The safety and efficacy of the ChAdOx1 nCoV-19 vaccine were confirmed following four randomised controlled trials in the UK, South Africa and Brazil, none of which reported an increased incidence of thrombosis or thrombocytopenia.² The MHRA granted temporary authorisation for prophylactic use of this vaccine for adults over 18 years of age. Initial vaccination was prioritised for the elderly (over 70 years of age) and frontline health and social care workers. Subsequently, adults of all ages have been invited for vaccination, prioritised according to coexisting medical problems and descending age order. As of 8 April 2021, over 31 million individuals have received the first dose of a SARS-CoV-2 vaccine in the UK,³ the majority of which have been ChAdOx1 nCoV-19. A rare complication of thrombosis associated with thrombocytopenia has been reported 5–28 days following the ChAdOx1 nCoV-19 vaccine and is now termed vaccine-induced thrombotic thrombocytopenia (VITT).^{4–7}

We describe this syndrome in three patients who presented to our centre 10–16 days after receiving the first dose of ChAdOx1 nCoV-19. Two patients

were diagnosed with cerebral venous sinus thrombosis (CVST) and developed secondary cerebral haemorrhage, which proved fatal. One patient presented with a large pulmonary embolism (PE) and went on to make a full recovery. We present all these cases in order of presentation to our hospital which occurred over a 5-day period (19–23 March 2021) which was prior to widespread recognition of the syndrome. Several countries have since reported cases of VITT, leading to restriction of this vaccine in the younger age group in many countries.

CASE PRESENTATION

Patient 1: presentation

A 61-year-old woman presented with a 3-day history of progressive dyspnoea, pain and swelling in the right leg. She had received the first dose of ChAdOx1 nCoV-19 16 days before presentation and had a history of asthma and hypertension. Her thrombotic risk factors included a high body mass index of 38 kg/m² and current use of hormone replacement therapy which had been ongoing for 20 years. The two-level Wells Score predicted a high probability for PE. D-dimer was elevated at 9376 ng/mL, and platelet count at presentation was 25 × 10⁹/L. A CT pulmonary angiogram confirmed bilateral PE (figure 1) with right heart strain. Prothrombin time (PT) international normalised ratio (INR) and activated partial thromboplastin time (aPTT) were normal, and fibrinogen was low at 1.26 g/L. Biochemical tests were unremarkable. Thrombotic thrombocytopenic purpura (TTP) and antiphospholipid syndrome (APLS) were excluded after appropriate screening investigations.

Patient 1: further investigations and management

At presentation, the patient was transfused one unit of platelets and commenced on two times per day low-molecular-weight heparin (LMWH). Due to the unusual presentation, the possibility of autoimmune heparin-induced thrombocytopenia (HIT) with no prior heparin exposure was considered. As such, a blood sample was taken for an HIT screen.

The HIT screening test with a rapid particle gel immunoassay (ID-PaGIA Heparin/PF4 Antibody Test, Bio-Rad) was weak positive. The sample was sent for HIT ELISA and functional assay. LMWH was stopped and anticoagulation was switched to treatment dose fondaparinux after 12 hours of presentation. Further platelet transfusion was withheld. The patient was



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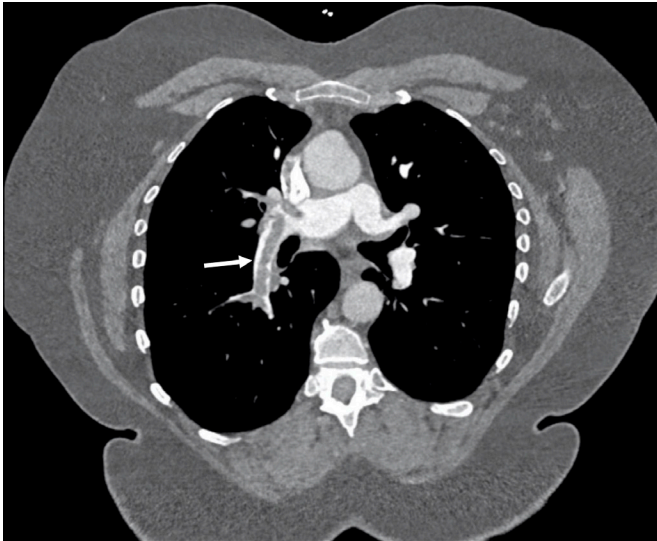


Figure 1 CT pulmonary angiogram demonstrating acute thrombus as filling defect (arrow) involving the right pulmonary artery branch extending into the right inferior pulmonary artery and segmental branches.

treated with intravenous immunoglobulin (IVIg) 1 g/kg single dose and pulsed dexamethasone 20 mg once daily for 4 days. Her platelet count improved steadily after 2 days of treatment. The HIT ELISA was reported as strong positive for anti-platelet factor 4 (PF4)/heparin antibodies by IgG-specific ELISA immunoassays (optical density (OD) 2.871; cut-off for positive reaction >0.4). In the functional assay in which platelet activation was tested with serum and heparin in high and low concentration, her platelet activation was inhibited by excess heparin effectively confirming strong positive antibodies against PF4.

Patient 1: outcome and follow-up

She was discharged on day 7 with a platelet count of $197 \times 10^9/L$ after switching anticoagulation to rivaroxaban for 3 months. At follow-up 1 week post discharge, she was asymptomatic with a normal full blood count. She has been advised not to take the second dose of the COVID-19 vaccine. [Figure 2](#), [table 1](#) provide an outline of her clinical presentation and management.

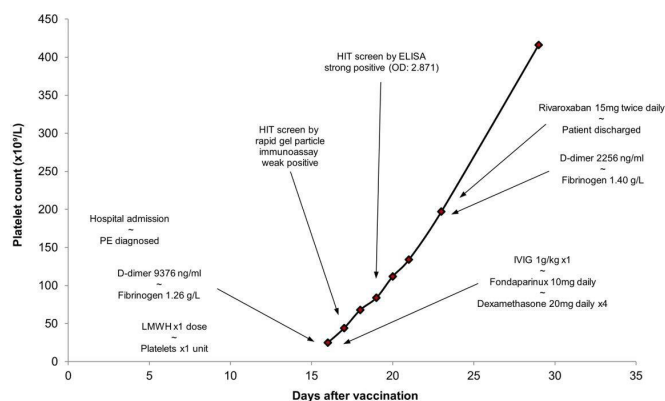


Figure 2 Time course and events in the clinical presentation of patient 1. HIT, heparin-induced thrombocytopenia; IVIg, intravenous immunoglobulin; LMWH, low-molecular-weight heparin; PE, pulmonary embolism.

Patient 2: presentation

A 53-year-old woman was referred to our centre's neurosurgical department from another centre where she had presented a few hours prior with sudden onset headache and facial weakness. She gave a history of worsening headaches for the past 3 days and weakness of the right arm and leg. She had received the first dose of ChAdOx1 nCoV-19 14 days prior to presentation. She had a medical history of fibromyalgia. Her initial blood tests showed an elevated D-dimer of 5620 ng/ml and a platelet count of $24 \times 10^9/L$. A CT scan of the head showed extensive intracerebral haemorrhage. She further had a CT venogram, which confirmed CVST ([figure 3](#)). PT INR and aPTT were normal with a borderline low fibrinogen of 1.9 g/L. Biochemical tests were normal. TTP and APLS were again excluded after relevant investigations.

Patient 2: further investigation and management

Twenty-four hours into admission, her level of consciousness deteriorated and she required intubation. Three units of platelets were transfused before urgent neurosurgical intervention. Anti-coagulation was not started due to the risk of life-threatening bleeding. Following referral to clinical haematology, a blood sample was taken for an in-house HIT screen by rapid particle gel immunoassay, which was reported as negative. However, our experience with patient 1 and emerging case reports prompted a high clinical suspicion for VITT. As such, a sample was sent to the reference laboratory. Her HIT ELISA was reported as strong positive (OD 2.631). Platelet functional assay was negative in this case.

Patient 2: outcome and follow-up

Her repeat scans showed further bleeding, with signs of increased intracranial pressure (ICP). She further deteriorated with seizures and coning and further neurosurgical intervention was not attempted due to futility. Her platelet count remained low at $23 \times 10^9/L$, and she died on the 16th day after vaccination. [Figure 4](#), [table 1](#) provide an outline of her clinical presentation and management.

Patient 3: presentation

A 55-year-old man with no comorbidities presented to the emergency department with a 2-day history of headache followed by the onset of dysphasia, right arm weakness and discoordination in the preceding few hours. He had received his first dose of ChAdOx1 nCoV-19 10 days prior to admission. At presentation, there was isolated thrombocytopenia with a platelet count of $21 \times 10^9/L$ and a very high D-dimer of 47 881 ng/ml. CT scan of the head showed extensive CVST with the extension of thrombus into the left internal jugular vein and secondary subarachnoid haemorrhage ([figure 5](#)). The PT INR and aPTT were normal, and fibrinogen was borderline low at 1.9 g/L. Biochemical tests were normal. TTP and APLS were again excluded after relevant investigations. As with patient 2, the in-house rapid particle gel immunoassay HIT screen was negative, but due to high clinical suspicion, samples were sent to the reference laboratory.

Patient 3: further investigation and management

Prior to the results of the reference laboratory testing, the patient was managed empirically for VITT with dexamethasone 20mg and anticoagulation with argatroban, given its reversibility. Platelets and cryoprecipitate were transfused to maintain the count above $50 \times 10^9/L$ and fibrinogen above 1.5 g/L. IVIg 0.5 g/kg was planned to be given. HIT ELISA was reported as

Table 1 Clinical and laboratory features of three patients

Characteristics	Patient 1	Patient 2	Patient 3
Age (years)	61	53	55
Sex	Female	Female	Male
Comorbid conditions	Asthma, hypertension, high body mass index	Fibromyalgia	Nil
Time from vaccination to admission (days)	16	14	10
Medication on admission	Hormone replacement therapy, indapamide	None	None
Presenting symptoms	Shortness of breath, pain and swelling in the right leg	Headaches, facial weakness, hemiparesis	Headaches, dysphasia, right arm weakness
Site of thrombosis	Right main pulmonary artery extending into upper, middle and lower pulmonary arteries and left segmental pulmonary arteries	Superior sagittal sinus, right sigmoid, right transverse sinus	Cortical veins, superior sagittal sinus, left transverse, left sigmoid sinus and left internal jugular vein
Platelet count nadir ($\times 10^9/L$ (reference range 150–450))	25	24	21
D-dimer peak (ng/mL (reference range 0–350))	9376	5620	47 881
PT INR peak (normal range 0.80–1.20)	1.0	1.2	1.1
aPTTR peak (normal range 0.80–1.17)	1.1	0.9	0.97
Fibrinogen (Clauss) nadir (g/L (reference range 1.9–4.8))	1.26	1.90	1.33
SARS-CoV-2 PCR test result	Not detected	Not detected	Not detected
Rapid particle gel immunoassay	Weak positive	Negative	Negative
PF4-ELISA (optical density (cut-off for positive reaction >0.400))	2.871	2.631	2.423
Platelet functional assay	Positive	Negative	Negative
Anticoagulation therapy	Initial split dose of LMWH then fondaparinux	Nil	Alteplase
Platelet transfusion	1 unit	Multiple	Multiple
Other treatment	IVIg (1 g/kg) Dexamethasone (20 mg once daily for 4 days)	None	Dexamethasone 20 mg Cryoprecipitate
Outcome	Full recovery	Death	Death

aPTT, activated partial thromboplastin time; IVIG, intravenous immunoglobulin; LMWH, low molecular-weight heparin; PF4, platelet factor 4; PT INR, prothrombin time international normalised ratio.

strong positive (OD=2.423) confirming antibodies against PF4. The platelet functional assay was negative.

Patient 3: outcome and follow-up

Despite intensive management he developed seizures and deteriorated further with falling level of consciousness. Repeat brain imaging showed a new subarachnoid haemorrhage causing significant midline shift and compression of the midbrain. He underwent emergency decompressive craniectomy and ICP bolt insertion under the cover of platelet transfusion. High ICP persisted and the patient deteriorated. Following discussion within the medical team and with the family, treatment was withdrawn and he died within 24 hours of presentation. [Table 1](#) and [figure 6](#) provide an outline of his clinical presentation and management.

DISCUSSION

We have summarised the clinical and laboratory characteristics of three patients who presented to our centre with VITT 10–16 days after receipt of the SARS-CoV-2 vaccine, ChAdOx1 nCoV-19.

All three patients presented with extensive venous thrombosis: two had fatal intracerebral haemorrhage secondary to CVST and one had PE. All three patients at admission had elevated D-dimer and borderline low fibrinogen. PT and aPTT were within the normal range. There were no features of haemolysis

or any schistocytes in the blood film of all three patients. APLS and TTP were excluded. All three patients tested negative for SARS-CoV-2 by PCR on a nasopharyngeal swab.

Reference laboratory testing of serum demonstrated anti-PF4 antibodies in all three patients despite no prior heparin exposure. Of concern, the in-house rapid gel particle immunoassay was only weak positive in one patient and negative in the other two. All three patients tested strongly positive for anti-PF4/heparin antibodies by IgG-specific ELISA immunoassays but only patient 1 tested positive on platelet functional assay.

VITT has emerged as a novel disease in the first part of 2021 secondary to vaccination with ChAdOx1 nCoV-19 against SARS-CoV-2.

The clinical picture of severe thrombocytopenia and extensive thrombosis is akin to that of HIT where the antigen recognition domain of IgG antibodies binds to complexes of PF4 and heparin.⁸ The Fc domain of these antibodies binds to platelet FcγR2A resulting in platelet activation, thrombosis, platelet consumption and life-threatening thrombosis.^{9–10} The term ‘autoimmune HIT’ has been used to describe this pathological process which can occur in the absence of heparin but it is a rare clinical entity.¹¹ In our report, all three patients demonstrated strikingly high levels of IgG antibodies to PF4–polyanion complexes by ELISA with an OD of >2, similar to other case reports and were the pathological cause of extensive thrombosis.¹²



Figure 3 CT venogram demonstrating filling defect and classic 'empty delta' sign (solid arrow) in the superior sagittal sinus. This is complicated by large volume left-sided intraparenchymal haemorrhage (*) with rightward midline shift (dashed arrows demonstrate shift of the falx cerebri).

Managing such patients is challenging and requires timely intervention. Involvement of a multidisciplinary team with urgent referral to haematology at the earliest suspicion is the key to achieving a good outcome. Radiological, neurosurgical, pathological and pharmacological support is mandatory to save lives by active intervention, especially during the first few hours. HIT ELISA testing should be done at the earliest suspicion and clinicians should not be falsely reassured by a negative rapid particle gel immunoassay or functional assay.

The optimal treatment of VITT is not fully established but national and international guidelines recommend IVIG, therapeutic anticoagulation and the avoidance of platelet transfusion.¹³ Anticoagulation with non-heparin anticoagulants

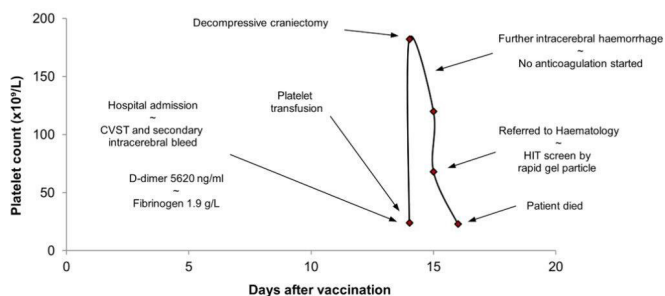


Figure 4 Time course and events in the clinical presentation of patient 2. CVST, cerebral venous sinus thrombosis; HIT, heparin-induced thrombocytopenia.

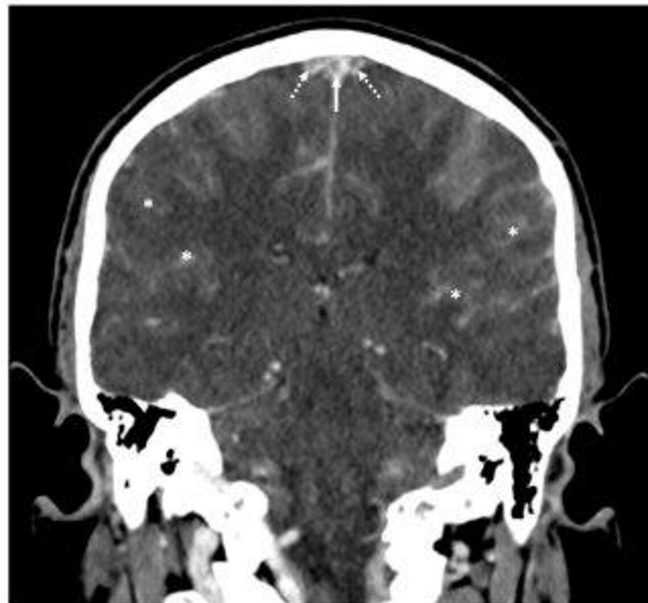


Figure 5 CT venogram demonstrating 'empty delta' sign in superior sagittal sinus (solid arrow) with thrombus extension into bilateral cortical veins (dashed arrows). This is complicated by extensive subarachnoid haemorrhage bilaterally seen as high attenuation lining the cerebral sulci (*).

such as danaparoid, argatroban, direct oral anticoagulants and fondaparinux is recommended.¹⁴ In unstable patients, we have favoured argatroban due to its short half-life. The initiation of anticoagulation in a thrombocytopenic patient with thrombosis necessitates careful evaluation of the risks and benefits. In the presence of catastrophic haemorrhage, this judgement is especially challenging. However, due to the pathophysiology of VITT, the balance of risk is in great favour of commencing therapeutic anticoagulation and avoiding platelet transfusion. Despite this, in some circumstances, anticoagulation will be contraindicated and these patients will likely be those with the most severe clinical presentations. Moreover, although prompt recognition and management is important, for some patients with catastrophic presentations, the efficacy of medical interventions will be limited and it is likely that VITT will remain a fatal complication of vaccination in isolated cases. Table 2 highlights potential diagnostic and therapeutic strategies and pitfalls.

Further investigation of the underlying pathophysiology and epidemiology of VITT is urgently underway to inform the

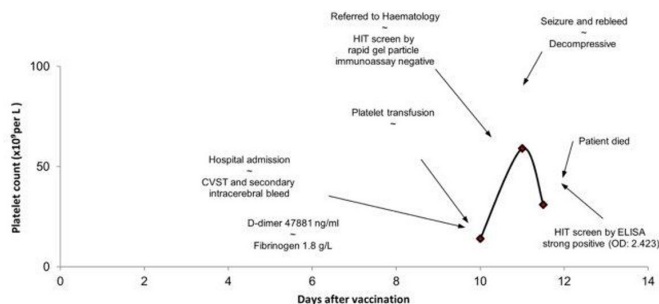


Figure 6 Time course and events in the clinical presentation of patient 3. CVST, cerebral venous sinus thrombosis; HIT, heparin-induced thrombocytopenia.

Table 2 Managing patients with suspected or confirmed vaccine induced thrombotic thrombocytopenia (VITT)

Dos	Don'ts
Laboratory testing by PF4 antibody assay (ELISA HIT assay)	Do not exclude VITT based on a negative HIT screen from a rapid particle gel immunoassay
Commence therapeutic anticoagulation with non-heparin-based therapies	Avoid heparin, including heparin-based flushes. Fondaparinux can be used
Urgently treat with IVIG	Avoid platelet transfusion
Consider giving corticosteroids	Avoid thrombopoietin receptor agonists
Report to regulatory health agencies	Do not give a second dose of any vaccine for SARS-CoV-2 until further data are available

HIT, heparin-induced thrombocytopenia; IVIG, intravenous immunoglobulin; PF4, platelet factor 4.

dynamic risk assessment which must balance individual and public health implications of vaccination and this rare side effect.

Following these three cases over 5 days, our institution developed a local guideline to raise awareness across the hospital and to trigger involvement of haematology at the earliest opportunity.

Patient's perspective

I had my vaccine about 2 weeks before I attended the hospital. I suffered from aches and pains shortly after the vaccine but they got better. A few days later I had pain in my right leg and bad headache which persisted. The next day I had pain in the chest and shortness of breath when I attended the hospital. I was diagnosed of a blood clot in my lungs. I am now much better after the blood thinning treatment and my walking is improving. I am walking my dog and getting back to normal. I have read about these vaccine complications but never thought I will be affected. I am just glad that it has got better.

Learning points

- ▶ Clinicians should have a high suspicion of investigating any acute onset thrombosis associated with thrombocytopenia presenting 5–28 days following the ChAdOx1 nCoV-19 vaccine.
- ▶ Check baseline full blood count, D-dimer and fibrinogen levels in all suspected cases.
- ▶ Seek advice from an experienced haematologist at earliest suspicion.
- ▶ Screen for platelet factor 4 antibodies by ELISA heparin-induced thrombocytopenia assay and treat positive cases with intravenous immunoglobulin.
- ▶ Further investigations are required to prove the link between the ChAdOx1 nCoV-19 vaccine and immune thrombocytopenia with associated thrombosis.

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