Arterial and venous thrombotic stroke after ChAdOx1 nCoV-19 vaccine

Authors: Adrian Wills, Gillian Swallow, Matthew A Kirkman, Krishna Rajan and Ganesh Subramanian

Vaccine-induced thrombosis with thrombocytopenia (VITT) is a recently-described condition associated with arterial and venous thrombosis following vaccination with the ChAdOx1 nCoV-19 (AstraZeneca) vaccine. This report describes two cases of stroke caused by arterial and venous thromboses presenting within 28 days of receiving the AstraZeneca vaccine. The patients were otherwise young and healthy with minimal risk factors for thrombosis yet developed a rapid, ultimately fatal neurological deterioration.

The patients were significantly thrombocytopenic with disproportionately raised D-dimers, both of which are widely reported in this condition. Both cases had measurable immunoglobulin G platelet factor-4 antibodies detected via enzyme-linked immunosorbent assay, similar to those described in heparin-induced thrombocytopenia.

These cases illustrate that physicians should be especially mindful of VITT in the context of evolving evidence on treatment and in view of the potentially rapid and catastrophic neurological deterioration, leading to fatality despite best supportive care.

KEYWORDS: thrombosis, COVID-19, thrombocytopenia, stroke, vaccination

DOI: 10.7861/clinmed.2021-0321

Introduction
Vaccine-induced thrombosis with thrombocytopenia (VITT) is a recently-described condition associated with arterial and venous thrombosis following vaccination with the ChAdOx1 nCoV-19 (AstraZeneca) vaccine. We describe two cases of stroke caused by arterial and venous thromboses presenting within 28 days of receiving the AstraZeneca vaccine. The patients were otherwise young and healthy with minimal risk factors for thrombosis yet developed a rapid, ultimately fatal neurological deterioration.

Case 1
In early March 2021, a 42-year-old woman presented with a wake-up stroke with left hemiplegia. She was a smoker with no personal or family history of venous thromboembolism or stroke. She had received the AstraZeneca vaccination 2 weeks previously. On arrival at the hyperacute stroke unit (HASU) her National Institute of Health Stroke Scale (NIHSS) score was 13. Blood tests revealed a platelet count of $85 \times 10^9/L$ (nadir was $52 \times 10^9/L$), normal clotting screen and raised inflammatory markers (Table 1). D-dimers and fibrinogen were not checked during admission. PCR for SARS-CoV-2 antigen was consistently negative. Computed tomography (CT) revealed low-density change in right middle cerebral artery (MCA) territory (Fig 1). CT angiography (CTA) showed thrombotic occlusion of the right internal carotid artery and a thrombus in the left common carotid artery bifurcation, but no evidence of more distal large vessel occlusion. She was initially treated with a therapeutic dose of low-molecular weight heparin (enoxaparin).

Three days after admission, she developed a cold pulseless left lower limb. CTA revealed extensive bilateral lower limb arterial filling defects. She underwent emergency femoral embolectomies, and a left leg fasciotomy; anticoagulation was converted to intravenous (IV) heparin. Three days later, she developed a rapid fall in her Glasgow Coma Scale (GCS) score (GCS 4/15) and a repeat CT of the brain showed additional low-density changes in bilateral anterior cerebral artery (ACA) and right MCA territories. Despite supportive care, she suffered ongoing neurological deterioration, widespread bruising and further ischaemic change in the left leg. She died 7 days after admission.

Table 1. Laboratory parameters at presentation

| Case | Platelet count (nadir), $\times 10^9/L$ | D-dimer, $\mu g/mL$ | Fibrinogen, $g/L$ | Platelet factor 4 ELISA (optical density)$^*$ |
|------|------------------------------------|------------------|-----------------|------------------------------------------|
| 1    | $85$ (52)  | $n/a$          | $n/a$           | Positive (2.94)                  |
| 2    | $11$ (10)  | $>20,000$      | $4.4$           | Positive (3.01)                  |

$^*$positive test is indicated by optical density $\geq 0.400$; ELISA = enzyme-linked immunosorbent assay.
Thrombotic stroke after ChAdOx1 nCoV-19 vaccine

Case 1

A 52-year-old woman presented to the emergency department with right-sided weakness and slurred speech. She was afebrile, normotensive, and had no history of cardiovascular disease. Her past medical history was notable for hypertension and hyperlipidaemia.

A CT scan of the head was performed, showing a low-density area in the right middle cerebral artery territory (Fig 1). An MRI of the head confirmed an acute infarct in the right middle cerebral artery territory. The patient was treated with IV thrombolysis with recombinant tissue plasminogen activator, resulting in partial thrombolysis and improvement in neurological function.

Discussion

Recently, a rare syndrome of thrombosis associated with thrombocytopenia has been reported following the AstraZeneca vaccination. This has been named vaccine-induced thrombosis with thrombocytopenia (VITT). Presentation is usually within 28 days of vaccination. The cases are unusual because, despite thrombocytopenia, there is progressive thrombosis with a high preponderance of cerebral venous sinus thrombosis. Bleeding can occur and be significant. However, arterial thrombotic events have also been noted, as in our cases. Laboratory investigation typically reveals a low platelet count (<150 × 10⁹/L) and very raised D-dimer, above the level expected in venous thromboembolism. Many patients develop a low fibrinogen. Antibodies to platelet factor 4 (PF4) have been identified in affected cases, hence there are similarities to heparin-induced thrombocytopenia (HIT) despite the absence of prior exposure to heparin. PF4 antibodies can be detected by the ELISA HIT assay but are not reliably detected by alternative HIT assays.

All our cases were investigated for PF4 antibodies. Case 1 was investigated retrospectively as presentation was prior to recognition of VITT. A stored plasma sample was used to perform the PF4 IgG enzyme-linked immunosorbent assay (Immundiagnostik) kit post-mortem and was strongly positive. ELISA testing for cases 2 was performed by NHS Blood and Transplant using the same assay; both results were positive.

Case 2

In early April 2021, a 47-year-old woman with a previous history of pulmonary embolism treated with apixaban, presented with a 3-day history of abdominal pain, nausea and vomiting. She had received the AstraZeneca vaccine 13 days previously. Initial CT of the urinary tract did not show any renal pathology. The following day, she developed haemoptysis, pyrexia, a severe headache, and a pale and pulseless right arm. She was found to have thrombocytopenia with a platelet count of 11 × 10⁹/L, an elevated D-dimer of >20,000 μg/mL and fibrinogen of 4.4 g/L (Table 1). CTA confirmed a pulmonary embolus, portal and splenic vein thrombus, and right brachial arterial thrombus. The initial unenhanced CT of her head did not show any abnormality, but cerebral magnetic resonance venography demonstrated acute multifocal watershed infarcts in the left cerebral hemisphere but no dural venous sinus thrombosis.

She was treated with IV methylprednisolone, IV argatroban (dosed as earlier) and IV IgG 1 g/kg daily for 2 days, with initial improvement. Due to subsequent fever and raised C-reactive protein, she required IV antibiotics. Poor IV access necessitated a temporary switch to subcutaneous fondaparinux; she received 7.5 mg of fondaparinux for 1 day only. Later, the same day, she had a precipitous drop in her GCS to 3/15 and developed a sluggishly reactive left pupil and hypertension. Cranial imaging demonstrated a left temporal intracerebral haemorrhage and evidence of thrombosis of the straight sinus, superior sagittal sinus and left transverse sinus. Her GCS improved to 13/15 spontaneously and she was transferred to the regional neuroscience centre for further management, including direct IV thrombolysis with 20 mg recombinant tissue plasminogen activator. This was performed the same evening and resulted in partial thrombolysis and improvement in physiological flow in the treated dural venous sinuses. Unfortunately, 24 hours later, she developed an unreactive left pupil (8 mm) and repeat imaging demonstrated diffuse left cerebral hemisphere infarction (Fig 2). She underwent a left supratentorial decompressive craniectomy but died later the same day.
Cases of VITT have been described in the UK since March 2021. The case definition is still evolving, and optimum management remains unknown. National and international guidance is available to aid clinicians in the diagnosis and management of VITT. The UK Expert Haematology Panel (EHP) live guidance was one of the earliest publications and is regularly updated, acknowledging the changing clinical situation about this novel condition. Current recommendations are still based on expert opinion and the effectiveness of this approach is unclear.

Current UK guidance recommends immediate management in cases of suspected VITT to prevent the progression of thrombosis. Treatment should be started while awaiting confirmatory testing. IV IgG is recommended and steroids should be considered, particularly if there is a delay in commencing IV IgG. Guidance recommends that all forms of heparin be avoided and advises to urgently commence anticoagulation treatment with non-heparin-based therapy. Antiplatelet agents are not currently recommended. While platelet transfusions should generally be avoided, when surgical intervention is required, decisions about their use should be made on a case-by-case basis. If neurosurgical intervention is necessary, this should be prompt.

Increased public awareness of VITT following COVID-19 vaccination, particularly the predilection for cerebral thrombosis has had other consequences; an increase in presentation of patients to the emergency medical services with headache following vaccination and reluctance to attend for vaccination are well described examples.

The COVID-19 vaccination is known to be effective against a virus that has the potential to cause significant morbidity and mortality. However, the identification of an association between the vaccine and this rare but potentially life-threatening complication has led to a dilemma within many vaccination programmes on how to balance these competing risks when offering vaccination. This is particularly relevant in the younger population who have a lower risk of complications related to COVID-19. Discussion regarding this is ongoing.

Stroke physicians should be aware of this syndrome, particularly because arterial thrombotic events may occur and because treatment protocols are dissimilar to those in classical arterial or venous thrombosis. Rapid progression of thrombosis may lead to an evolving syndrome causing rapid neurological deterioration, despite best supportive care. A multidisciplinary approach is required in managing these patients.

References

1. Greinacher A, Thiele T, Warkentin T et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021;384:2092–101.
2. Scully M, Singh D, Lown R et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2202–11.
3. British Society for Haematology. Guidance produced from the Expert Haematology Panel (EHP) focussed on syndrome of thrombosis and thrombocytopenia occurring after coronavirus vaccination. BSH, 2021. https://b-s-h.org.uk/media/19498/guidance-version-07-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210330_.pdf [Accessed 04 July 2021].
4. Nazy I, Sachs UJ, Arnold DM et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: Communication from the ISTH SSC Subcommittee on Platelet Immunology. J Thromb Haemost 2021;19:1585–8.
5. Oldenburg J, Klamroth R, Langer F et al. Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: Guidance statement from the GTH. Hamostaseologie 2021;41:184–9. and Oldenburg J, Klamroth R, Langer F et al. Erratum: Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: Guidance statement from the GTH. Hamostaseologie 2021;41:e1.

Address for correspondence: Dr Ganesh Subramanian, Acute Stroke Services, Queens Medical Centre, Derby Road, Nottingham NG7 2UH, UK.
Email: ganesh.subramanian@nuh.nhs.uk