Cerebral arterial and venous thrombosis due to COVID-19 vaccine-induced immune thrombotic thrombocytopenia

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SUMMARY
Vaccine-induced immune thrombotic thrombocytopenia (VITT) rarely develops after many COVID-19 vaccines. A 51-year-old woman re-presented to hospital with a 4-day history of headache, vomiting, diarrhea and left calf pain, 11 days after her first dose of ChAdOx1nCoV-19 (AstraZeneca) vaccine. Her neurological examination was normal. Blood tests demonstrated a low platelet count, raised D-dimer and CRP, and a positive heparin/anti-PF4 antibody assay. CT venogram demonstrated widespread cerebral venous sinus thrombosis. She was commenced on fondaparinux and intravenous immunoglobulins. The following day she developed an asymmetric quadriplegia and aphasia. CT angiogram demonstrated new bilateral cervical internal carotid artery (ICA) thrombi. She underwent stent-retriever mechanical thrombectomy of bilateral ICA and cerebral venous sinuses. Next day she had right hemiparesis and expressive dysphasia, which are improving. Thromboses due to VITT can progress rapidly to involve cerebral arteries and venous sinuses, and may warrant urgent arterial and venous thrombectomy to reduce morbidity and mortality.

BACKGROUND
A new syndrome (vaccine-induced immune thrombotic thrombocytopenia, VITT) has been described characterised by thrombosis and thrombocytopenia that develops 4–30 days after initial vaccination with several COVID-19 vaccines including ChAdOx1nCoV-19 (AstraZeneca), Ad26.COV2.S (Janssen), BNT162b2 (Pfizer-BioNTech) and mRNA-123 (Moderna).4–11 Many of these patients had thrombosis at unusual sites such as cerebral venous sinuses or in the portal, splanchic or hepatic veins. Other patients presented with deep venous thrombi, pulmonary emboli or acute arterial thromboses.4–11 We present a case of VITT with cerebral venous sinus thrombosis followed rapidly by bilateral internal carotid artery thromboses requiring emergent mechanical clot extraction. This case illustrates the rapid progression of cerebrovascular thrombosis in VITT involving both arterial and venous systems, requiring mechanical thrombectomy in addition to medical treatment. This is the first case of VITT treated with cerebral arterial and venous sinus mechanical thrombectomy that we know of.12

CASE PRESENTATION
A 51-year-old Caucasian woman presented to a hospital emergency department with occipital headache, photophobia, fever and abdominal pain 7 days after receiving her first dose of the ChAdOx1nCoV-19 vaccine. She was previously well except for type II diabetes mellitus and remote right nephrectomy. She took metformin 1 g two times per day and Sitagliptin 50 mg two times per day for diabetes. Her Body Mass Index (BMI) was 31.5. Her examination and routine investigations were normal, including platelet count of 170×109/L (table 1). She was sent home after reassurance and instructions to return if symptoms persisted or got worse. Four days later she re-presented with marked exacerbation of her headache with associated vomiting, diarrhea and left calf pain. She was alert and her neurological examination was normal. Blood tests demonstrated a low platelet count of 19×109/L, raised D-dimer >20 mg/L and CRP of 71 mg/L (table 1). The heparin/anti-PF4 antibody assay (Stago AsserachromHPIA-IgG) was strongly positive. CT venogram demonstrated widespread venous sinus thrombosis of the superior and inferior sagittal, bilateral transverse and left sigmoid sinuses, and vein of Galen (figure 1A). She was diagnosed with VITT-related cerebral venous sinus thrombosis and was commenced on subcutaneous fondaparinux 7.5 mg daily and intravenous immunoglobulins 2 g/kg divided over 2 days.

The following day she developed an asymmetric (right > left) quadriplegia and aphasia. CT head and CT angiogram demonstrated new bilateral cervical internal carotid artery (ICA) thrombi (near-occlusive on the left and partially occlusive on the right, figure 1B,C). She underwent stent-retriever mechanical thrombectomy of bilateral cervical ICA, and superior sagittal and transverse venous sinuses. Follow-up MRI brain showed left hemispheric internal watershed infarcts (figure 1D) and a small right cerebellar venous haemorrhage. The next day she had right hemiparesis and expressive dysphasia. Fondaparinux was changed to intravenous bivalirudin infusion and she was given a 5 day course of intravenous methylprednisolone, followed by a short tapering course of oral prednisolone. There was an improvement in D-dimer and normalisation of platelet counts by day 5 of her admission (table 1).

INVESTIGATIONS
Additional investigations included an echocardiogram, duplex ultrasonography of her lower limbs and CT of her abdomen and pelvis, which were all normal.

Blood tests (table 1).

DIFFERENTIAL DIAGNOSIS
Differential diagnoses include heparin-induced thrombocyto-
openia, thrombotic thrombocytopenic purpura, hereditary or acquired thrombophilia, thrombocytopathy secondary to drugs or other medical conditions, immune thrombocytopathy purpura (ITP), post-vaccine ITP, atypical haemolytic uremic syndrome, paroxysmal nocturnal haemoglobinuria and haematological malignancies. She had no exposure to heparin or any medications likely to cause thrombocytopenia or thrombophilia. There was no previous history of thrombocytopathy or thrombotic events.

TREATMENT
She had emergent stent retriever mechanical thrombectomy. Other treatment based on guidelines included non-heparin anticoagulation, intravenous immunoglobulin and intravenous and oral steroids, in addition to supportive treatment in the acute stage. She is currently at home and having outpatient rehabilitation including physiotherapy and speech therapy.

OUTCOME AND FOLLOW-UP
One month after thrombectomy she continues to improve. Dysphasia has resolved but she has right hemiparesis. She was able to stand and walk with assistance. She was independent with most self-care (including feeding and dressing herself). She has remained on anticoagulation (apix-aban 5 mg two times per day) and has not developed any further medical complications.

DISCUSSION
More than 6 billion doses of COVID-19 vaccines have been administered worldwide to control the coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2. Injection site pain and influenza-like symptoms such as joint and muscle pain, headache and fatigue that persist for 1–2 days after vaccination are a common adverse effect after vacci-
nation. Although the risk of serious adverse effects is low, many cases of vascular, haematological and cardiac abnor-
malities have been reported, resulting in media attention and public alarm. These include immune mediated thrombosis at unusual sites, thrombotic thrombocytopenic purpura, thrombotic thrombocytopathy, anaphylaxis, myocarditis or pericarditis, Guillian-Barre syndrome and Capillary leak syndrome.

VITT is characterised by thrombosis and thrombocytopenia that develops 4–30 days after initial vaccination with ChAdOx1 nCoV-19 (AstraZeneca), Ad26.COV2.S (Janssen), BNT162b2 (Pfizer-BioNTech) or mRNA-123 (Moderna). Three independent case series of 39 patients with VITT were initially described in the New England Journal of Medicine associated with the ChAdOx1 nCoV-19 vaccine. These patients had received the vaccine 5–24 days prior to presentation. All patients had a negative SARS-CoV-2 polymerase-chain-reaction assay at presentation. Over 80% of patients in the reports were women,
with those <55 years also more commonly affected. They were previously healthy or in medically stable condition, and very few were known to have had previous thrombosis or a pre-existing prothrombotic condition. Some of them were receiving oestrogen-replacement therapy or oral contraceptives. Many had thrombosis at unusual sites—cerebral venous sinus thrombosis (CVST) or thrombosis in the portal, splanchnic or hepatic veins. Other patients presented with deep venous thrombi, pulmonary emboli or acute arterial thromboses. Other cases of CVST and cerebral artery thrombosis have been reported after ChAdOx1nCoV-19 (AstraZeneca), Ad26.COV2.S (Janssen), BNT162b2 (Pfizer-BioNTech) and mRNA-123 (Moderna) vaccination.1,3,4,16–21 Physicians are being made aware that VITT should be suspected in those with severe, persistent (lasting over 3 days) or recurrent headache, abdominal pain, vomiting, dyspnoea, chest pain, leg pain or leg swelling which are present 4–30 days after receiving any COVID-19 vaccine.11,12,22

Although the pathogenesis of this syndrome of VITT is not yet clear, almost all patients were found to have high levels of antibodies to platelet factor 4 (PF4)–polyanion complexes identified by ELISA.1 This serology pattern is similar to findings in patients with ‘atypical’ or ‘autoimmune’ heparin-induced thrombocytopenia, in whom thrombi develop in the absence of known previous exposure to heparin.1,2 There is limited information about optimal treatment of Cerebral Venous Sinus Thrombosis (CVST) with VITT, but recommendations include anticoagulation with non-heparin anticoagulants, intravenous immunoglobulin and administration of steroids.11,12,22 Some patients with cerebral venous sinus thrombosis were managed with endovascular rheolyis (in addition to anticoagulation).4 While some patients have a relatively good outcome with medical therapy,1,6 a proportion may have progression of thrombosis requiring thrombectomy to prevent morbidity and mortality.

Australia has experienced relatively few cases of COVID-19 infections, severe acute respiratory syndrome and death due to COVID-19. There has been public alarm with the thrombotic adverse effects of ChAdOx1nCoV-19 (AstraZeneca) vaccine resulting in changes in public health policy.3 Current Australian data estimates that the risk of developing TTS (Thrombosis with Thrombocytopenia Syndrome) is approximately 2–3 in 100 000 persons following the administration of an adenoviral vector vaccine. Current information also suggests that TTS is more frequently reported following the first dose of an adenoviral vector vaccine. The risk of developing TTS following second dose occurs at a much lower rate of approximately 1.7 cases per million doses administered.23

**Learning points**

- The initial presentation of VITT may be with mild symptoms of headache and fever, and with normal examination and investigations (including a normal platelet count). Since vaccine associated influenza-like symptoms are common, they present challenges to physicians.
- Thrombosis may progress rapidly even after institution of non-heparin anticoagulation and immunotherapy.
- Mechanical thrombectomy should be considered urgently for significant cerebral arterial and venous thromboses.

**Patient’s perspective**

When asked about her experience with her vaccine-induced complication the patient wrote as follows.

The first time I presented in emergency in acute care hospital was May 17. I had fevers and chills, strange headaches (like nothing previously experienced), confusion and acute abdominal pain. I had to lie on the floor for over an hour after I was unloaded from the ambulance. Eventually I was seen by a doctor and categorically informed it was not AstraZeneca related and sent home 30 min later with no diagnosis.

The second time I presented at that hospital on May 20 I had the same symptoms. Again, AstraZeneca vaccine was dismissed as a cause. Sometime in the 22 hours I was in that hospital, it was eventually noticed I had had a stroke.

I was then transferred to another acute care hospital for an urgent thrombectomy. By this time my platelet count was at 16 (I was later informed).

The surgery was successful at removing the clots. But I awoke unable to speak (I could understand everything) and with right side hemiplegia.

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**Contributors**

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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Case report


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