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

Elaine Pang,1 Soumya Ghosh,1,†,1 Thomas Chemmanam,1 Carolyn Grove,2 Tim Phillips3

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, diarrhoea 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.

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, diarrhoea 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 thrombocytopenia, thrombotic thrombocytopenic purpura, hereditary or acquired thrombophilia, thrombocytopenia secondary to drugs or other medical conditions, immune thrombocytopenia, thrombosis secondary to de novo infections, and hereditary or acquired thrombophilia. She had no exposure to heparin or any medications likely to cause thrombocytopenia or thrombophilia. There was no previous history of thrombocytopenia 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. At last review, she had mild to moderate weakness of her right upper and lower limbs. 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 (apixaban 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 vaccination. Although the risk of serious adverse effects is low, many cases of vascular, haematological and cardiac abnormalities have been reported, resulting in media attention and public alarm. These include immune mediated thrombosis at unusual sites, immune thrombocytopenia, thrombotic thrombocytopenic purpura, anaphylaxis, myocarditis or pericarditis, Guillain-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 (Johnson & Johnson), 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.
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.

Acknowledgements We thank all health workers involved in the care of the patient.

Contributors All authors were involved in the care of the patient, made substantial contributions to the conception of the work and interpretation of data for the work. They drafted (EP) or revised (SG, TC, CG, TP) it critically for important intellectual content. All authors approved of the submitted manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests EP is employed by the Department of Health, Government of Western Australia. She declares no conflict of interest. SG is employed by the Department of Health, Government of Western Australia, and the Perron Institute for Neurological and Translational Science, QEII Medical Centre, Western Australia. He has been on medical advisory boards of Abbvie and Ipsen. He declares no conflict of interest. TC is employed by the Department of Health, Government of Western Australia, and St John of God Health Care at the Midland Public Hospital, Western Australia. He declares no conflict of interest. CG is employed by the Department of Health, Government of Western Australia. She has received travel support to attend an educational meeting (Novartis). She has been on medical advisory boards for Abbvie and Astra. She declares no conflict of interest. TP is employed by the Department of Health, Government of Western Australia. He has consultancy agreements with Styker Neurovascular, Medtronic, Microvention and Penumbra. TP sits on medical advisory boards for Styker Neurovascular and Argencia. TP has no relevant stock ownership.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ’s website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

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.

ORCID iD
Soumya Ghosh http://orcid.org/0000-0001-8508-0641

REFERENCES
Thrombocytopenia and Intracranial Venous Sinus Thrombosis with Vaccine-Induced Immune Thrombotic Thrombocytopenia

Case report