

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

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

¹Neurology, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

²Haematology and Path West, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

³Neurointerventional Service of Western Australia, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

Correspondence to

Professor Soumya Ghosh;
soumya.ghosh@health.wa.gov.au

Accepted 25 November 2021

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 (AstraZenica) 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).^{1–11} Many of these patients had thrombosis at unusual sites such as cerebral venous sinuses or in the portal, splanchnic or hepatic veins. Other patients presented with deep venous thrombi, pulmonary emboli or acute arterial thromboses.^{1–11} We present a case of VITT with cerebral venous sinus thromboses 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.⁴

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 $170 \times 10^9/L$ (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 $19 \times 10^9/L$, 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).



© BMJ Publishing Group Limited 2022. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Pang E, Ghosh S, Chemmanam T, et al. *BMJ Case Rep* 2022;**15**:e245445. doi:10.1136/bcr-2021-245445

Table 1 Blood tests

Tests	Normal values	First presentation	Admission date	Thrombectomy	Post-thrombectomy	
		17/05/2021	20/05/2021	21/05/2021	22/05/2021	24/05/2021
Haemoglobin (g/L)	115–160	147	154	124	105	110
White cell count ($10^9/L$)	4.0–11.0	10.47	6.81	8.63	8.6	13.13
Platelets ($10^9/L$)	150–400	170	19	12	33	206
D-dimer (mg/L)	<0.5		>20			14.23
PT (s)	12–16.5		16.8	16.1	20.6	20.9
APTT (s)	27.5–38.5		31.7	28.3	52.9	53.3
Fibrinogen (g/L)	2.0–4.0		2.6	2.4	2	2.1
Sodium (mmol/L)	135–145	135	140	136	137	137
Potassium (mmol/L)	3.5–5.2	3.8	4.1	4.3	3.7	3.5
Urea (mmol/L)	3.0–8.0	6.5	5.3	6	6.2	6.6
Creatinine ($\mu\text{mol/L}$)	45–90	59	57	51	51	54
eGFR	>60 mL/min/1.732 m ²	>90	>90	>90	>90	>90
CRP (mg/L)	<5		71			
Bilirubin ($\mu\text{mol/L}$)	<20	21	13			8
ALP (U/L)	30–110	76	83			61
PF4 antibodies ELISA			Strongly positive			
Lipase (U/L)	<60		11			

ALP, Alkaline Phosphatase; APTT, Activated Partial Thromboplastin Time; CRP, C-Reactive Protein; eGFR, estimated Glomerular Filtration Rate; PF4, Platelet Factor 4; PT, Prothrombin Time.

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 thrombocytopenic purpura (ITP), post-vaccine ITP, atypical haemolytic uremic syndrome, paroxysmal nocturnal haemoglobinuria and haematological malignancies.¹¹ 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 guidelines¹² 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 worldwide¹³ 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.¹⁴ 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.^{15 16} These include immune mediated thrombosis at unusual sites,^{15 16} immune thrombocytopenia,¹⁷ thrombotic thrombocytopenic purpura,¹⁸ anaphylaxis,¹⁹ myocarditis or pericarditis,²⁰ Guillian-Barre syndrome¹⁰ and Capillary leak syndrome.¹⁰

VITT is characterised by thrombosis and thrombocytopenia that develops 4–30 days after initial vaccination with ChAdOx-1nCoV-19 (AstraZeneca), Ad26.COV2.S (Janssen), BNT162b2 (Pfizer-BioNTech) or mRNA-123 (Moderna).^{1–11 15 16} 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.^{1–3} 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,

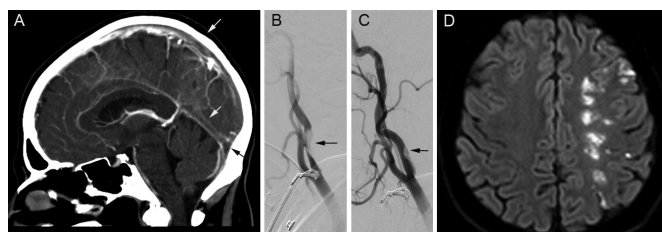


Figure 1 CT, angiogram and MRI images of thromboses and stroke. (A) Initial CT venogram demonstrating thromboses in superior sagittal and straight sinuses and torcula (arrows). (B, C) Angiograms during mechanical thrombectomy show near occlusive thrombus in the left internal carotid artery (B) and partially occlusive thrombus in the right internal carotid artery (C). (D) MRI (diffusion weighted image) shows an internal watershed infarct in the left hemisphere.

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),^{4–7} Ad26.COV2.S (Janssen), BNT162b2 (Pfizer-BioNTech) and mRNA-123 (Moderna) vaccination.^{8–11 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.¹⁵ 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 rheolysis (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.²³ 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

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 Astellas. She declares no conflict of interest. TP is employed by the Department of Health, Government of Western Australia. He has consultancy agreements with Stryker Neurovascular, Medtronic, Microvention and Penumbra. TP sits on medical advisory boards for Stryker Neurovascular and Argenica. 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

- 1 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.
- 2 Greinacher A, Thiele T, Warkentin TE, *et al*. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021;384:2092–101.
- 3 Greinacher A, Thiele T, Warkentin TE, *et al*. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021;384:2124–30.

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.

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.

- 4 Wolf ME, Luz B, Niehaus L, *et al.* Thrombocytopenia and intracranial venous sinus thrombosis after "COVID-19 Vaccine AstraZeneca" exposure. *J Clin Med* 2021;10:1599.
- 5 Al-Mayhany T, Saber S, Stubbs MJ, *et al.* Ischaemic stroke as a presenting feature of ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia. *J Neurol Neurosurg Psychiatry* 2021;92:1247–8.
- 6 Blauenfeldt RA, Kristensen SR, Ernstsen SL, *et al.* Thrombocytopenia with acute ischemic stroke and bleeding in a patient newly vaccinated with an adenoviral vector-based COVID-19 vaccine. *J Thromb Haemost* 2021;19:1771–5.
- 7 Suresh P, Petchey W. ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis (CVST). *BMJ Case Rep* 2021;14:e243931.
- 8 Sadoff J, Davis K, Douoguih M. Thrombotic thrombocytopenia after Ad26.COVS2 vaccination—response from the manufacturer. *N Engl J Med* 2021;384:1965–6.
- 9 Laporte J-R, Coma E, Fina F. Vaccines against COVID-19, venous thromboembolism, and thrombocytopenia. A population-based retrospective cohort study. *medRxiv* 2021.
- 10 European Medicines Agency Covid-19 vaccine safety update [internet], 2021. Available: ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-covid-19-vaccine-janssen-14-july-2021_en.pdf
- 11 Aleem A, Nadeem AJ. Coronavirus (COVID-19) vaccine-induced immune thrombotic thrombocytopenia (VITT). In: *StatPearls*. Treasure Island, FL: StatPearls Publishing, 2021. <https://www.ncbi.nlm.nih.gov/books/NBK570605/>
- 12 Furie KL, Cushman M, Elkind MSV, *et al.* Diagnosis and management of cerebral venous sinus thrombosis with vaccine-induced thrombotic thrombocytopenia. *Stroke* 2021;52:2478–82.
- 13 World Health Organization. *WHO coronavirus (COVID-19) Dashboard*. Geneva, 2021. <https://covid19.who.int/>
- 14 Menni C, Klaser K, May A, *et al.* Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *Lancet Infect Dis* 2021;21:939–49.
- 15 Cines DB, Busnel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med* 2021;384:2254–6.
- 16 See I, Su JR, Lale A, *et al.* US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COVS2 vaccination, March 2 to April 21, 2021. *JAMA* 2021;325:2448.
- 17 Lee E-J, Cines DB, Gernsheimer T, *et al.* Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol* 2021;96:534–7.
- 18 Yocum A, Simon EL. Thrombotic thrombocytopenic purpura after Ad26.COVS2 vaccination. *Am J Emerg Med* 2021;49:441.e3.
- 19 Australian Technical Advisory Group on Immunisation provider guide to obtaining informed consent for COVID-19 vaccine, 2021. Available: <https://www.health.gov.au/documents/2021/04>
- 20 Gargano JW, Wallace M, Hadler SC, *et al.* Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices—United States, June 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:977–82.
- 21 Muir K-L, Kallam A, Koepsell SA, *et al.* Thrombotic thrombocytopenia after Ad26.COVS2 vaccination. *N Engl J Med* 2021;384:1964–5.
- 22 Long B, Bridwell R, Gottlieb M. Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines. *Am J Emerg Med* 2021;49:58–61.
- 23 Melbourne Vaccine Education Centre, 2021. Available: <https://mvec.mcri.edu.au/references/thrombosis-with-thrombocytopenia-syndrome/>

Copyright 2021 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
 BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow