Radiology

ORIGINAL RESEARCH • CASE SERIES

Imaging and Hematologic Findings in Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 (AstraZeneca) Vaccination

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Conflicts of interest are listed at the end of this article.

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This case series reports six patients (four men and two women; median age, 38 years; interquartile range, 26–48 years) who presented with vaccine-induced thrombocytopenia and thrombosis beginning 3–26 days after receiving the first dose of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine for COVID-19. The patients were admitted to a general hospital between 9 and 31 days after the first dose. All patients had strongly detected antiplatelet factor 4 antibodies and severe thrombosis. Laboratory features included thrombocytopenia and elevated D-dimer levels. Thrombotic events were predominantly venous; two patients had arterial or mixed arterial and venous thrombosis. All patients recovered after receiving intravenous immunoglobulin and nonheparin-based anticoagulation.

An earlier incorrect version appeared online. This article was corrected on August 18, 2021.

This case series demonstrates rare thromboembolic events and thrombocytopenia after receiving the first dose of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine. To our knowledge, no thromboembolic events have been found in randomized safety studies of the AstraZeneca vaccine (1,2).

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare syndrome of immune-driven thrombosis and thrombocytopenia, which typically presents 5–28 days after vaccination. At present, there is no clear indication of risk factors, although younger age has been suggested. Clinical features include thrombocytopenia, high D-dimer levels, positive antiplatelet factor 4 (PF4) antibodies, and thrombotic events (3,4).

Detected anti-PF4 antibodies on heparin-induced thrombocytopenia (HIT) enzyme-linked immunosorbent assay of the immunoglobulin G subclass can recognize PF4-platelet neoantigens. They evoke a pronounced immune response, leading to thrombosis by platelet activation, and are heparin independent in contrast to HIT. Reported sites of thromboembolism are atypical. They include venous, arterial, intracranial, and abdominal sites (5), which is more akin to patients with myeloproliferative disorders or paroxysmal nocturnal hemoglobinuria. This hospital-based case series highlights imaging and hematologic findings in VITT.

Materials and Methods

Waiving ethical approval, this is a retrospective single-center study of consecutive patients admitted to a large district general hospital (Queen Alexandra Hospital, Portsmouth, England), with VITT between March 2021 and May 2021. Enzyme-linked immunosorbent assay (PF4 IgG, Immucor GTI Diagnostics) was used to help detect anti-PF4 antibodies; an optical density greater than 0.4 was the cutoff for a positive HIT test result. Arterial and venous thromboses were depicted with CT, MRI, and abdominal US.

Results

Patient Characteristics

Six patients (four men; median age, 38 years; interquartile range [IQR], 26–48 years]) were admitted following vaccination with thrombocytopenia. Four patients had cerebral venous thrombosis, two had pulmonary emboli, one had portomesenteric thrombosis, one also had pelvic arterial thrombosis, and another developed coronary artery thrombosis. Two patients were transferred to a tertiary center, and one required intensive care. Clinical information, laboratory results, and treatment are summarized in the Table.

All patients were admitted between 9 and 31 days following the first vaccine dose with symptoms developing 3–26 days after inoculation. One patient was taking the oral contraceptive pill, and another had a history of secondary polycythemia. All patients continued to improve on 1-month follow-up. Treatment included nonheparin-based anticoagulation, steroids, intravenous immunoglobulin, and therapeutic plasma exchange.

Laboratory Testing

Nadir platelet count ranged from 8–117 $\times$ 10^9 per liter, with a median value of 50 $\times$ 10^9 per liter (n = 6 [IQR, 18–111 $\times$ 10^9]). The D-dimer level was elevated in all patients (median, 5690 mcg/liter; n = 5 [IQR, 5395–42750 mcg/liter]). Activated partial thromboplastin time and the

Abbreviations

HIT = heparin-induced thrombocytopenia, IQR = interquartile range, PF4 = platelet factor 4, VITT = vaccine-induced immune thrombotic thrombocytopenia

Summary

Vaccine-induced thrombotic thrombocytopenia rarely complicates ChAdOx1 nCoV-19 (AstraZeneca) vaccination and presents with extensive thrombosis, blood clots at atypical sites, asymptomatic thrombus, thrombocytopenia, and raised D-dimer levels.

international normalized ratio were normal in all patients. Fibrinogen level was very low (0.1 g/L) in patient 4 leading to cryoprecipitate support (median value, 2.1; n = 5 [IQR, 0.8–2.85]). High troponin level was found in patients 1 and 3 who presented with coronary artery thrombosis and pulmonary embolism, respectively. No patient had prior history of thrombosis, signs of hemolysis, or evidence of red cell fragments on blood film. All patients had high optical densities on HIT enzyme-linked immunosorbent assay (optical density median value, 2.5 [IQR, 0.8–2.85]).

CT, MRI, and US Findings

Patient 1 was admitted with a posterior-inferior ST-elevation myocardial infarction. Diagnostic angiogram demonstrated thrombosis within the proximal circumflex and the posterior descending arteries, and the patient underwent percutaneous coronary intervention. No significant atheroma was identified. The CT pulmonary angiogram obtained on day 4 due to increased oxygen requirement showed multiple pulmonary emboli and a large left atrial appendage thrombus (Fig 1A) in addition to bilateral ground-glass opacification within the lungs (Fig 1B). He developed acute kidney injury on day 6 and imaging did not confirm intra-abdominal thrombosis. Laboratory features included thrombocytopenia, high D-dimer level, and strongly positive anti-PF4 antibodies (Table).

Patient 2 was admitted with a headache and blurred vision. Noncontrast head CT demonstrated hyperdensity involving the superior sagittal sinus and bilateral transverse sinuses. CT venography confirmed thrombotic disease within this distribution (Fig 2A, 2B). His condition deteriorated further as he developed seizures and his Glasgow Coma Scale score decreased. He was transferred to a tertiary intensive therapy unit for consideration of decompressive craniotomy. A week following initial admission, the patient developed new left-sided weakness, variable sensory signs, and brisk reflexes. Brain MRI images demonstrated high T2 signal within the frontal lobes bilaterally thought to represent venous infarcts (Fig 2C, 2D).

Patient 3 presented with shortness of breath, hemoptysis, and pleuritic chest pain; an admission CT pulmonary angiogram

Summary of Clinical Information, Laboratory Results, and Management of Each Patient with Vaccine-induced Immune Thrombotic Thrombocytopenia

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	47	28	21	48	54	26
Sex	Male	Male	Female	Male	Male	Female
Vaccination dose	1st	1st	1st	1st	1st	1st
Vaccination to admission time (d)	9	12	31	15	19	11
Time from vaccine to symptoms (d)	7	3–4	26	3	11	11
Presenting complaint	Chest pain	Severe headache, blurred vision, vomiting	Pleuritic chest pain, hemoptysis, shortness of breath	Headache, retro-orbital pain, abdominal pain	Headache	Headache
Past medical history	Hypertension, diverticulitis	Cardiomyopathy, secondary polycythemia	Left hip arthroscopy	Depression	Guillain Barre (in April 2019) COVID-19 infection (in 2020)	Asthma, depression PCOS, current smoker
Previous exposure to heparin	No	No	No	No	Yes	No
Platelet nadir (10^9/L)	8	37	111	18	117	64
D-dimer level on admission (mcg/L)	5370	5690	19500	66000	5420	NA

Table (*Continues*)

***(Continued)*: Summary of Clinical Information, Laboratory Results, and Management of Each Patient with Vaccine-induced Immune Thrombotic Thrombocytopenia**

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Fibrinogen nadir (g/L)	1.5	2.1	3.6	0.1	2.1	NA
SARS-CoV-2 antibody test	Negative	Negative	Negative	Negative	Negative	Negative
HIT ELISA to detect PF4 antibody	Positive, OD of 3.5	Positive, OD of 2.2	Positive, OD of 3.0	Positive, OD of 2.04	Positive, OD of 2.5	Positive (OD carried out at tertiary hospital)
Cerebral venous thrombosis	No	Yes	No	Yes	Yes	Yes
Porto-mesenteric thrombosis	Unknown	Unknown	No	Yes	No	Yes
Pulmonary embolus	Yes	Unknown	Yes	Unknown	No	No
Other	Coronary artery and left atrial appendage thromboses	NA	NA	Right internal iliac artery thrombus	NA	NA
Anticoagulation	Fondaparinux, argatroban (during TPE), DOAC	Fondaparinux	Fondaparinux, DOAC	Fondaparinux, argatroban (during TPE), warfarin	Fondaparinux, warfarin	Treatment dose LMWH, fondaparinux, warfarin
Other treatments	IVIG (two doses), steroids, TPE, clopidogrel	IVIG (1 dose)	IVIG, steroids	IVIG, steroids, TPE	IVIG (two doses), steroids, TPE	IVIG (five doses), steroids
Outcome	Full recovery	Transferred to tertiary center (full recovery)	Full recovery	Full recovery	Full recovery	Transferred to tertiary center (full recovery)

Note.—DOAC = direct oral anticoagulant, ELISA = enzyme-linked immunosorbent assay, HIT = heparin-induced thrombocytopenia, IVIG = intravenous immunoglobulin, LMWH = low-molecular-weight heparin, NA = not available, OD = optical density, PCOS = polycystic ovary syndrome, PF4 = platelet factor 4, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, TPE = therapeutic plasma exchange.

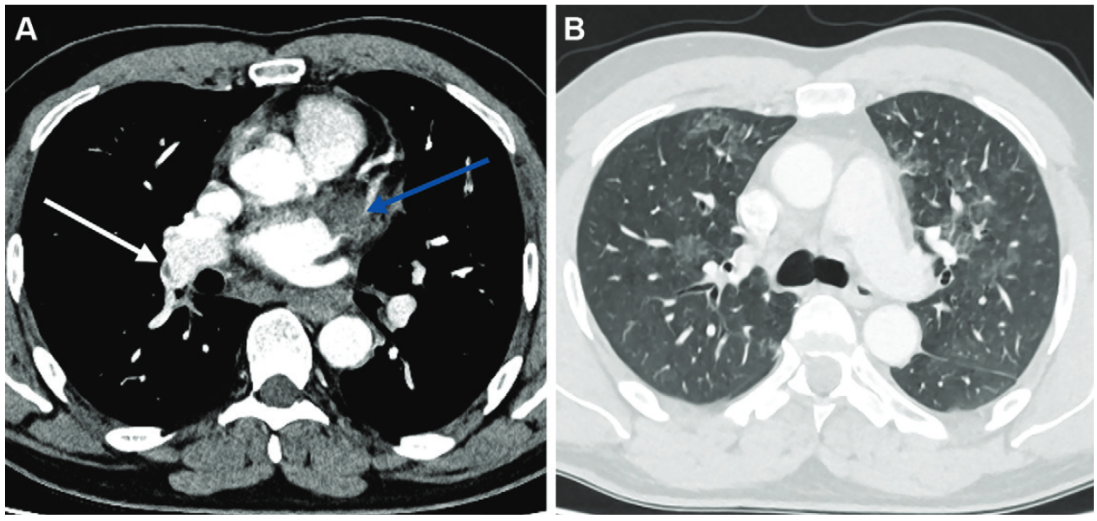


Figure 1: Axial CT pulmonary angiogram images in a 47-year-old man demonstrate **(A)** a left atrial appendage thrombus (blue arrow), right lobar pulmonary embolus (white arrow), and **(B)** bilateral ground-glass opacification.

showed extensive pulmonary emboli (Fig 3A), features of right heart strain (Fig 3B), and pulmonary infarcts (Fig 3C). Abdominal US and CT venography did not demonstrate portal vein, hepatic vein, or cerebral venous thrombosis. An echocardiogram showed right ventricular impairment and tricuspid regurgitation.

Patient 4 presented with headache, retro-orbital pain, pleuritic chest pain, and abdominal pain. He had a low platelet count and high D-dimer level. CT venography showed thrombosis within the right transverse sinus (Fig 4A) and right jugular vein. CT of the abdomen and pelvis demonstrated extensive occlusive thrombi within the main portal vein, right and left portal vein branches (Fig 4B), superior mesenteric vein, and splenic vein. In addition, CT showed acute thrombus within the right renal infarct (Fig 4C) and within the right internal iliac artery (Fig 4D).

Patient 5 presented with a headache, and CT demonstrated asymmetric hyperdensity within the left transverse, sigmoid, and straight sinuses. Extensive filling defects within the left transverse, sigmoid, and straight sinuses (Fig 5A, 5B) in addition to the left jugular vein was confirmed with subsequent CT venography. No further thrombosis was identified at CT of the chest, abdomen, and pelvis. One day following admission, the patient developed new seizures. A repeat head CT showed a 2-cm left temporal cortical venous hemorrhage (Fig 5C).

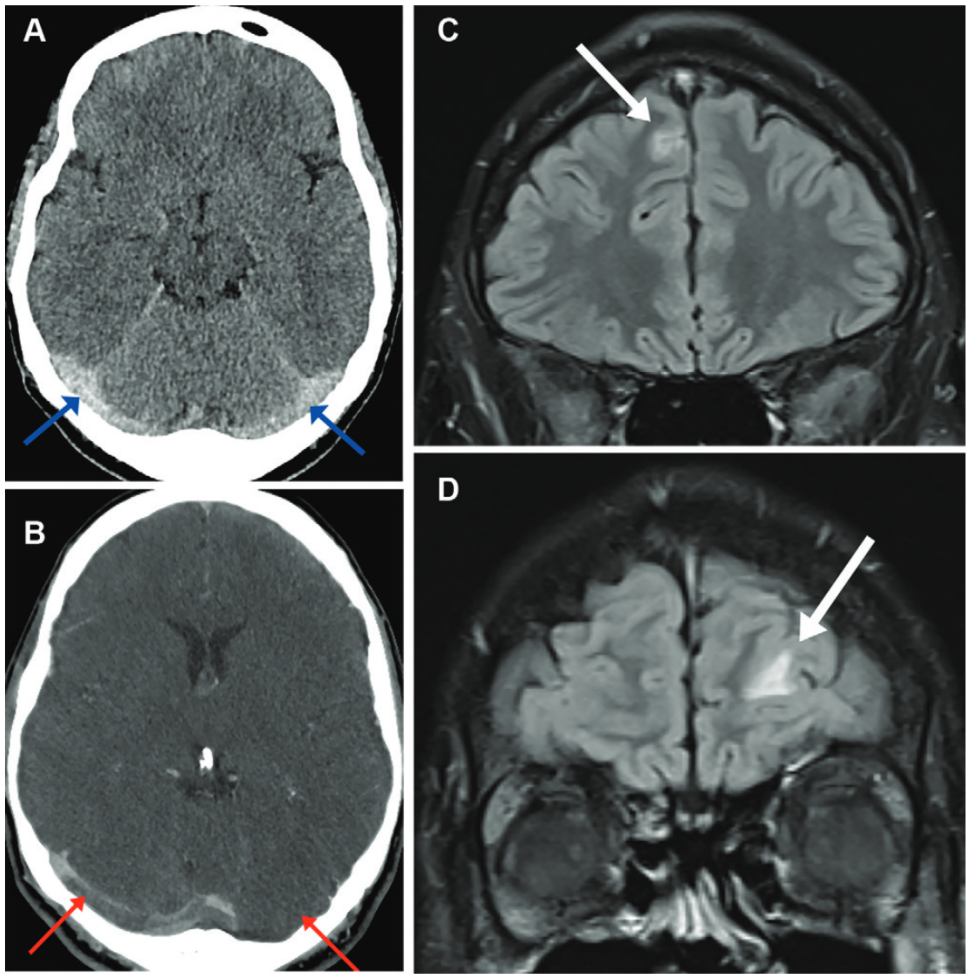


Figure 2: **(A)** Axial head CT image in a 28-year-old man shows hyperdense bilateral transverse cerebral sinuses (arrows) and **(B)** axial CT venogram image demonstrates filling defects within the transverse cerebral sinuses bilaterally (arrows). **(C, D)** T2 coronal fluid-attenuated inversion recovery brain MRI images demonstrate small foci of high T2 signal within the frontal lobes bilaterally thought to represent venous infarcts (arrows).

Patient 6 was admitted with headaches, photophobia, and nausea. Head CT demonstrated hyperdensity of the inferior sagittal and transverse sinuses (Fig 6A). The patient was transferred to the tertiary neurologic center. Thrombus within the straight sinus, bilateral transverse sinuses (Fig 6B), and right internal jugular vein was confirmed with subsequent CT venography. Abdominal US was performed on day 6 due to raised alanine transaminase level, which confirmed intrahepatic main and right portal vein thrombosis (Fig 6C) with suspected cavernous transformation.

Discussion

This case series describes the imaging and hematologic findings in six patients with vaccine-induced immune thrombotic thrombocytopenia following AstraZeneca vaccination. Similar to published data, we found that cerebral venous sinus thrombosis was the most common thrombosis site, followed by intra-abdominal thrombosis (5,6). Patients, as in our series, typically present with symptoms 5–28 days following vaccination with moderate to severe thrombocytopenia and thrombosis in unusual sites (4,6–8). Patients had a high D-dimer level, low platelet count, and atypical arterial or venous thrombosis; they developed symptoms 4 weeks or less following the first vaccine dose. Fibrinogen levels were mostly normal.

There are limited United Kingdom guidelines, which include those published by Royal Colleges and the British Society of Haematology (3,9,10). These will be revised and evolve with better clinical understanding. We identified asymptomatic intracardiac thrombus in one patient. An argument could be made for imaging additional asymptomatic regions in patients with VITT, especially for coexisting asymptomatic cerebral venous thrombosis, potentially altering oral anticoagulation choice. Reporting radiologists should remain alert to the possibility of additional thrombotic load, both in atypical sites and as incidental findings.

Current understanding is insufficient to know whether there is any genetic preexisting comorbidity or immune underlay predicting VITT.

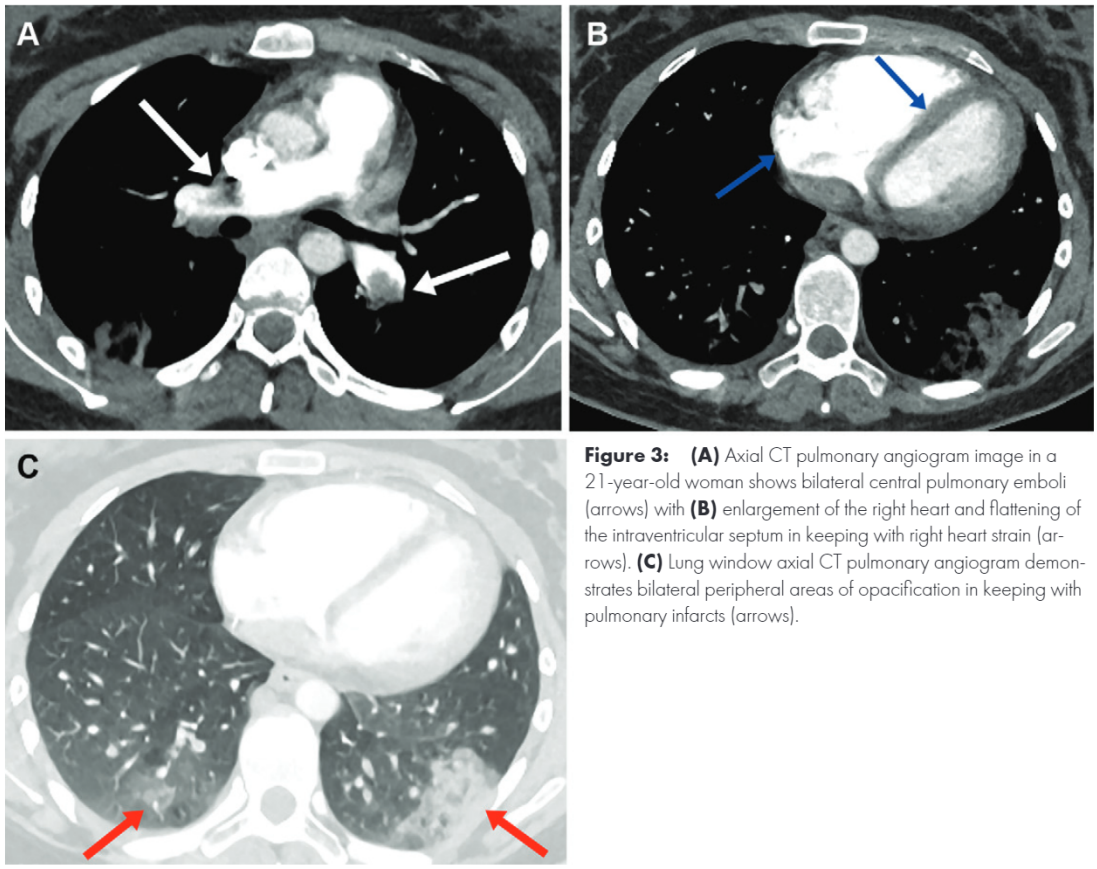


Figure 3: **(A)** Axial CT pulmonary angiogram image in a 21-year-old woman shows bilateral central pulmonary emboli (arrows) with **(B)** enlargement of the right heart and flattening of the intraventricular septum in keeping with right heart strain (arrows). **(C)** Lung window axial CT pulmonary angiogram demonstrates bilateral peripheral areas of opacification in keeping with pulmonary infarcts (arrows).

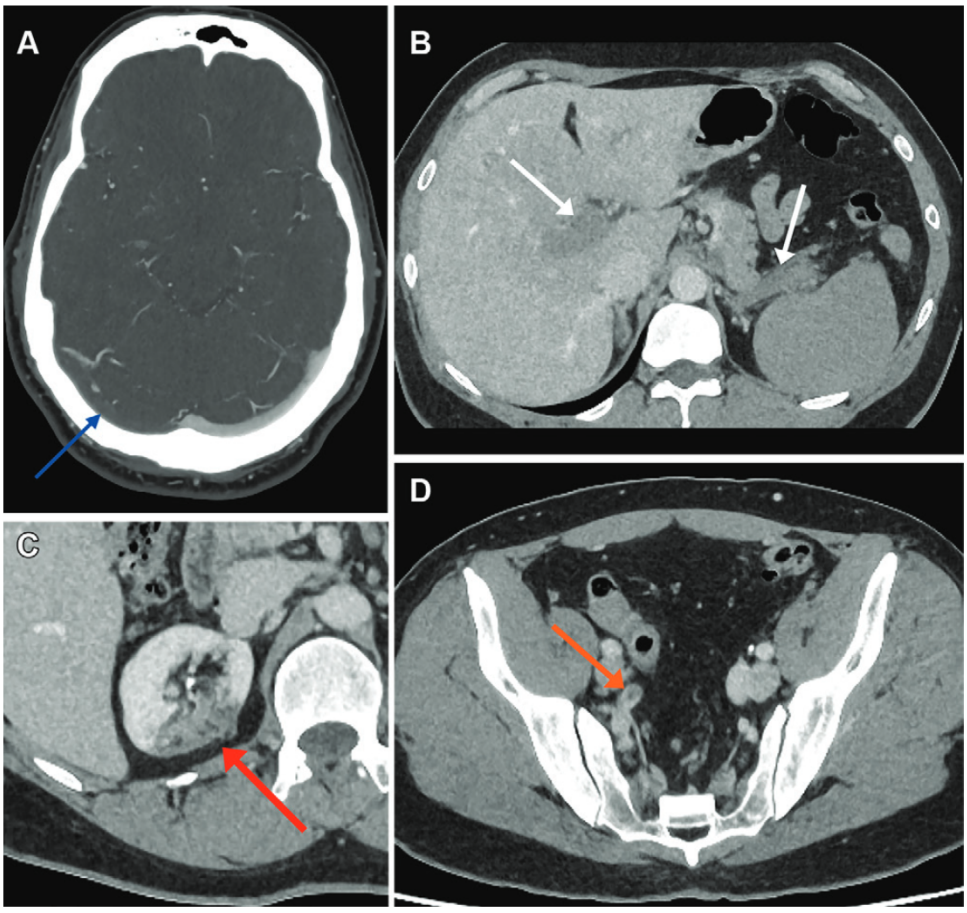
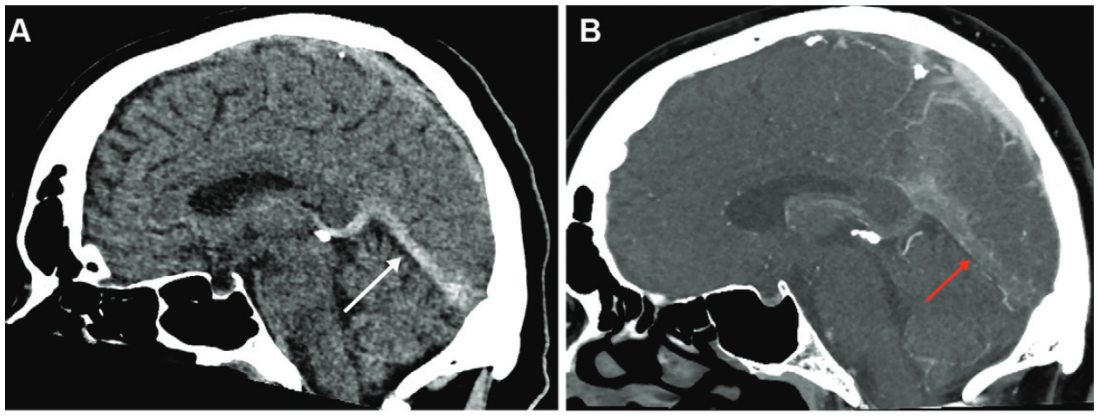


Figure 4: **(A)** Axial CT venogram image in a 48-year-old man shows a right transverse sinus filling defect in keeping with thrombosis (arrow). **(B)** Axial portal venous CT of the abdomen and pelvis demonstrates portal vein and splenic vein thromboses (arrows) in addition to **(C)** right upper pole renal infarct (arrow) and **(d)** acute right internal iliac artery thrombus (arrow).



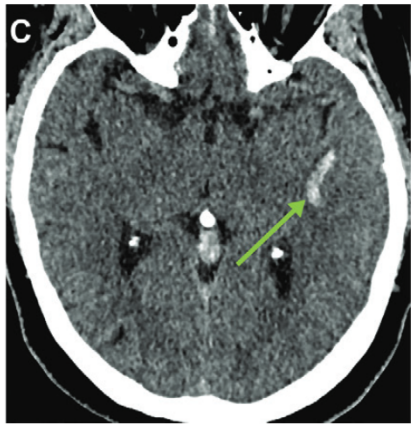


Figure 5: **(A)** Sagittal head CT in a 54-year-old man shows a hyperdense straight sinus (arrow) confirmed with **(B)** CT venogram (arrow). **(C)** Axial head CT shows a 2-cm left temporal lobe cortical venous hemorrhage (arrow).

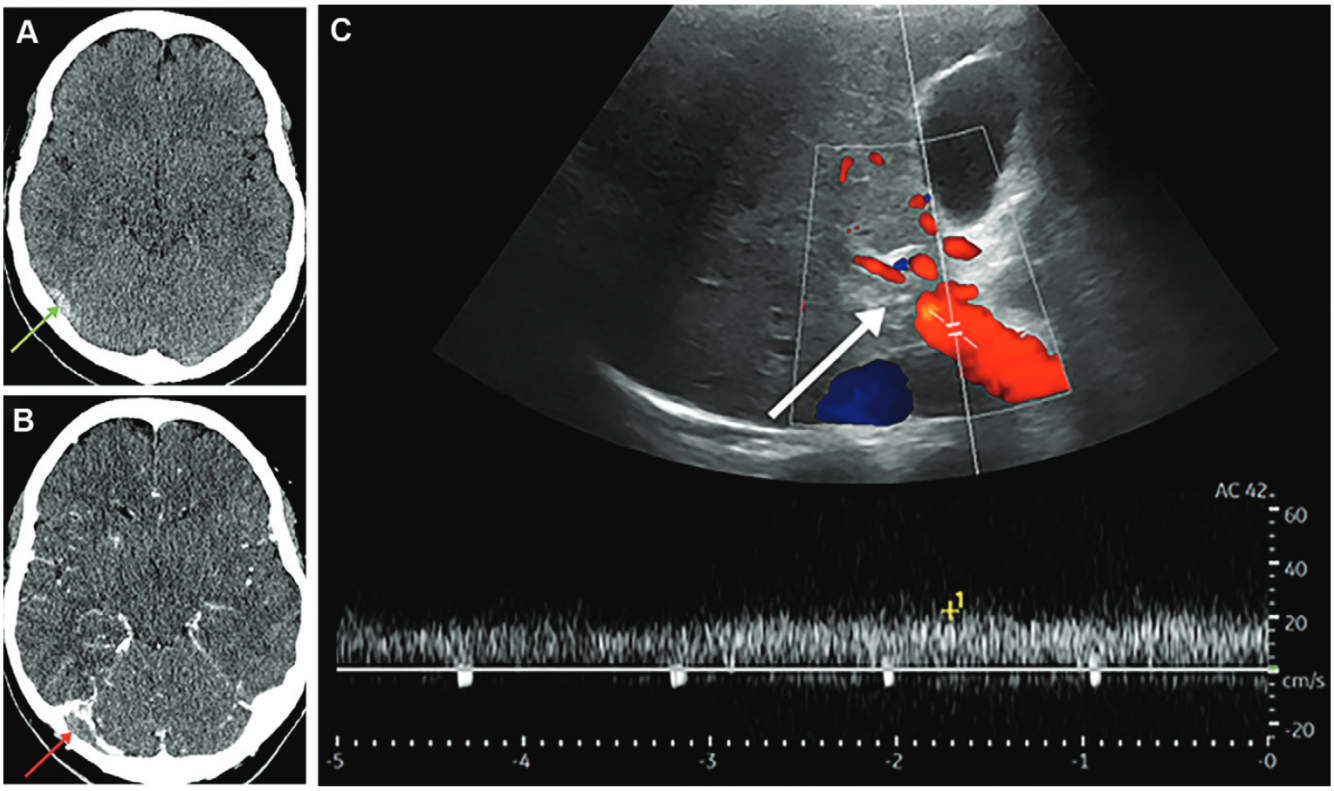


Figure 6: **(A)** Axial noncontrast head CT in a 27-year-old woman shows a hyperdense right transverse sinus (arrow) confirmed with **(B)** CT venogram with a filling defect (arrow). **(C)** Doppler US image shows no flow within the intrahepatic main portal vein in keeping with thrombosis (arrow).

Thrombotic thrombocytopenic purpura, another differential diagnosis, was not suspected because of patient history, absence of hemolysis, and no excess of red blood cell fragments on smear analysis. Vaccination stimulates the immune system and can promote nontolerance of self-antigens, resulting in immune thrombocytopenic purpura and hemolytic anemia.

A common denominator in all six patients was a high level of anti-PF4 antibodies, higher than typically seen in HIT (11). Proposed mechanisms of VITT include neoantigen formation between PF4 and vaccine proteins, leading to immunogenicity and high anti-PF4 titers. These antibodies, as in HIT, drive thrombosis by platelet, leukocyte, and endothelial activation. The VITT antibodies can mimic the effect of heparin by binding to a similar site on PF4, leading to thrombosis with platelet activation (12).

These patients were managed according to interim guidelines and discussion with the UK Expert Haematology Panel. All six patients received intravenous immunoglobulin, five of them were given steroids, and fondaparinux was the most common nonheparin anticoagulant. Therapeutic plasma exchange was used in three patients, either due to being refractory to initial management including intravenous immunoglobulin or extensive clot load. Those with cerebral venous sinus thrombosis or arterial ischemia were offered warfarin rather than novel oral anticoagulants. No patient had a fatal outcome. Primary care was advised against a second vaccine dose.

Additional multicenter studies are required to assess the incidence, pathophysiology, and location of thromboses to develop best practice guidelines.

Author contributions: Guarantors of integrity of entire study, **A.G.**, **R.A.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **A.G.**, **B.M.**, **M.G.**; clinical studies, **B.M.**, **M.G.**, **R.A.**; statistical analysis, **A.G.**, **B.M.**; and manuscript editing, all authors

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Erratum

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Anmol Gangi and **Behnaz Mobashwera** share equal contribution.