Radiology

Thrombus Distribution in Vaccine-induced Immune Thrombotic Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

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Abbreviations

VITT – Vaccine-induced immune thrombotic thrombocytopenia

CVST - Cerebral venous sinus thrombosis

PVT – Portomesenteric venous thrombosis

PE - Pulmonary embolism

Summary

MRI, CT, and US helped detect occult sites of thrombosis in a large majority of patients presenting with vaccine-induced thrombocytopaenia and thrombosis after receiving their first dose of the ChAdOx1 nCoV-19 vaccine.

Abstract

This case series reports 40 patients (median age, 41 years [interquartile range (IQR) 32- 52, 22 men) with confirmed vaccine-induced immune thrombotic thrombocytopaenia after administration of their first ChAdOx1 nCov-19 (AstraZeneca) vaccine: 80% (n=32) developed symptoms within the first 14 days and 20% (n=8) within 14-28 days. The location and extent of thrombi were evaluated using CT, MRI and ultrasound. Of the 40, 73% (n=29) presented with neurological symptoms and had confirmed cerebral venous sinus thrombosis, 30% (n=12) had extension of their primary thrombus, and 20% (n=8) died. 83% of those who underwent additional imaging (25 of 30) had occult thrombosis.

Introduction

Vaccination strategies have been at the forefront of controlling the Covid-19 pandemic [1]. An association between vaccine-induced immune thrombotic thrombocytopenia (VITT) and one of these vaccines, the ChAdOx1 nCov-19 vaccine (AstraZeneca), is now recognized [2–5]. VITT is related to auto-antibody generation against platelet factor four (PF4), with all confirmed patients exhibiting high titers[2–4]; patients phenotypically demonstrate thrombosis.

The management of VITT follows limited evidence: guidelines suggest treating the thrombosis with non-heparin anticoagulants and possible fibrinogen replacement therapy [6] or interventional techniques [7–10], and managing the immune response with intravenous immunoglobulins and possibly corticosteroids, plasma exchange or rituximab[6].

The anatomical location and frequency of thrombosis has not previously been well established in the literature on VITT. The role of imaging in VITT is to diagnose thrombosis and complications, and to guide intervention. International guidance suggests targeting imaging to the localizing symptoms[10–15]. However, no guidance specifically recommends whole-body imaging to assess for occult sites of thrombosis despite the high likelihood of developing multiple sites of thrombosis. Thus, we investigated the frequency and location of thrombosis in each vascular system using CT, MRI and ultrasound to identify additional sites of thrombus in a UK-wide sample of patients with confirmed VITT.

Materials and Methods

UK Health Research Authority confirmed that this multicenter retrospective observational study, using routine anonymous patient data, could proceed without the need for review by an ethics committee.

Thirty-two radiology centers identified through the national collaborative Radiology Academic Network for Trainees were invited from the United Kingdom; seven of these contributed to this study. All patients with confirmed VITT between February 3, 2021 and May 12, 2021 that met the inclusion criteria were included.

The inclusion criteria were presentation within 28 days following administration of the ChAdOx1 nCov-19 vaccine, presence of anti-PF4 antibodies, thrombocytopenia <150 x 10^9/liter and new radiologically confirmed thrombosis on at least one contrast-enhanced CT scan. The exclusion criteria were a history of thrombophilia, a positive Covid-19 PCR serological test, and if PF4 antibody testing or imaging information was unavailable.

Patients were identified by a search of local hematology databases, anti-PF4 testing and cross-referencing with imaging on local Picture Archiving and Communication Systems (PACS). The electronic health record for each included case was reviewed to collect the demographic data, clinical information, laboratory results and outcomes (Table E1). Patient demographics, clinical, biochemical and imaging information were recorded on standardized data collection sheets. Imaging was reviewed locally by consultant radiologists or senior radiology trainees (with at least 4 years of experience in cross-sectional imaging) unblinded.

CT, US, and MRI were performed according to local hospital protocols (table 1a). Readers commented on thrombus in the following vascular systems, to a subsegmental level where possible (table 1b): a) cerebral venous sinus thrombosis, b) systemic deep venous thrombosis (lower limb deep vein thrombosis, inferior and superior venae cavae, hepatic, renal and adrenal veins), c)

portomesenteric venous thrombosis (portal, superior and inferior mesenteric and splenic veins), d) systemic arterial thrombosis (including intracranial and visceral arterial thrombosis), and e) pulmonary embolism (PE).

Images were stratified into three categories: cerebral imaging (head CT, brain MRI and venogram CT), whole-body imaging (chest, abdomen and pelvis CT) and partial-body imaging (any patient that did not have a complete chest, abdomen and pelvis CT examination, which included focused ultrasound assessment).

Statistical Analysis

Descriptive statistics were used to describe proportions of scans and/or patients with thrombus at each anatomical site, using Microsoft Excel version 16.60. Continuous variables were not normally distributed and are described as medians with interquartile (IQR) and full range, whereas categorical variables are described as a number and/or percentage.

Results

Patient Characteristics

Between February 3, 2021 and May 12, 2021, 40 patients met inclusion criteria from 7 different centers across the United Kingdom (supplemental table).

The median age was 41 years [interquartile range (IQR) 32- 52, range 21 to 66]: 22 of 40 were men (55%). 32 of 40 patients (80%) developed symptoms within 14 days of their first ChAdOx1 nCov-19 vaccine, and 8 of 40 patients (20%) presented 14-28 days post-vaccine. None of the patients had received their second vaccine dose at presentation (supplemental table).

Sites and multiplicity of thrombus across all patients

At presentation, 10 of 40 patients (25%) underwent targeted imaging based on symptoms alone; 30 of 40 patients (75%) underwent additional imaging as detailed below (table 1a). Whole-body imaging with contrast-enhanced axial CT was performed in 26 of 40 patients (65%), and partial-body imaging (defined in methods) in 4 of 40 (10%) within 48 hours of admission.

Further imaging during the study period identified additional sites of thrombosis in a total of 25 of the 30 patients who underwent additional imaging (83%). The commonest additional sites were a combination of cerebral venous sinus thrombosis and pulmonary embolism in 16 of 40 patients (40%), or cerebral venous sinus thrombosis and portomesenteric venous thrombosis in 9 of 40 patients (23%). The total numbers of thromboses identified in each vascular system across all 40 patients were: 34 of 40 cerebral venous sinus thrombosis; 17 of 40 pulmonary embolism; 10 of 40 portomesenteric venous thrombosis; 11 of 40 with deep venous thrombosis, and 8 of 40 with systemic arterial thrombosis.

Analysis by mode of presentation

29 of 40 patients (73%) presented with predominantly neurological symptoms (fig 1-3) including severe headache, blurred vision, seizure or collapse. In all 29 patients, CT or MR venogram identified cerebral venous sinus thrombosis (table 1b). In 15 of 29 of these patients (52%), intracranial hemorrhage was associated, which was bilateral in 3 of 15 patients (20%). Further imaging was completed in 20 of 29 patients (69%) with whole-body imaging in 17 and partial imaging in 3. Of the 20 of 29 patients who received further imaging, additional site(s) of thrombus were identified in 17 patients (85%): pulmonary embolism in 12 (60%), portomesenteric venous thrombosis in 5 (25%), deep venous thrombosis in 6 (30%), and systemic arterial thrombosis in 4 (20%).

6 of 40 patients (15%) presented with thoracic symptoms of dyspnea, cough, chest pain or hemoptysis. In all 6 patients, pulmonary embolism (PE) or intracardiac or coronary thrombus was confirmed (table 1b). Further imaging was performed in 5 of 6 (83%) of these patients. Of these 5, 1 (20%) had solitary PE, 3 (60%) had additional cerebral venous sinus thrombosis, and 3 (60%) had additional intra-abdominal thrombosis (portomesenteric venous thrombosis and deep venous thrombosis).

4 of 40 patients (10%) presented with gastrointestinal symptoms including abdominal pain, vomiting, and rectal bleeding. In all 4 of these patients, an intra-abdominal thrombosis was found (table 1b): 2 with portomesenteric venous thrombosis (50%) and 2 with adrenal and renal vein thrombosis (50%). Further imaging in these 4 patients demonstrated 2 patients (2 of 4) had cerebral venous sinus thrombosis (50%), 1 pulmonary embolism (25%), and 1 combined cerebral venous sinus thrombosis and intracranial arterial thrombosis (25%).

In all patients with occult portomesenteric venous thrombosis and pulmonary embolism, clinical monitoring was undertaken and serial imaging was indicated if there were clinical signs of developing venous bowel ischemia or right-heart strain.

Treatment:

Treatments consisted of anticoagulation, plasma exchange, steroids and intravenous immunoglobulins. Of 40 patients, 7 (18%) underwent platelet transfusion and 1 patient (2.5%) was treated with eltrombopag (Revolade 25 mg tablets, Novartis Pharmaceuticals UK Ltd). In 2 patients, (5%) of splanchnic venous occlusion and small bowel compromise, patients were transferred to tertiary hepatobiliary centers for further management (supplemental table).

Patient outcomes:

Median follow-up was 44 days; during this period 8 of 40 patients (20%) had died, all of brain herniation secondary to large volume cerebral edema. 12 of 40 patients (30%) had clinical deterioration and underwent repeat imaging. In 8 of these 12 patients (67%) this showed extension of intracranial thrombus, in 4 of these 12 patients (33%) there was extension of thrombus in a second vascular system. Of the 4 patients with progressing thrombus, 2 of the 4 (50%) had died of complications of VITT.

Discussion

International guidance suggests symptom-specific imaging for vaccine-induced immune thrombotic thrombocytopenia, but there remains a paucity of data on the prevalence of multi-site thrombosis and the implications of this on management. This is the largest study to date of patients with vaccine-induced immune thrombotic thrombocytopenia with whole-body imaging and multi-system thrombosis.

In the 25 of 40 patients undergoing additional imaging (imaging in addition to that focused on the presenting site), a very high proportion (83%) of patients had additional-site thrombosis. This is much higher than the reported diagnoses of VITT where multi-site thrombosis was seen in 27-50% of patients, likely reflecting that fact that many of these studies did not perform comprehensive whole-body imaging [2–4,16–20]. In our study, progressive thrombosis was observed within the first seven days after presentation in a substantial proportion of patients. The overall mortality in our study sample was 20%, and mortality in those with confirmed progressive thrombosis this was 50%. These findings emphasize that VITT is a multisystem disorder and suggest that whole-body contrast-enhanced imaging is likely to identify further thrombosis.

Additional imaging was performed in 30 of 40 (75%) patients, mostly with CT Pulmonary Angiogram or CT Abdomen and Pelvis . For example, in neurologically unwell patients with VITT and cerebral venous sinus thrombosis, signs and symptoms of developing splanchnic venous thrombosis may be asymptomatic. Whole-body imaging can identify patients who require early referral to specialist vascular or hepatobiliary centers for catheter-directed thrombolysis or transjugular intrahepatic portosystemic shunting, for instance. [10,21]

A strength of our study was the involvement of the Radiology Academic Network for Trainees network to identify a large number of patients across the United Kingdom. The retrospective study design imposed some limitations: patients were excluded if specific hematological (PF4 antibody) testing or imaging information was unavailable and inclusion was limited to symptomatic patients presenting to hospital. To date, imaging patients for asymptomatic thrombosis in vaccine-induced immune thrombotic thrombocytopenia is not within routine clinical practice in the United Kingdom. It is therefore possible that in instances of limited whole-body imaging, the number of occult thromboses may be considerably higher than reported.

Conclusion

In conclusion, patients with vaccine-induced immune thrombotic thrombocytopenia are likely to present with multiple sites of thrombosis, most frequently cerebral venous sinus thrombosis in combination with pulmonary embolism and portomesenteric venous thrombosis. Whole-body imaging with contrast-enhanced CT imaging can identify occult thrombosis.

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Tables

Table 1a: Imaging Modality within 48 Hours of Admission in Relationship to Presenting Symptoms

Presenting Symptom	Number of patients	CT head + CT/ MRI venogram	CT pulmonary angiogram	CT Abdomen / Pelvis with contrast	CT Chest Abdomen / Pelvis with Contrast/CT aortogram	MRI Abdomen with contrast	US duplex abdomen	US duplex peripheral veins
Neurological	29	29	9	6	9	0	2	2
GI	4	4	2	2	2	1	0	0
Chest	6	5	4	1	3	0	1	0
Other*	1	1	0	0	1	0	0	0
Total	40	39	15	9	15	1	1	1

*other: pyrexia and night sweats

Table 1b: Site of Vascular Thrombus after ChAdOx1 nCov-19 Vaccination in Relationship to Presenting Symptom

Presenting Symptom	Number of patients	Pulmonary embolism	Portosystemic venous thrombosis	Cerebral venous sinus thrombosis	Deep vein thrombosis	Systemic arterial thrombosis
Neurological	29	12	5	29	6	4
GI	4	1	2	2	3	1
Chest	6	4	2	3	1	3
Other	1	1	1	0	0	0
Total	40	18	10	34	10	8

Figures

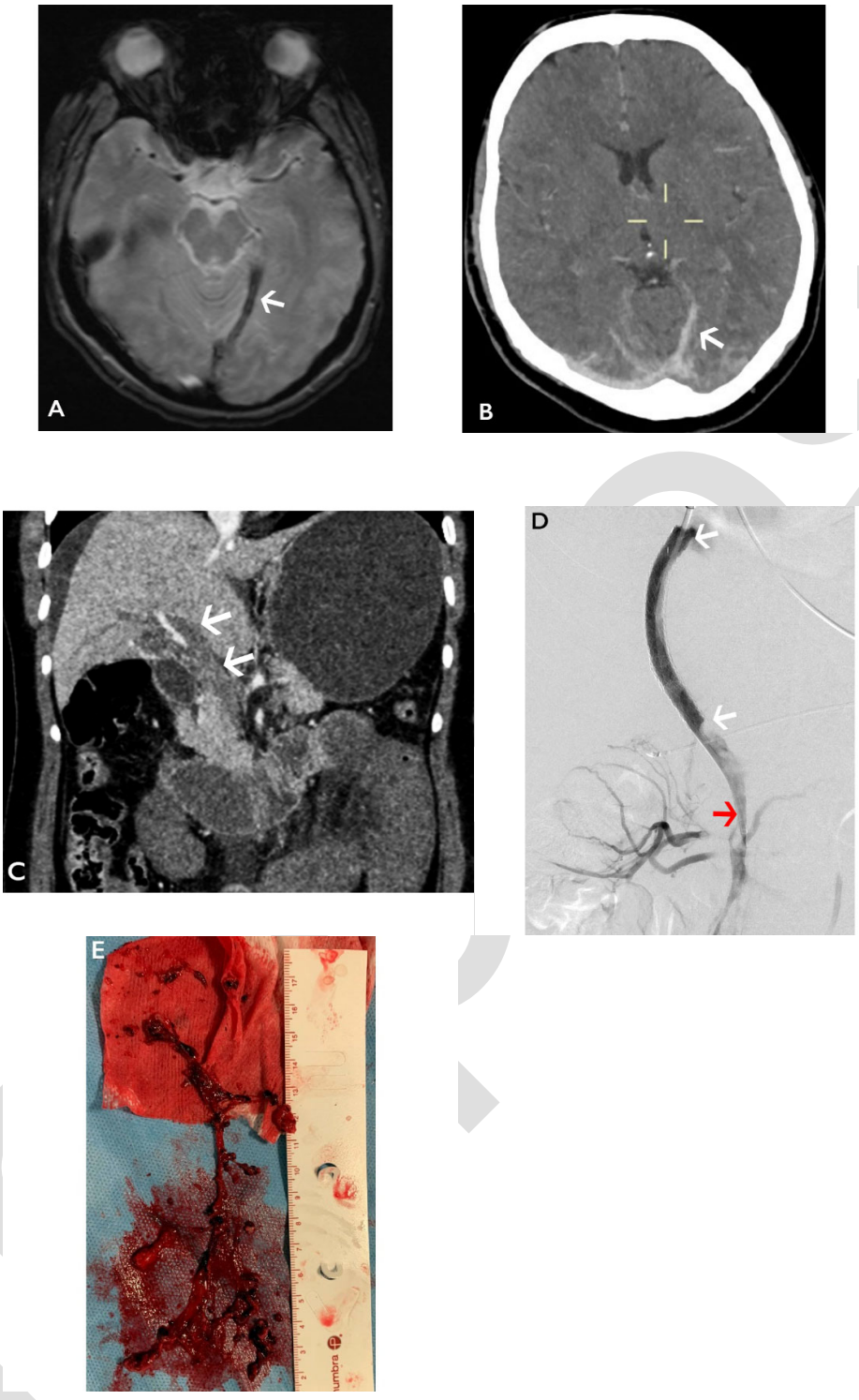

Figure 1: Multiple modality images in a 28-year-old woman who presented with headache and subsequent collapse. Cerebral venous sinus thrombosis was

diagnosed and whole-body imaging demonstrated large volume splanchnic vein thrombosis, which was treated with a transjugular intrahepatic portosystemic shunt insertion and catheter directed thrombolysis. **(A)** Susceptibility weighted axial brain MRI showing a thrombosed internal cerebral vein branch leading to the straight sinus (arrow). **(B)** Unenhanced axial head CT showing hyperattenuating clot within the cortical vein and transverse sinuses (arrow) **(C)** Coronal portal venous phase abdomen CT showing thrombosed portal and superior mesenteric veins (arrows) **(D)** Fluoroscopic angiogram images taken from a thromboaspiration catheter (red arrow) within the partially occluded superior mesenteric vein through a transjugular intrahepatic portosystemic shunt (between the white arrow). Contrast can be seen filling some segmental superior mesenteric vein branches with several filling defects in the confluence of the portal vein. **(E)** Photograph of the thrombus cast of the superior mesenteric vein and portal vein aspirated from the splanchnic system via the portosystemic shunt using an aspiration thrombectomy catheter (Indigo, Penumbra).

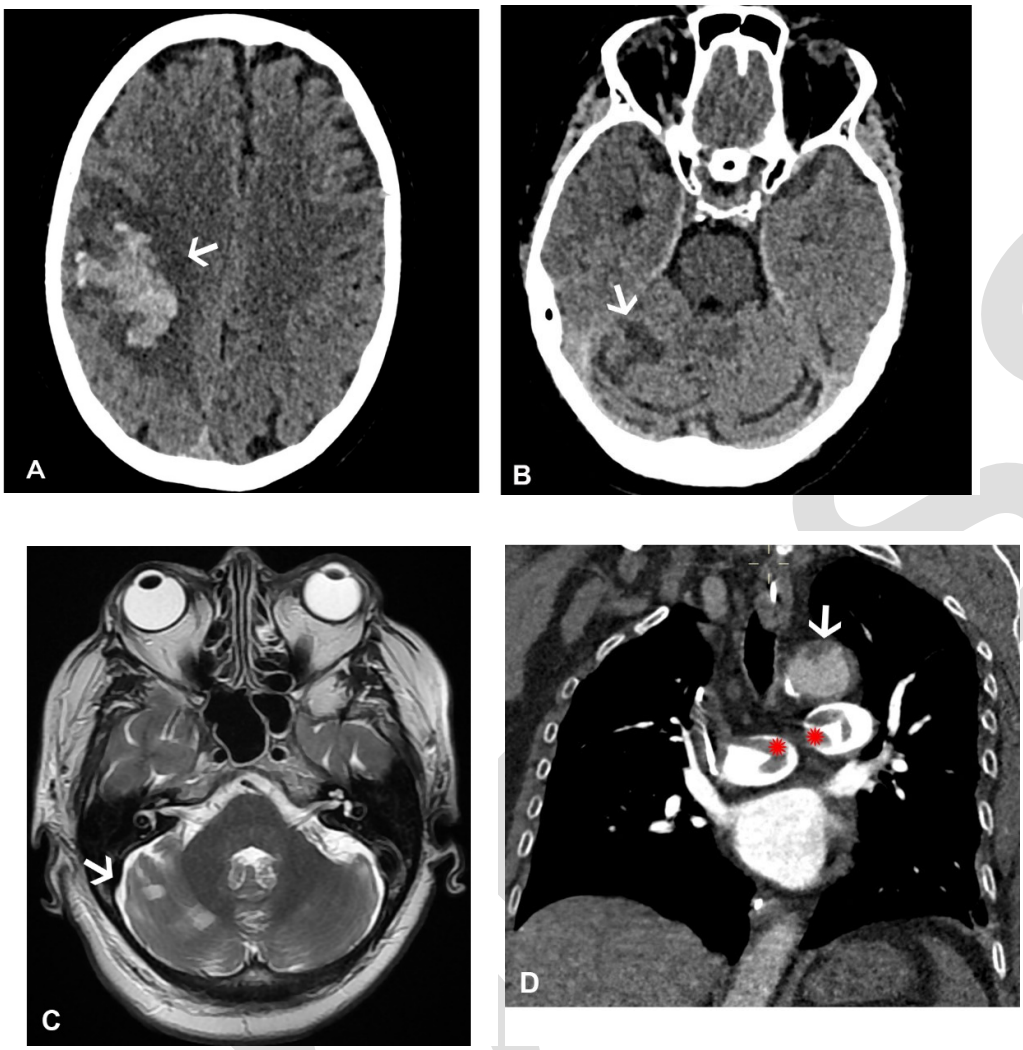

Figure 2: Images in a 64-year-old woman who presented with confusion and collapse and was diagnosed with intracranial hemorrhage associated with cerebral venous sinus thrombosis secondary to VITT. **(A)** Axial unenhanced head CT image demonstrates a large right parietal lobe intraparenchymal hemorrhage and **(B)** bilateral infarcts in the cerebellum confirmed on Axial brain T2-weighted MRI. **(D)** CT pulmonary angiogram coronal reformatted image shows eccentric mural thrombus within the aorta (white arrow) and large central saddle embolus (red asterisks).

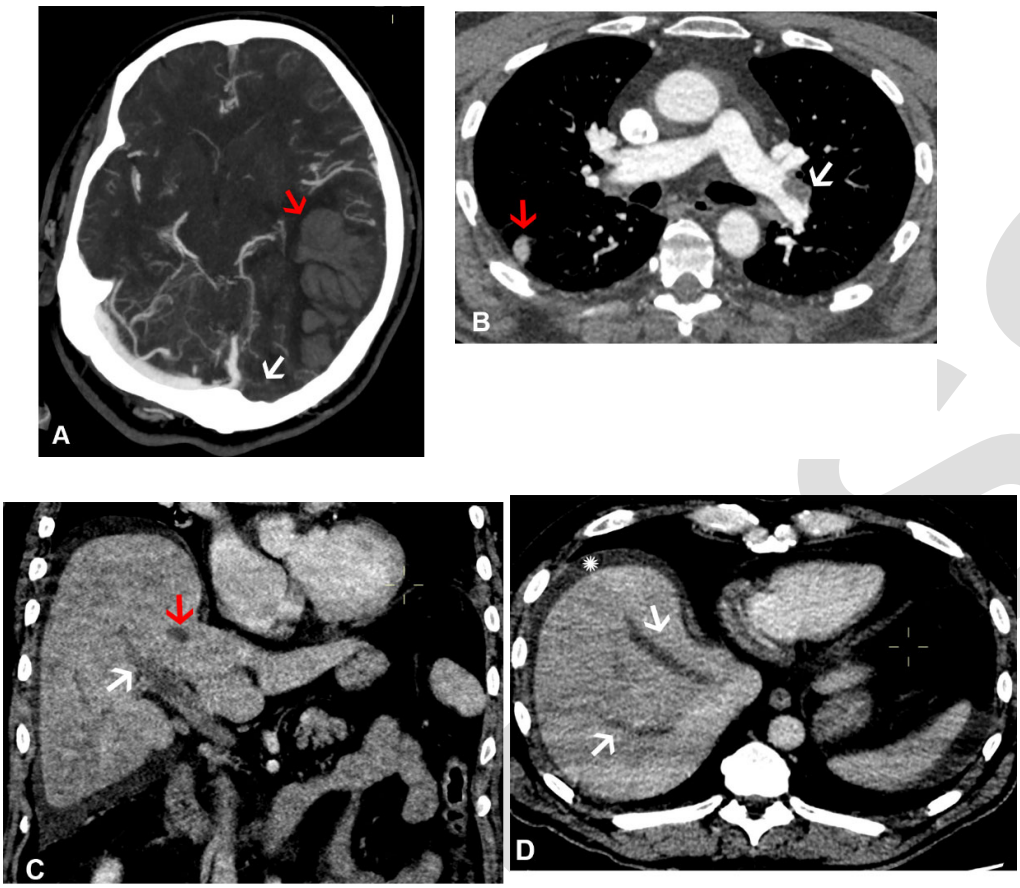

Figure 3: Images in a 56-year-old man with sudden loss of consciousness 2 weeks after vaccination for COVID-19 and subsequently diagnosed with VITT. **(A)** Axial contrast enhanced CT venogram Maximum Intensity Projection shows occlusive thrombus within the left transverse sinus (white arrow) and adjacent large volume parenchymal hemorrhage in the left parietal lobe (red arrow). Subsequent whole body imaging was performed. **(B)** Axial CT pulmonary angiogram showing a segmental PE (white arrow) and peripheral upper lobe infarct (red arrow) and in **(C)** Coronal contrast enhanced abdominal CT showing large volume main and right portal vein thrombosis (white arrow) and hepatic vein thrombosis (red arrow)

confirmed in **(D)** an axial image from the same study showing hepatic vein thrombus in both the middle and right hepatic veins.

Table E1: Demographic Data, Presenting Symptoms, Imaging Modalities, Laboratory Results and Outcomes of Each Patient with Vaccine-induced Immune Thrombotic Thrombocytopenia

Sex	Age at presentation	Vaccine to symptoms (days)	Presenting symptoms	Relevant medical history	Thrombus	Treatment	Platelet Nadir (10^9/liter)	D-dimer (DDU)	Outcome
M	66	12	Abdominal pain	Diabetes, DVT, MG	DVT, PE, adrenal haemorrhage	LMWH, DOAC	15	10388	Alive
M	27	11	Headache	NA	CVST, ICH	DOAC, argatroban	37	NA	Died
M	32	21	Headache, vomiting	NA	CVST, ICH	LMWH, DOAC	87	NA	Alive
F	57	17	Headache, confusion	NA	CVST, ICH	DOAC	173	4985	Alive
F	64	14	Headache, confusion	Alcoholic liver disease	ICH, PE, SAT (aorta, superior mesenteric artery, cerebellar infarct)	LMWH	51	NA	Alive
M	53	10	Chest, left arm pain	Hypertension	CVST, SAT (left ventricle)	Platelet transfusion	19	10836	Died
M	64	14	Shortness of breath	NA	Aortic thrombus, SAT (aorta, renal artery, subclavian artery)	DOAC, argatroban	46	NA	Died
M	39	9	Headache	NA	CVST, ICH	LMWH	31	10316	Alive
M	59	15	Headache, expressive dysphasia and right sided neglect	NA	CVST, PE, systemic DVT (hepatic vein)	LMWH, DOAC, argatroban	58	9652	Alive

M	49	12	Vomiting, diarrhea, rectal bleeding	NA	CVST, PVT	Argatroban, IVIG, steroids, plasma exchange	13	22495	Alive
M	55	19	Headache, confusion	NA	PE, systemic DVT (hepatic vein)	IVIG and plasma exchange	121	4500	Alive
F	37	12	Headache	Cocaine use	CVST, PE, systemic DVT (common iliac vein)	UFH, IVIG, steroids, plasma exchange	9	24070	Alive
M	22	13	Headache, hemiparesis	NA	CVST, PE, PVT	Argatroban, IVIG, steroids, plasma exchange	22	25580	Alive
M	21	2	Abdominal pain, headache	Asthma	CVST, PVT, superior vena cava thrombus	DOAC and IVIG	91	3840	Alive
F	30	12	Headache	NA	CVST, PE, PVT, systemic DVT (splanchnic vein)	UFH IVIG, steroids, eltrombopag, platelet transfusion	14	16280	Alive
F	35	10	Headache and hemiparesis	NA	PVT, SAT (middle cerebral artery)	UFH, IVIG, plasma exchange, platelet transfusion	64	11220	Died
F	38	14	Abdominal pain	Osteoarthritis	Renal vein thrombus, adrenal vein thrombus	DOAC, argatroban, IVIG, steroids	72	4160	Alive
M	46	17	Chest pain	Smoker	CVST, systemic DVT (adrenal vein), SAT (right coronary artery and intracardiac thrombus)	UFH, IVIG, steroids, plasma exchange	11	24900	Alive
M	46	20	Headache, visual disturbance, vomiting	Essential thrombocytosis	CVST	UFH, IVIG, steroids, plasma exchange	95	17780	Alive
F	42	12	Left-sided weakness, dysarthria, sensory inattention, hemianopia	Smoker, High body mass index	SAT (internal carotid artery and common femoral arteries)	LMWH	85	NA	Died
M	32	11	Headache, blurred vision.	Hypothyroidism	SAT (internal carotid artery)	Argatroban, IVIG	6	59048	Died
F	47	13	Hemoptysis, left-side facial rash, vomiting, left flank pain.	Depression, previous	CVST, PE, PVT, SAT (aorta, middle cerebral artery, posterior	Fondaparinux, argatroban, IVIG	10	20000	DIed

				unprovoked PE, Smoker	cerebral artery, brachial artery)				
M	29	11	Headache, photophobia	Mild learning difficulties	CVST	Fondaparinux, argatroban, IVIG	45	13000	Alive
M	51	7	Headache	NA	CVST, DVT	Fondaparinux, IVIG	55	17355	Alive
F	48	13	Headache	Asthma	CVST, PE	Fondaparinux, DOAC, IVIG, steroids	56	43087	Alive
M	46	8	Tonic clonic seizure	NA	SAT (middle cerebral artery)	Fondaparinux, IVIG, platelet transfusion	15	7678	Alive
M	34	11	Reduced GCS, headache, vomiting, photophobia, hemiparesis	Bipolar disorder	CVST, PE	UFH, DOAC, plasma exchange, steroids, platelet transfusion	23	37293	Alive
F	59	14	Headache, left-hand weakness.	NA	CVST, PE, systemic DVT (hepatic vein)	DOAC, argatroban, IVIG, steroids, platelet transfusion	18	38588	Alive
F	39	11	Headache, photophobia, nausea, foot pain.	NA	CVST	DOAC, argatroban, IVIG, steroids, platelet transfusion	43	4184	Alive
F	23	7	Headache, photophobia, vomiting, seizure, chest pain.	NA	PE, PVT, right ventricular thrombus, adrenal haemorrhage	UFH, DOAC, argatroban, steroids,	73	17548	Alive
M	64	14	Collapse	ORIF right ankle	PE	DOAC, argatroban, IVIG,	36	8010	Alive
M	39	16	Pyrexia, night sweats	Bipolar disorder	PE, PVT	DOAC, argatroban, IVIG, steroids	35	42155	Alive
F	25	6	Headache	Primary sclerosing cholangitis, migraines	CVST	UFH, IVIG, steroids, platelet transfusion	7	NA	Died
F	40	11	Headache, confusion	Migraines	CVST	IVIG, steroids	49	8000	Alive

M	47	7	Chest pain	Hypertension, diverticulitis	SAT (circumflex coronary artery and posterior descending coronary artery)	DOAC, plasma exchange, steroids	8	5370	Alive
M	28	13	Headache	Cardiomyopathy, acquired polycythemia secondary to smoking	CVST	IVIG, steroids	3	5690	Alive
F	21	28	Shortness of breath, hemoptysis, pleuritic chest pain	NA	PE	DOAC, IVIG, steroids	11	1900	Alive
M	48	3	Headache, blurred vision, retro-orbital pain, abdominal pain	Depression	CVST, PVT, SAT (aorta, renal artery, internal iliac artery)	Argatroban, IVIG, steroids	18	66	Alive
M	54	11	Headache	Hiatus hernia	CVST	DOAC, IVIG, steroids	117	5420	Alive
F	26	11	Headache, neck stiffness, photophobia, nausea	NA	CVST	IVIG, steroids	42	NA	Alive

Note—CTV = CT venogram; CTA = CT angiogram; CT AP = CT abdomen and pelvis; CT CAP= CT chest, abdomen and pelvis; CT KUB = CT kidney, ureter and bladder; CTPA = CT pulmonary angiogram DOAC = direct oral anticoagulant; DVT = deep venous thrombosis; GCS = Glasgow Coma Scale; IVIG = intravenous immunoglobulin; LMWH = low-molecular-weight heparin; MG = myasthenia gravis; MRV = MRI venogram; ORIF = open reduction and internal fixation; PE = pulmonary embolism; UFH= unfractionated heparin