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

**Manuscript Type:** Case Series

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Key Results:
1. Six patients admitted to a general hospital between 9 and 31 days after receiving the first dose of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine presented with strongly detected anti-platelet factor 4 antibodies and severe thrombosis; symptoms developed 3 to 26 days after inoculation.
2. Thrombotic events, predominately venous, were detected by CT, MRI, or ultrasound examination.
3. All patients recovered after receiving intravenous immunoglobulin and non-heparin based anti-coagulation.

Abbreviations:
CTPA: CT pulmonary angiogram
HIT: Heparin-Induced Thrombocytopenia
IQR: Interquartile range
IVIG: Intravenous immunoglobulins
OD: Optical density
PF4: Platelet factor 4
TPE: Therapeutic plasma exchange
VITT: Vaccine-induced immune thrombotic thrombocytopenia

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

Abstract:
This case series reports six patients (4 men; median age 38 years; interquartile range 26-48) presenting with vaccine-induced thrombocytopenia and thrombosis beginning 3 to 26 days after receiving the first dose of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine. The patients were admitted to a general hospital between 9 to 31 days after the first dose. All patients had strongly detected anti-platelet 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/venous thrombosis. All patients recovered after receiving intravenous immunoglobulin and non-heparin based anti-coagulation.
**Introduction:**
This case series demonstrates rare thromboembolic events and thrombocytopenia after receiving the first dose of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine. 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 to 28 days post-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 anti-platelet factor 4 (PF4) antibodies and thrombotic events (3-4). Detected anti-PF4 antibodies on HIT (Heparin-Inducted Thrombocytopenia) Enzyme-Linked Immunosorbent Assay) of the IgG 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, intra-cranial, 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 hematology 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 2020. Enzyme-Linked Immunosorbent Assay (PF4 IgG, Immucor GTI Diagnostics) was used to detect anti-PF4 antibodies; an optical density greater than 0.4 was the cut-off for a positive HIT test. Arterial and venous thrombosis were detected by CT, MRI and abdominal ultrasound.

**Results:**

**Patient Characteristics**
Six patients [4 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 additionally 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 to 26 days after inoculation. One patient was on the oral contraceptive pill, and another had a history of secondary polycythemia. All patients continue to improve on 1-month follow-up. Treatment included non-heparin anti-coagulation, steroids, intravenous immunoglobulin (IVIG), and therapeutic plasma exchange (TPE).

**Laboratory testing**
Nadir platelet count ranged from 8-117 $10^9$/liter, median value of $50 \times 10^9$/liter (n=6; IQR 18-111). D-Dimer was elevated in all patients (median 5690 mcg/liter, IQR 5395-42750 mcg/liter, n=5). Activated partial thromboplastin time and the International normalized ratio (INR) were normal in all patients. Fibrinogen was very low (0.1g/liter) in patient 4 leading to cryoprecipitate support (median 2.1, IQR 0.8-2.85, n=5). High troponin 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 (OD) median 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. CT pulmonary angiogram (CTPA) carried out on day 4 due to increased oxygen requirement showed multiple pulmonary emboli (white arrow) and a large left atrial appendage thrombus (blue arrow) [Figure 1(A)] in addition to bilateral ground-glass opacification within the lungs [Figure 1(B)]. He developed acute kidney injury on day 6 and imaging did not confirm intra-abdominal thrombosis. Laboratory features included thrombocytopenia, high D-dimer and strongly positive anti-PF4 antibodies [Table].

Patient 2 was admitted with a headache and blurred vision. Non-contrast head CT demonstrated hyperdensity (blue arrows) involving the superior sagittal sinus and bilateral transverse sinuses. CT venography confirmed thrombotic disease within this distribution (red arrows) [Figure 2(A) and (B)]. His condition deteriorated further as he developed seizures and dropped his Glasgow Coma Scale. He was transferred to a tertiary intensive therapy unit for consideration of decompressive craniotomy. A week following initial admission, the patient developed 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 (white arrows) [Figure 2(C) and (D)].

Patient 3 presented with shortness of breath, hemoptysis and pleuritic chest pain; an admission CTPA [Figure 3] showed (A) extensive pulmonary emboli (white arrows), (B) features of right heart strain (blue arrows) and (C) pulmonary infarcts (red arrows). 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. CT venography showed thrombosis within the right transverse sinus (blue arrow) [Figure 4(A)] and right jugular vein. CT abdomen/pelvis demonstrated extensive occlusive thrombi within the main portal vein (white arrow), right and left portal vein branches [Figure 4(B)], superior mesenteric vein, and splenic vein (white arrow). In addition, CT showed acute thrombus within the right renal infarct (red arrow) [Figure 4(C)] and within the right internal iliac artery (orange arrow) [Figure 4(D)].

Patient 5 presented with a headache, and CT demonstrated asymmetrical hyperdensity within the left transverse, sigmoid and straight sinuses. Extensive filling defects within the left transverse, sigmoid, and straight (white and red arrows) sinuses [Figure 5(A) and (B)] in addition to the left jugular vein was confirmed on subsequent CT venography. No further thrombosis was identified on CT of the chest, abdomen, and pelvis. One day following admission, the patient developed new seizures. A repeat head CT showed a 2cm left temporal cortical venous hemorrhage (green arrow) [Figure 5(C)].
Patient 6 was admitted with headaches, photophobia, and nausea. Head CT demonstrated hyperdensity of the inferior sagittal and transverse (green arrow) sinuses [Figure 6(A)]. The patient was transferred to the tertiary neurological center. Thrombus within the straight sinus, bilateral transverse sinuses (red arrow) [Figure 6(B)] and right internal jugular vein was confirmed on subsequent CT venography. Abdominal US was performed on day 6 due to raised alanine transaminase, which confirmed intrahepatic main and right portal vein thrombosis (white arrow) [Figure 6(C)] with suspected cavernous transformation.

Discussion:
This case series describes the imaging and hematology findings in six patients with VITT 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 (7-10). Patients had a high D-dimer, low platelet count, atypical arterial or venous thrombosis and developed symptoms four 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, 11-12). These will be revised and evolve with better clinical understanding. We identified asymptomatic intra-cardiac thrombus in one patient. An argument could be made for scanning additional asymptomatic regions in patients with VITT, especially for co-existing asymptomatic cerebral venous thrombosis, potentially altering oral anti-coagulation 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 co-morbidity or immune underlay predicting VITT.

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 non-tolerance 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 (13). 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, leucocyte, and endothelial activation. VITT antibodies can mimic the effect of heparin by binding to a similar site on PF4, leading to thrombosis with platelet activation (14).

These patients were managed according to interim guidelines and discussion with the UK Expert Haematology Panel. All six patients received IVIG, five of them were given steroids, and Fondaparinux was the most common non-heparin anti-coagulant. TPE was used in three patients, either due to being refractory to initial management including IVIG 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.
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Table: Summary of Clinical Information, Laboratory Results and Management of Each Patient with Vaccine-induced Immune Thrombotic Thrombocytopenia

| Patient | Age | Sex  | Vaccination dose | Vaccination to admission time (days) | Time from vaccine to symptoms (days) | Presenting complaint | Past medical history | Platelet nadir (10^9/L) | D-Dimer on admission (mcg/L) | Fibrinogen nadir (g/L) | SARS-CoV-2 antibody test | HIT ELISA to detect PF4 antibody | Anticoagulation | Other | Outcome |
|---------|-----|------|------------------|--------------------------------------|--------------------------------------|---------------------|---------------------|----------------------|----------------------------|----------------------|------------------------|----------------------------|------------------------|-------|---------|
| 1       | 47  | Male | 1st              | 9                                    | 7                                    | Chest pain          | Hypertension        | 8                   | 5370                       | 1.5                  | Negative   | Positive, OD 3.5          | Fondaparinux          | NA    | NA      |
| 2       | 28  | Male | 1st              | 12                                   | 3-4                                  | Severe headache     | Diverticulitis      | 37                  | 5690                       | 2.1                  | Negative   | Positive, OD 2.2          | Argatroban (during TPE) | Unknown | No      |
| 3       | 21  | Female| 1st              | 31                                   | 26                                   | Blurred vision      | Cardiomyopathy      | No                   | 19500                      | 3.6                  | Positive   | Positive, OD 3.0           | DOAC                   | Yes   | Yes     |
| 4       | 48  | Male | 1st              | 15                                   | 3                                    | Vomiting            | Secondary polycythemia | No                   | 66000                      | 0.1                  | Negative   | Positive, OD 2.04          | Fondaparinux          | Unknown | No      |
| 5       | 54  | Male | 1st              | 19                                   | 11                                   | Pleuritic chest     | Depression          | No                   | 5420                       | 2.1                  | Positive   | Positive – OD carried out at tertiary hospital | Warfarin              | Unknown | No      |
| 6       | 26  | Female| 1st              | 11                                   | 11                                   | Hemoptysis          | Depression Barre    | Yes                  | Not available              | Not available      | Positive   | Positive – OD carried out at tertiary hospital | Treatment dose Fondaparinux Warfarin | No     | No      |

DOAC = direct oral anticoagulant; ELISA = enzyme-linked immunosorbent assay; HIT = heparin induced thrombocytopenia; IVIG = intravenous immunoglobulin; LMWH = low-molecular-weight heparin; OD = optical density; PCOS = polycystic ovary syndrome; PF4 = platelet factor 4; TPE = therapeutic plasma exchange; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
Figure 1: (A) Axial CTPA images in a 47-year-old man demonstrating a left atrial appendage thrombus (blue arrow), right lobar pulmonary embolus (white arrow) and (B) bilateral ground-glass opacification.
Figure 2: (A) Axial head CT image in a 28-year-old man showing hyperdense bilateral transverse cerebral sinuses (blue arrows) and (B) axial CT venogram image demonstrating filling defects within the transverse cerebral sinuses bilaterally (red arrows). (C-D) T2 coronal fluid-attenuated inversion recovery brain MRI images demonstrating small foci of high T2 signal within the frontal lobes bilaterally thought to represent venous infarcts (white arrows).
Figure 3: (A) Axial CTPA image in a 21-year-old woman showing bilateral central pulmonary emboli (white arrows) with (B) enlargement of the right heart and flattening of the intraventricular septum in keeping with right heart strain (blue arrows). (C) Lung window axial CTPA demonstrating bilateral peripheral areas of opacification in keeping with pulmonary infarcts (red arrows).
Figure 4: (A) Axial CT venogram image in a 48-year-old man showing a right transverse sinus filling defect in keeping with thrombosis (blue arrow). (B) Axial portal venous CT abdomen/pelvis demonstrating portal vein and splenic vein thromboses (white arrows) in addition to (C) right upper pole renal infarct (red arrow) and (D) acute right internal iliac artery thrombus (orange arrow).
Figure 5: (A) Sagittal head CT in a 54-year-old man showing a hyperdense straight sinus (white arrow) confirmed on (B) CT venogram (red arrow). (C) Axial head CT showing a 2cm left temporal lobe cortical venous hemorrhage (green arrow).
Figure 6: (A) Axial non-contrast head CT in a 27-year-old woman showing a hyperdense right transverse sinus (green arrow) confirmed on (B) CT venogram with a filling defect (red arrow). (C) Doppler US image showing no flow within the intrahepatic main portal vein in keeping with thrombosis (white arrow).