Adenovirus-Vectored COVID-19 Vaccine-Induced Immune Thrombosis of Carotid Artery: A Case Report

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ABSTRACT

Objective: Venous thromboses and thrombocytopenia after vaccination with the adenovirus-vectored COVID-19 vaccine ChAdOx1 nCov-19 (AstraZeneca) have been linked to serum antibodies against platelet factor 4 (PF4)–polyanion complexes. We here report vaccine-induced isolated carotid arterial thrombosis.

Methods: Imaging and laboratory findings, treatment decisions and outcome of this case are presented.

Results: Eight days after having received the first dose of ChAdOx1 nCov-19 vaccine, a 31-year-old man was admitted to our stroke unit with acute headache, aphasia, and hemiparesis. D-dimers were slightly elevated, but platelet count and fibrinogen level were normal. MRI-confirmed mainstem occlusion of middle cerebral artery resolved within 1 hour after start of IV thrombolysis. A wall-adherent, non-occluding thrombus in the ipsilateral carotid bulb was identified as the source of embolism. Cardiac or paradoxical (venous) embolism was excluded. Screening for presence of heparin-induced thrombocytopenia-related antibodies was positive, and highly elevated serum IgG antibodies against PF4–polyanion complexes were subsequently proven. Treatment with aspirin and subcutaneous danaparoid, followed by phenprocoumon, led to thrombus shrinkage and dissolution within 19 days, and favorable clinical outcome.

Discussion: Vaccine history is important in patients not only with venous but also with arterial thromboembolic events. Vaccine-induced immune thrombosis of brain-supplying arteries may well be handled.
To fight the COVID-19 pandemic, the European Medicines Agency approved four vaccines until March 2021. Of these, ChAdOx1 nCoV-19 (AstraZeneca) is a replication-defective chimpanzee adenovirus-vectored vaccine containing the full-length SARS-CoV-2 spike glycoprotein gene.\(^1\) In recently reported 23 heparin-naïve patients with ChAdOx1 nCov-19 vaccine-induced thromboses and thrombocytopenia (VITT) highly elevated serum IgG antibodies to platelet factor 4 (PF4)–polyanion complexes were found.\(^2\)\(^-\)\(^4\) VITT typically manifests with, often cerebral, venous thromboses, but also a few arterial thromboses were noted.\(^2\)\(^-\)\(^5\) Here, we describe a case with isolated arterial thrombosis in presence of strong reacting platelet activating antibodies directed against PF4.

**METHODS**

The local ethics committee approved this study (identifier: A2021-0089). The patient provided written informed consent.

**RESULTS**

**Clinical presentation**

A 31-year-old childcare worker was admitted to our stroke unit with acute headache, aphasia, and incomplete right-sided hemiparesis. He had received his first dose of ChAdOx1 nCoV-19 vaccine eight days before, and suffered minor symptoms (fatigue, myalgia, mild headache) over a few days but then remained asymptomatic until day 8, when he experienced sudden-onset severe headache. The headache persisted despite taking cumulatively 2g paracetamol.
He was feeling weary and spent most of the day sleeping. When waking him up, his partner noticed hemiplegia and speech arrest, and called emergency.

He had no pre-existing medical condition and did not regularly take any medication. The only cardiovascular risk factor was cigarette smoking (10/day) since 12 years. His grandfather had had a stroke in high age; there were no further cardiovascular events in family history.

**Diagnostic findings**

MRI on admission revealed acute ischemia of left middle cerebral artery (MCA) territory due to distal MCA mainstem occlusion (Fig. 1). IV thrombolysis with alteplase was started, and urgent thrombectomy was planned. On catheter angiography, however, the MCA-M1 and MCA-M2 segments were re-perfused 50 min after start of alteplase; a wall-adherent carotid thrombus was noted, but no arterial dissection. Next-day CT showed two small areas of brain infarction. CT-angiography and ultrasonography confirmed a parietal solid thrombus in the left carotid bulb (Fig. 2), with a mobile tail at its proximal end (Supplemental Video). Transesophageal echocardiography and transcranial Doppler testing with agitated saline excluded an aortic, cardiac, or paradoxical (venous) source of embolism. Thus the carotid thrombus was regarded being the source of embolism into the MCA.

Initial blood tests showed slightly increased D-dimers, leucocyte counts and C-reactive protein (Table 1). Platelet count and fibrinogen level were normal, as well as standard laboratory workup, including serum lipids, homocysteine, lipoprotein (a), screening for thrombophilia (antithrombin III, factor V, factor VIII, protein C, activated protein C resistance, antiphospholipid antibodies, search for prothrombin mutation g.20210G>A), and tests for antinuclear antibodies, and antineutrophil cytoplasmic antibodies. Since the
thrombosis occurred within the typical time window for VITT,\textsuperscript{2} we screened for heparin-induced thrombocytopenia (HIT)-related antibodies despite normal platelet count, with a positive test result. Subsequent workup proved highly elevated serum IgG antibodies against PF4–polyanion complexes. These antibodies activated platelets in presence of PF4 in a washed platelet-activation assay.\textsuperscript{2}

Treatment and outcome

IV thrombolysis entailed dramatic neurological recovery within one hour. Symptoms persisting on days 9-28 were slight phonemic paraphasia and difficulties in complex cognitive tasks. Combined anticoagulation with aspirin 100 mg/day and subcutaneous danaparoid 2x750 mg/day on days 9-13, followed by phenprocoumon (target INR 2-3),\textsuperscript{6} led to marked thrombus shrinkage (Fig. 2, Video 1) and complete dissolution by day 28.

DISCUSSION

We report on a young patient with ischemic stroke in a typical time window for VITT,\textsuperscript{2-5} without definite thrombocytopenia. For immunogenic thrombocytopenia, a platelet count fall of >50% in 48h is also relevant, which may have occurred within normal platelet counts. He had isolated carotid arterial thrombosis with secondary embolism into the MCA, along with highly elevated antibodies against PF4–polyanion complexes, but normal platelet counts. Therefore, standard IV thrombolysis with alteplase and subsequent aspirin followed by oral vitamin-K-antagonist anticoagulation was initiated and led to favorable outcome. Vitamin-K-antagonist anticoagulation in early stage of VITT occurring with thrombocytopenia and disseminated intravascular coagulation is not recommended due to the rapid decline of protein
C, which could potentially aggravate thrombosis. However, we considered the use as safe, because no thrombocytopenia and no signs of disseminated intravascular coagulation were present in our patient. To avoid heparin administration, danaparoid was given for prophylaxis of deep vein thrombosis. Treatment with intravenous immunoglobulins, recommended particularly for vaccination-induced CVST to interrupt Fcγ receptor–mediated platelet activation, was omitted here because of normal platelet counts.

We conclude that any unusual thrombosis 4-20 days after vector-based vaccination against COVID-19 should prompt investigation of VITT antibodies.

Video 1-http://links.lww.com/WNL/B480

References


Table 1. Laboratory and sonographic findings 8-28 days after vaccination (stroke onset on day 8)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Findings on post-vaccination day No.</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>18</th>
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<th>28</th>
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<td>Platelet count, $10^9$/L</td>
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<td>Leucocyte count, $10^9$/L</td>
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<td>C-reactive protein, mg/L</td>
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<td>Fibrinogen, g/L</td>
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<td>D-dimers, mg/L</td>
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<td>SARS-CoV-2 RT-PCR test</td>
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<td><strong>Sonographic findings</strong></td>
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<td>Carotid thrombus volume, mm$^3$</td>
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ELISA denotes enzyme-linked immunosorbent assay; HIT, heparin-induced thrombosis; INR, international normalized ratio; Neg, negative; PF4, platelet factor 4; Pos, positive; RT-PCR, reverse transcriptase-polymerase chain reaction. Abnormal findings in bold.

$^1$ Values increased on oral anticoagulant therapy with vitamin K antagonist (phenprocoumon)
Figure legends

Figure 1. Imaging of brain and intracranial arteries.

Multimodal imaging findings of brain and intracranial arteries of the patient with acute ischemic stroke on post-vaccination day 8. A, B) Diffusion-weighted MRI showing acute ischemia in the territory of left middle cerebral artery (MCA). C) Time-of-flight MR-angiography showing distal mainstem occlusion of left MCA (arrow). D) Digital subtraction angiogram 50 min after start of IV thrombolysis therapy confirmed reperfusion of the M1- and M2-segments of left MCA, with only a small temporal M3-branch remaining occluded (arrow). E, F) CT performed 24 hours after thrombolysis therapy showing small infarctions in the left insular and temporal cortex (arrows).
Figure 2. Imaging of extracranial carotid arteries.

Multimodal imaging findings of left common carotid artery (CCA) and internal carotid artery (ICA) on post-vaccination days 11, 16, and 23. A) CT angiogram (day 11) showing a parietal thrombus in the CCA bulb, extending into the offspring of ICA, causing a lumen stenosis of <50% (arrow). B) Coronal sonogram (day 11) of this wall-adherent 190-mm³ thrombus (arrow). C) Axial sonogram (day 11) of this mostly solid, non-occluding thrombus with a slightly mobile tail at its proximal end (arrow; see also the Video 1). D) Axial sonogram (day 16) at the same level as shown in (C), demonstrating beginning shrinkage (140 mm³) of the thrombus (arrow). E) Axial sonogram (day 23) at the same level as shown in (C), demonstrating marked shrinkage (50 mm³) of the thrombus (arrow). F) Sagittal sonogram (day 23) of the residual thrombus (arrow).
Legends to Video 1

Real-time cervical ultrasonography findings in the recipient of the ChAdOx1 nCoV-19 vaccine who suffered acute ischemic stroke 8 days after vaccination. Shown are coronal and axial sonograms of the thrombus in the cervical bulb of left common carotid artery (CCA), extending into internal carotid artery (ICA), at different time points after vaccination.

**Segment 1.** Coronal and axial sonograms of the thrombus (arrow) obtained at day 11, after 2 days of treatment with aspirin 100 mg/day and subcutaneous danaparoid 2x750 mg/day. Note the mobile tail at the proximal end of the thrombus, wobbling with the pulse.

**Segment 2.** Coronal and axial sonograms of the thrombus (arrow) obtained at day 16, after 7 days of treatment with aspirin 100 mg/day and subcutaneous danaparoid 2x750 mg/day. Note the disappearance of the mobile tail of the thrombus.

**Segment 3.** Coronal and axial sonograms of the thrombus (arrow) obtained at day 23, after 6 days of effective oral anticoagulation with a vitamin K antagonist (phenprocoumon; INR >2). Note the marked shrinkage of the thrombus.
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