Syndrome of cerebral venous sinus thrombosis and thrombocytopenia after vaccination for COVID-19

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Case Report

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Abstract

Experience in the management of COVID-19 vaccine induced thrombosis and thrombocytopenia is currently lacking. In this case series we report the presentation and our experience in the management of cerebral venous sinus thrombosis and thrombocytopenia post ChAdOx1 nCoV-19 vaccination. Two of the three cases had confirmed anti-platelet factor 4 antibodies and extracranial thrombosis. In all the cases, plasma exchange, intravenous immunoglobulins and steroids normalised the platelet count and intravenous argatroban was used for initial anticoagulation. Two cases received a platelet transfusion and required decompressive hemicraniectomy due to raised intracranial pressure, secondary to cerebral oedema and haemorrhage. Prompt assessment of a new persistent headache occurring between 5 and 28 days of receiving the ChAdOx1 nCoV-19 vaccine is warranted irrespective of age. In cases with venous thrombosis on imaging or abnormal laboratory findings (thrombocytopenia, abnormal clotting or elevated D-dimer), urgent transfer to a tertiary centre is recommended for multidisciplinary care and prevention of life-threatening complications from this rare syndrome.

Introduction

The cost to life and socioeconomic burden caused by the severe acute respiratory syndrome coronavirus 2 (SARS2-CoV-2) pandemic necessitated an unprecedented speed in vaccination design and delivery. Whilst multiple vaccinations have been approved by regulators based on phase III trial data, signals for much rarer adverse effects will only become clear as mass vaccination programmes are rolled out. Recently, several countries suspended the use of the AstraZeneca (AZ) ChAdOx1 nCoV-19 vaccine due to safety concerns arising from several patients developing an immune-mediated thrombocytopenia associated with widespread thrombosis, following vaccine administration[1,2]. Here we report our experience with the management of three cases admitted to the John Radcliffe Hospital in Oxford.

Case 1

A 34-year-old gentleman presented to the Emergency Department with drowsiness, agitation and right sided weakness following a 10-day history of constant, holocephalic headache and a 2-day history of photophobia and vomiting. He had received the AZ ChAdOx1 nCoV-19 vaccine 14 days previously. He had a history of bipolar disorder treated with lithium and was otherwise well. On admission the Glasgow Coma Score (GCS) was 10 (eyes 4, voice 3, motor 3), his pupils were equal and reactive and he had a dense right sided hemiparesis. Multiple discrete petechiae were noted on the legs and a bruise was apparent on the left shoulder. Computed tomography (CT) of the brain revealed a superior sagittal sinus hyperdensity associated with a 47 mm intraparenchymal haemorrhage in the left perirolandic region (Fig. 1). A CT venogram confirmed an extensive cerebral venous sinus thrombosis (CVST) in the superior sagittal sinus extending to both transverse venous sinuses, and thrombosis in the left vein of Trolard. Whole body CT revealed a right lower lobe segmental pulmonary embolus. His blood tests revealed a normal haemoglobin 152 g/L and white cell count 11.15 cells x 10^9/L, but low platelets (23 x 10^9/L) without platelet clumping or red cell fragmentation on blood film. A clotting screen revealed a raised prothrombin time of 14.8 seconds, a raised international normalised ratio (INR) of 1.5, a normal activated prothrombin time (APTT) of 23.9 seconds and a low Clauss fibrinogen of 0.7 g/L. D-dimer was significantly raised (37,293 mg/L). SARS2-CoV-2 polymerase chain reaction (PCR) from a throat swab was negative. His anti-S titre was 125.2 (≥50 is reported as detected) with a negative anti-N antibody result consistent with recent vaccination. He was found to have a lupus anticoagulant but did not have anticardiolipin or anti-β2 glycoprotein-1 antibodies. ADAMSTS13 activity was normal and AcuStarHIT-IgG was negative. He was sedated, intubated and transferred to the Intensive Care Unit (ICU). He was transfused with 2 adult units of platelets due to his thrombocytopenia and bleeding. He commenced plasma exchange with 1.5 plasma volumes using Octoplas on two occasions and received 1g/kg intravenous immunoglobulins (IVIg). Due to the emerging evidence of a potential association of the ChAdOx1 nCoV-19 vaccine with an autoimmune thrombocytopenia and concurrent bleeding, anticoagulation with heparin was avoided in favour of argatroban, a small molecule thrombin inhibitor with a short half-life of 50 minutes. Later, STAGO Asserachrom HPIA ELISA for anti-platelet factor 4 (PF4) antibodies was positive. Of note, the platelet count incremented and normalised to 191 x 10^9/L within two days of admission and anticoagulation continued, maintaining APTT at 1.5-3 times baseline. Despite maximal medical therapy, the GCS began to fluctuate and dilatation of the left pupil was noted with intermittently reduced responsiveness to light. Repeat CT brain scanning revealed worsened cerebral oedema with right sided midline shift and early uncal herniation. Anticoagulation was paused 8h before a decompressive hemicraniectomy and insertion of

an intracranial pressure (ICP) monitor and restarted 10 h post-operatively and after a satisfactory CT scan. Persistently high ICP recordings necessitated the insertion of an external ventricular drain after stopping anticoagulation, which led to improvement. Ultimately, the monitor had to be removed due to blockage and concerns about ventriculitis, for which he received antibiotics. His condition slowly stabilised and sedation was weaned. Once surgical interventions were no longer anticipated, anticoagulation with apixaban – an oral Xa inhibitor – was commenced at 5 mg twice daily. At present, he is off ventilation with a tracheostomy and has stepped down to a high dependency unit. He has a dense right hemiparesis and aphasia.

Case 2

A 59-year-old woman presented initially to her local hospital with a 3-day history of headache, jaw pain and left-hand weakness and subconjunctival haemorrhage. She had received the AZ ChAdOx1 nCoV-19 vaccine 2 weeks prior to her presentation and had also experienced abdominal pain over the same period. She had a previous lumbar discectomy but was otherwise well. On examination she had a left pronator drift. An initial non-contrast CT head scan was reportedly normal, and she was managed as a suspected ischaemic stroke with 300mg aspirin and 300mg clopidogrel. She subsequently had a focal motor seizure and dense left hemiparesis with neglect and minimal sensation on the left side. At this stage her platelet count was 21 x 10^9/L with mildly raised prothrombin time of 14.5 seconds, INR 1.2, and raised D-dimer (12,174µg/L). She was loaded with 1g of levetiracetam and underwent an MRI head which revealed loss of flow void in the anterior aspect of the superior sagittal sinus with susceptibility artefact on the gradient echo. These features were considered indicative of a cortical vein thrombosis with adjacent cortical haemorrhage. A small area of restricted diffusion around the precentral gyrus, suspicious for haemorrhagic infarction was also noted. An MR venogram was performed 4 hours later which confirmed thrombosis in the superior sagittal and right transverse sinuses as well as a substantial progression of the right haemorrhagic infarction to a frontal haematoma associated with midline shift. Due to the possibility of vaccine associated thrombocytopenia and thrombosis, she received IVIg (1g/kg) and 500mg intravenous methylprednisolone and was transferred to our hospital for further management. On arrival, she became unresponsive with GCS 7 (Eyes 1, Voice 1, Motor 5) with a fixed, dilated right pupil. She was transferred to the ICU for intubation and ventilation. A repeat non-contrast CT scan after intubation showed worsening cerebral oedema secondary to haemorrhage with associated midline shift. Repeat blood tests revealed a thrombocytopenia (18 x 10^9/L) and lymphopenia (0.41 x 10^9/L) without fragments or platelet clumps on the blood film. She had deranged liver function with raised bilirubin (26 mmol/L) and alanine aminotransferase (144 IU/L). A clotting screen showed a raised prothrombin time of 13.6 seconds, INR 1.3, a normal APTT of 24.4 seconds and a normal Clauss fibrinogen 2.0g/L. The D-dimer was further raised at 38,588 mg/L, AcustarHIT negative and anti-PF4 ELISA was positive. A SARS-CoV-2 PCR from a throat swab was negative. In light of her thrombocytopenia and recent treatment with antiplatelet agents, she was given 4 adult units of platelets to ensure platelet count > 100 x 10^9/L and then underwent an uncomplicated hemicraniectomy and intracerebral clot evacuation using imaging guidance. Intraoperatively, she also received 2 units of cryoprecipitate and had an intracerebral pressure monitor inserted. Post-surgery, her coagulation had normalised with platelets of 115 x 10^9/L. Both pupils became reactive to light. A post-operative CT scan showed satisfactory evacuation of the right intraparenchymal clot with an ICP around 17cmH_20. She was started on argatroban infusion 9 h post-operatively maintaining APTT 1.5-3 times baseline and received 2 days of 1.5 plasma volume plasma exchange. Whole body CT revealed right lower lobe pulmonary emboli and a thrombosed right hepatic vein which explained her impaired liver function and abdominal pain on presentation. Seven days after her initial presentation, her platelet count fell to 77 x 10^9/L. Two further infusions of IVIg (0.5g/kg) were administered leading to platelet normalisation (302 x 10^9/L) two days later. She was successful extubated, and currently she obeys commands, intermittently opens her eyes to voice and has a dense left hemiparesis.

Case 3

A 39-year-old woman presented initially to her local hospital Emergency Department 10 days after having the first dose of AZ ChAdOx1 nCoV-19 vaccine. She complaint of right calf pain associated with a cold sensation of the limb and a left temporal headache. Whilst in the Emergency Department she experienced mild photophobia. She was discharged home as the symptoms were resolving but she woke up the same night with a severe headache, photophobia, phonophobia and nausea that did not resolve with paracetamol or codeine. She also noticed a petechial rash across her legs and abdomen. She represented to the Emergency Department 1 day later and received a CT venogram which showed left transverse and sigmoid sinus thrombosis with involvement of the sagittal sinus and thrombosed left jugular vein. A full blood count showed a fall in the platelet count from 255 x 10^9/L at

initial presentation to a nadir of 63 x 10^9/L within 48 hours post admission. The admission clotting screen showed a raised PT of 15.1 seconds, a raised APTT of 33.2 seconds, an INR of 1.1, a normal Clauss fibrinogen of 3.2g/L and a high D-dimer of 6,050 mg/L. The haemoglobin was 132g/L, the white cell count was slightly elevated (12.9 x 10^9/L) with a normal urea and electrolytes and a normal CRP. She was transferred to her local stroke unit where she was treated with IVIg (1g/kg) for 3 days and fondaparinux 7.5mg once daily. She was subsequently transferred to our hospital for further management. Her cranial nerve, motor and sensory examination was normal. She also had warm and well perfused limbs with both pedal pulses present. Her fondaparinux was stopped due to its long half-life in case neurosurgical intervention was required and she was started an argatroban infusion as well as a 1mg/kg prednisolone. She underwent 2 x 1.5 plasma volume plasma exchange with Octoplas, with minimal improvement in the platelet count. The D-dimer rose to 20,289 mg/L. Her AcutstarHIT was negative. Her initial anti-PF4 ELISA returned as negative. Three further 1 x plasma volume plasma exchanges ensued with platelet recovery. Once the platelet count exceeded 100 x 10^9/L, argatroban was changed to apixaban 5mg BD. At present she remains stable with no focal neurology.

Discussion

The presentation of these cases is consistent with the syndrome of vaccine induced thrombosis with thrombocytopenia reported throughout Europe. At the time of writing, the Medicines and Healthcare products Regulatory Agency (MHRA) have stated that those under the age of 30 can be offered alterative, non-AZ vaccines. Both thrombocytopenia and CVST have been reported in patients with coronavirus infection[3,4] and prothrombotic events are a recognised complication of SARS2-CoV-2 infection[5]. Our patients had no risk factors for immune-mediated thrombocytopenia or thrombosis and tested negative for SARS2-CoV-2 infection. Although a causative association has not been definitively demonstrated, an immune-mediated process triggered by the vaccine is possible. It is noteworthy that the presence of anti-PF4 antibodies was confirmed in two of the cases despite none having had a previous exposure to heparin. Accordingly, aggressive immunomodulation with a combination of plasma exchange to rapidly remove potentially pathogenic antibodies, IVIg and steroids normalised the platelet counts. Recurrent or persistent thrombocytopaenia was seen up to 7 days later, requiring repeat plasma exchange to achieve a normal platelet level. Our small case series (summarised in Table 1) suggests that prompt assessment of a new persistent headache occurring between 5 and 28 days of receiving the AZ ChAdOx1 nCoV-19 vaccine is warranted irrespective of age. In cases with venous thrombosis on imaging or abnormal laboratory findings (thrombocytopenia, abnormal clotting or elevated D-dimer), urgent transfer to a tertiary centre is recommended for multidisciplinary care and prevention of life-threatening complications from this rare syndrome.

Declarations

Potential conflicts of interest: Nothing to report

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Consent: Consent for publication of the cases was obtained from each patient or their immediate next of kin

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Tables

Case	Age & Sex	Presenting symptoms	Days from vaccination to symptom onset	Platelets on admission Normal range: 150-400	Clotting screen on admission Normal range: PT: 9-12 (seconds) APTT: 20-30 (seconds) INR: 9-5 (IU)	Claus Fibrinogen Normal range: 1.5-4.0 (g/L)	Peak D-dimer Normal range: 0-500 (mg/L)	PF4 antibody ELISA	Extracranial thrombosis
1	34 Male	10 days of headache Right sided hemiparesis	13	23 X 10^9/L	PT 14.8 INR 1.5 APTT 23.9	0.7	37,293	Positive	Right lower lobe segmental pulmonary embolus
2	59 Female	3 days of headache Left hand weakness	14	21 X 10^9/L	PT 14.5 INR 1.2 APTT 24.4	2.0	38,588	Positive	Thrombosed right hepatic vein and right lower lobe pulmonary emboli
3	39 Female	Right calf pain left temporal headache	10	255 X 10^9/L then dropping to 86 then 63	PT 15.1 INR 1.1 APTT 33.2	3.2	20,289	Negative	Nil

Table 1. Comparison of demographic and laboratory characteristics of all three patients. *Units in parentheses. Abbreviations: PF4 platelet factor 4. PT prothrombin time; APTT activated partial thromboplastin time.*

Figures

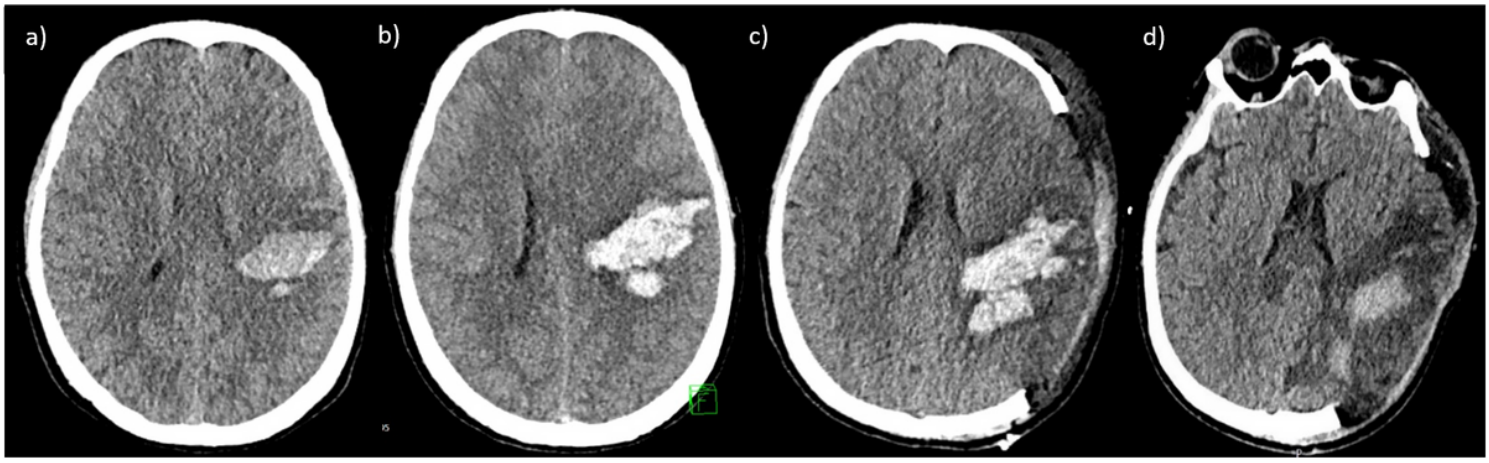

Figure 1

Serial CT brain images from Case 1. a) Day 1 admission imaging. b) Day 4 following dilated left pupil revealing 4mm midline shift to right. c) Day 5 following craniectomy. d) Day 19 latest imaging following external ventricular drain removal.