Rare case of COVID-19 vaccine-associated intracranial haemorrhage with venous sinus thrombosis

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SUMMARY

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a relatively novel term which describes patients who have developed a low platelet count and prothrombotic tendencies secondary to receiving a vaccine. The concept has been derived from the well-established phenomenon of heparin-induced thrombocytopenia, and several cases of VITT have now been reported in patients who have received the AstraZeneca (ChAdOx1 nCov-19) vaccine. Unfortunately, some of these patients have gone on to develop intracranial venous sinus thrombosis. We present a case of VITT-associated sinus thrombosis secondary to the AstraZeneca (ChAdOx1 nCov-19) vaccine, which was complicated by a large intracerebral haemorrhage.

BACKGROUND

With a total mortality figure now approaching 5 million people, the current coronavirus pandemic caused by the SARS-CoV-2 virus (termed COVID-19), has grippled countries worldwide. A global race to develop an effective vaccine has led to the successful development of some messenger RNA-based vaccines by pharmaceutical companies including Pfizer–BioNTech (BNT162b2) and Moderna (mRNA-1273). Another group of vaccines has focused on delivering a small quantity of a vector encoding the spike glycoprotein of SARS-CoV-2. One such vaccine was produced by AstraZeneca (ChAdOx1 nCov-19) which uses a recombinant adenovirus vector derived from chimpanzees.[1]

Concerns have been raised surrounding the prothrombotic nature of the AstraZeneca (ChAdOx1 nCov-19) vaccine, with cases of venous sinus thrombosis being reported in previously fit and well recipients. In this case study, we report on a 55-year-old man who received the ChAdOx1 nCov-19 vaccine and subsequently developed a venous sinus thrombosis complicated by a large volume intracerebral haemorrhage. We will discuss the complexity of management in such prothrombotic patients where there is a concurrent bleed.

CASE PRESENTATION

A previously fit and well 55-year-old man presented to the emergency department 18 days after receiving his first dose of the ChAdOx1 nCov-19 vaccine (AstraZeneca), reporting a 2-day history of a frontal headache. This was combined with a 7-day history of abdominal pain associated with several episodes of diarrhoea. The patient reported no significant medical history and was not taking any regular medication. In the emergency department, the patient appeared to be alert and oriented with a Glasgow Coma Score (GCS) of 15 and the absence of any focal neurological signs. A diagnosis of a tension headache was made and the patient was discharged on the same day with simple analgesia.

The following day, he had developed severe confusion, dysphasia and began to have episodes of emesis. On arrival to the emergency department, he was found to have a reduced GCS of 13, with a National Institutes of Health Stroke Score score of 3 and visual inattention on his right side. An urgent CT of the head was requested and showed a large 7.0×4.4×5.0 cm intracranial haemorrhage in the left temporoparietal region with surrounding oedema and effacement of the left lateral ventricle causing an 8 mm midline shift (figure 1A,B). A CT venogram showed a left-sided venous sinus thrombosis (figures 2 and 3) with associated large volume haemorrhage, as well as thromboses in the left internal jugular vein and transverse sinus. A CT of the abdomen and pelvis was also performed in view of the abdominal pain and demonstrated multiple disseminated thrombi within the portal vein and the left kidney.

OUTCOME AND FOLLOW-UP

Blood tests revealed a thrombocytopenia with a platelet count of 70×10^9/L and a raised D-dimer at 6177 ng/mL. Interestingly, his fibrinogen level was within normal range at 2.85 g/L.

Other laboratory investigations included: haemoglobin 132 g/L; international normalised ratio 1.6; prothrombin time 16.5 s; activated partial thromboplastin time 28.0 s; alanine aminotransferase 537 U/L; alkaline phosphatase 149 U/L; albumin 34 g/L. Serum creatinine was 59 µmol/L with an estimated glomerular filtration rate of 108 mL/min/1.73 m^2. An ELISA detected antibodies to platelet factor 4 (PF4). Von Willebrand factor–cleaving protease (ADAMTS13) levels, reticulocytes and lactate dehydrogenase levels were within normal range. Advice was sought from the haematology team at UCLH (University College London Hospital), and the patient was treated with intravenous immunoglobulin (IVIG) and started on non-heparin-based anticoagulation (fondaparinux). He was subsequently transferred from Southend Hospital to the neurointensive care department at UCLH for ongoing care which included plasmapheresis.

In total, the patient received five sessions of plasmapheresis. Approximately 1 week after treatment, the

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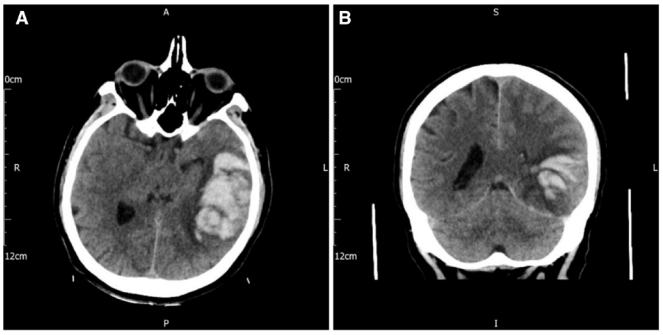

Figure 1 Non-contrast CT of the head in axial (A) and coronal (B) plane, showing left temporo-parietal haemorrhage measuring 7.0×4.4×5.0 cm.

patient's anti-PF4 antibody titre was negative and his platelet count began to recover. He was therefore switched from fondaparinux to apixaban, and was subsequently stepped down from intensive care and transferred to the Centre for Neurology in Queen's Square for neurorehabilitation. The patient had an episode of a seizure while undergoing rehabilitation and was therefore started on the anti-epileptic levetiracetam. He made a prompt recovery and was successfully discharged home on apixaban and levetiracetam.

DISCUSSION

ChAdOx1 nCov-19 vaccine (AstraZeneca) and venous sinus thrombosis

In July 2020, *Nature* journal published a study suggesting the use of the ChAdOx1 nCov-19 vaccine can prevent the development of SARS-CoV-2 in rhesus macaques.[2] This was closely followed in August 2020 by *The Lancet*, which published a preliminary report of a phase 1/2 randomised controlled trial (RCT), where they assessed the safety and immunogenicity of the ChAdOx1 nCov-19 vaccine (AstraZeneca).[3] The authors reported favourably on the vaccine, with boosted antibody responses and an acceptable safety profile, and recommended a larger scale evaluation as part of a phase 3 trial. In December 2020, results from a phase 2/3 RCT reported a positive immunogenic response to the ChAdOx1

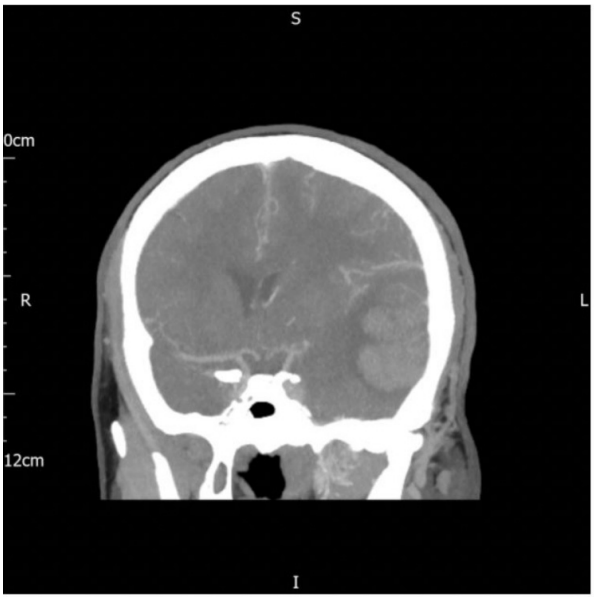

Figure 2 Coronal view of CT venogram depicting a filling defect within the left sigmoid sinus in keeping with a venous sinus thrombosis.

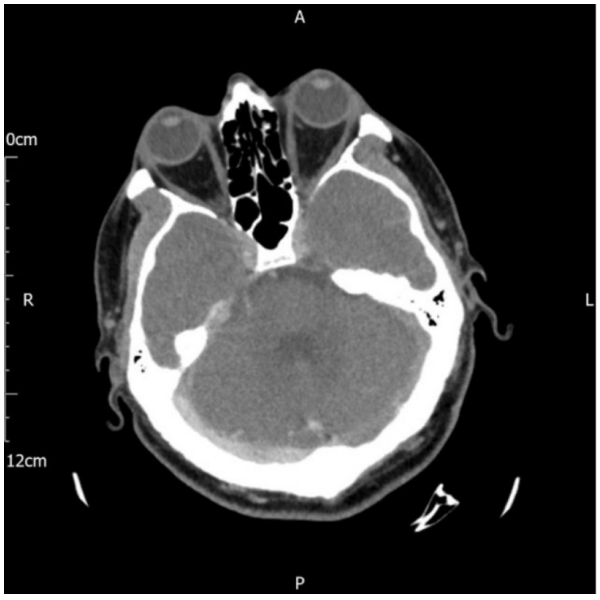

Figure 3 Axial view of CT venogram showing a filling defect in the left transverse sinus.

nCov-19 vaccine across all age groups with no serious adverse events being directly related to the vaccine.[4] Since then, further international RCTs have all demonstrated an acceptable safety profile of the ChAdOx1 nCov-19 vaccine,[5] and it has formed a key component of many national vaccination programmes across Europe.

Some clinicians have stipulated that patients developing venous sinus thrombosis post-ChAdOx1 nCov-19 vaccine are at the same risk as the general population for developing such events. However, given the relatively young and healthy population groups inflicted with such thrombotic events, it is understandably not easy to accept such a pure coincidental explanation. This is especially the case when these patients have a consistent abnormal serological profile. In March 2021, the European Medicine Agency (EMA) stated that the incidence of thromboembolic events in people receiving the ChAdOx1 nCov-19 vaccine was no higher than the incidence in the general population.[6] However in April 2021, the EMA later conceded that there was a probable association between the two with an event rate of approximately 1 per 200 000 doses.[7] Some authors have even used the Bradford-Hill criteria to demonstrate a causal relationship between the ChAdOx1 nCov-19 vaccine and immune thrombotic thrombocytopenia.[7] It is worth noting that a few cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) have also been reported following mRNA-based vaccines, namely Pfizer–BioNTech (BNT162b2) and Moderna (mRNA-1273).[8] However, this being said, no convincing causal relationship has been demonstrated to date.

Serological markers

In the majority of cases where patients have developed thrombotic complications as a result of the ChAdOx1 nCov-19 vaccine, blood tests usually reveal a low platelet count (thrombocytopenia) which may be associated with raised D-dimer levels alongside low fibrinogen levels.[9] This biochemical picture mirrors that of heparin-induced thrombocytopenia (HIT), which is a well-documented phenomenon caused by platelet-activating antibodies, namely PF4, which arise shortly following the administration of heparin-containing medication. Despite causing a dramatic fall in the

platelet count, patients with HIT tend to be in a prothrombotic state where they are likely to develop complications including disseminated emboli. It is worth mentioning that this HIT phenomenon has previously been witnessed in patients even in the absence of heparin administration. For instance, the serological picture has been found in cases of bacterial and viral infections,[10] and even in postoperative surgical patients.[11] Such spontaneous cases of HIT have been grouped together and termed autoimmune HIT.[12]

VITT is one such example of autoimmune HIT, and is being reported with increasing frequency in patients who have received the AstraZeneca (ChAdOx1 nCov-19) vaccine. Serum analysis of these patients often displays an exaggerated response on the PF4-heparin ELISA, with anti-PF4 antibodies being associated with greater levels of platelet activation.[1] Greinacher *et al* suggest one potential mechanism for this platelet activation may relate to the presence of free DNA within the ChAdOx1 nCov-19 vaccine. The authors did not test this phenomenon in other available COVID-19 vaccines, but do report that to date only patients receiving the AstraZeneca (ChAdOx1 nCov-19) vaccine have been found to display VITT.[1]

Management

Immunomodulation in the form of high-potency glucocorticoids and IVIG forms key aspects of the acute management of patients who develop VITT. Prompt treatments with such measures have been shown to effectively raise the platelet count, and thus reduce the chances of haemorrhagic complications. One of the mechanisms IVIG may act is by blocking FcRγIIA receptors found on platelets.[13] This can directly downregulate platelet activation; much like in classic HIT. In treatment-resistant cases, plasma exchange may be used in a critical care setting as a means of temporarily reducing the titre of anti-PF4 antibodies.[14] Plasmapheresis was given to our patient as he displayed disseminated thrombotic events in addition to an intracranial haemorrhage.

With regard to prophylaxis against the development of venous thromboembolic events, most clinicians agree that non-heparin-based anticoagulants ought to be used in preference to heparin-based medication.[9 14] It is also recommended to avoid platelet transfusions in patients with VITT, as there is a significantly increased risk of developing thrombotic events.

Patient's perspective

I had the Astrazeneca vaccine back in March, and initially thought I was okay. It's hard to remember what happened next. My whole life has changed. Before this, I can't remember the last time I saw my GP. I was completely independent and working, now my life has been turned completely upside down. With my rehab, I can feel my body and my mind getting stronger and stronger. I am having ongoing sessions with speech and language therapists as well as physiotherapists. There were definitely moments where I felt down; I feel for the other people who have had similar reactions to vaccines. I hope that if they are finding things hard they can hear my story and find some motivation. In terms of the vaccine, I know there are many different types. We are still learning more and more about them and I wish I could have been told the risks. Now, I feel like I am getting stronger and stronger. I am looking forward to what the rest of the year holds for me, and waiting for someone to make a film about the whole thing.

Learning points

- We have presented a case of vaccine-induced immune thrombotic thrombocytopenia (VITT) secondary to the AstraZeneca (ChAdOx1 nCov-19) vaccine.
- The patient in this case developed a venous sinus thrombosis, which was complicated by a large intracerebral haemorrhage. The combination of these devastating conditions occurring simultaneously makes management of such patients particularly challenging.
- This case study highlights key features and management strategies for patients who are likely to suffer from VITT and subsequently develop major complications.

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