

Post-COVID-19 vaccination occurrence of splenic infarction due to arterial thrombosis

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Accepted 2 November 2021

SUMMARY

We present the case of an 82-year-old woman admitted to a regional emergency general surgery centre with severe left upper quadrant abdominal pain and tenderness within 21 days of receiving the first dose of the ChAdOx1 nCov-19 vaccine (Vaxzevria, AstraZeneca). Following further investigation through CT imaging, a thrombus was discovered in the patient's splenic artery resulting in a large splenic infarct. Splenic infarcts are rare and it is important to note the association between time of administration of the first dose of vaccine and the occurrence of thromboembolic complications in the noted absence of other risk factors for this condition. We hypothesise a link between Vaxzevria vaccine injection and a rare form of thromboembolic complication: thrombosis of the splenic artery.

BACKGROUND

The COVID-19 pandemic has had a massive impact on the world and how it operates. One of the prophylactic measures used to reduce the global and national burden of COVID-19 is administration of antiviral vaccines. COVID-19 vaccine production has had quick implementation from the initial outbreak of the illness. Vaccines were initially meant to be administered in susceptible populations but have superseded more conventional testing due to the urgent need to prevent transmission of SARS-CoV-2. Therefore, it is not unlikely that certain side effects are only manifested on administration of vaccines to a larger population.¹

Of the 45.2 million individuals who have received the recombinant chimpanzee adenoviral vector encoding the SARS-CoV-2 spike glycoprotein vaccine (ChAdOx1 nCov-19), which was renamed Vaxzevria (AstraZeneca), approximately 1.7% have had a reaction reported to the Yellow Card reporting body and 0.00207% have had fatal outcome related to vaccination.^{2,3} From initial testing, the most common side effects of the vaccine affected over 10% of patients; these include tenderness, pain and bruising at the injection site, headache, tiredness, muscle pain, feeling unwell, chills, fever, joint pain and nausea.⁴ Slightly less common side effects, affecting less than 10%, include thrombocytopenia, diarrhoea, vomiting, and swelling and redness at the injection site. Even less common adverse effects, occurring in less than 1% of patients, are lymphadenopathy, decreased appetite, sleepiness, dizziness, sweating, abdominal pain, itching and rash.⁴ Even rarer still is thrombosis in combination with thrombocytopenia, which occurred in 0.01% of patients.⁴

For the most part, splenic infarctions are rare complications secondary to other pathophysiology, and it is very unusual for patients without these predispositions to have arterial thromboembolism in the splenic artery as the first symptomatic presentation of a haematological condition.⁵ The exact incidence and prevalence of splenic infarctions at the population level are unknown,^{5,6} with some data suggesting an incidence of as low as 1 in 125 000 individuals per year.⁷

The British National Formulary states: 'Serious reactions include those that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation, or a congenital abnormality; they should be reported even if the effect is well recognised'.⁸ A splenic infarct would meet these criteria; however, no source currently states thromboembolism as a potential adverse effect of COVID-19 vaccines.⁹⁻¹¹

It is important to flag such events as potential consequences of adverse reactions of COVID-19 vaccines as it is still important to monitor the national efforts to provide blanket immunity to the population and try to ensure as safe as possible treatment to the population. If an adverse reaction occurred in one of the primary groups who were administered vaccines, the effect may have already been or may be repeated in others, and without further investigation these may be attributed to other causes.¹² Lack of reporting may also undermine public trust in vaccination efforts.^{13,14}

CASE PRESENTATION

The patient is an 82-year-old woman presented to the accident and emergency department at a regional general surgery and trauma centre with first-time presentation of acute left-sided abdominal pain (onset on 3 February 2021), worse on inspiration, as well as nausea, decreased appetite and tenderness.

As for other possible aetiologies responsible for a splenic infarct, the patient did not have a history of smoking, had not been previously diagnosed with a haematological or bloodborne malignancy, was not known to be in a hypercoagulable state, did not have a thromboembolic disorder, did not have pancreatic pathology, and had had no recent history of abdominal trauma or infection.

The patient had recently received the first dose of the COVID-19 vaccine, followed by a period of mild reaction post vaccination mainly noted to be pain in the arms. She received the Vaxzevria vaccine (AstraZeneca; batch no AB0001, expiration 1 April 2021) on 13 January 2021.



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To cite: Anderson A, Seddon M, Shahzad K, et al. *BMJ Case Rep* 2021;**14**:e243846. doi:10.1136/bcr-2021-243846

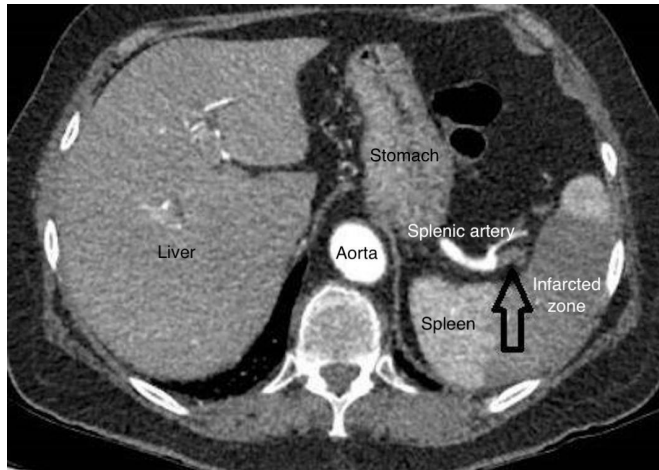


Figure 1 Contrast-enhanced CT scan of the abdomen on admission. The arrow indicates complete obstruction of the distal portion of the splenic artery (thrombosis). A well-demarcated, centrally located, hypodense area of the spleen is the infarcted zone, approximately 60%–70%. Both the superior and inferior poles of the spleen are well perfused.

The patient was repeatedly tested for COVID-19 and was negative on admission to the accident and emergency department and had no close contact with anyone affected. She also did not recall at any point in the last 12 months having COVID-19 type of symptoms. She has no family history of haematological or other malignancy as well as of thromboembolic/pancreatic disorders. She reported taking no medications before admission. In 2013, she underwent laparoscopic cholecystectomy and an endoscopic ultrasound scan of the extrahepatic bile ducts.

INVESTIGATIONS

After initial assessment, the patient received chest and abdominal X-ray. Following this, she received a CT scan of the abdomen highlighting a large middle segment splenic infarct with an extensive thrombus causing complete obstruction of the distal splenic artery (figure 1). Atherosclerosis was also present in the superior mesenteric artery and the coeliac axis; however, these were patent. Some atherosclerosis was also present in the aorta, as well as some calcifications. Sigmoid diverticulosis with no secondary radiological feature was diagnosed. She had multiple blood tests and transthoracic echocardiogram to eliminate the differentials of splenic artery thrombosis and infarct of the spleen (table 1).

DIFFERENTIAL DIAGNOSIS

Initial clinical presentation was not specific and did not have a lot of nuances that allowed for immediate diagnosis of the problem. From an abdominal pain aspect, diverticular disease and renal colic would have been suspected until they were disproved by CT imaging and blood tests.

Lung and cardiac pathologies were also initially suspected on an earlier imaging, where X-ray and primary CT scan showed bilateral basal atelectasis, a small focus of consolidation within the left lung base and a small-volume pericardial effusion; however, on later imaging, these appear to have resolved on their own.

Following this, once the splenic infarct had been identified, it was necessary to rule out the more common causes of this state. Using blood and imaging results, it was possible to discount

Table 1 Results and interpretation of selected tests

Test	Results	Interpretation
SARS-CoV-2 test	Negative (10 February, 11 February, 17 February)	COVID-19 not proven
Blood cultures	No growth	No bacteraemia
D-dimer	3.88 mg/L FEU (normal range 0.01–0.99)	Haemostatic system activated: clot
HbA1c test	34 mmol/mol (normal range 0–41)	Normal
Amylase	36 units/L	Normal
Lactate	1.4 mmol/L	Normal
Platelet	286×10 ⁹ /L	Normal
Prothrombin time and APTT	Within normal range	Normal
Iron	6 µmol/L (normal range 10–30)	Below lower limit
Iron binding	39 µmol/L (normal range 40–70)	Below lower limit
CRP	95 mg/L	Non-specific inflammatory reaction
WCC	14.5×10 ⁹ /L	Non-specific inflammatory reaction
Renal profile	K+, Na+, urea, creatinine	Normal
Vitamin B ₁₂	160 ng/L (normal range 200–770)	Deficit
Serum folate	2.20 µg/L (normal range 3.9–26.8)	Deficit
Serum ferritin	137 µg/L (normal range 13–150)	Normal
GPI	No deficit	No PNH
JAK2 p.V617F	Negative	No myeloproliferative neoplasms
Transthoracic echocardiogram	Normal	No evidence of endocarditis
HIT screen	Negative	Carried out on 14 May 2021: not diagnostic
B2GPI antibody screen	Negative	No evidence of antiphospholipid syndrome, carried out on 14 May 2021
Thrombophilia screen	Negative	Not sufficient evidence of VITT/VATT

Explanations: myeloproliferative neoplasms include polycythaemia rubra vera, essential thrombocythaemia and primary myelofibrosis (the test does not entirely exclude them). HIT, IgG-specific heparin platelet factor 4 antibody (or heparin-PF4 screening test), assesses for VITT/VATT. B2GPI is antibody screen for antiphospholipid syndrome. APTT, activated partial thromboplastin time; CRP, C reactive protein; FEU, fibrinogen equivalent unit; GPI, glycosylphosphatidylinositol; HbA1c, haemoglobin A1c or glycated haemoglobin test; JAK2, Janus kinase-2 gene; K+, potassium; Na+, sodium; PNH, paroxysmal nocturnal haemoglobinuria; VATT, vaccine-associated thrombotic thrombocytopenia; VITT, vaccine-induced thrombotic thrombocytopenia; WCC, white cell count.

many of the likely causes of splenic infarction secondary to arterial thrombosis. There was no evidence supporting a bloodborne disease or occult malignancy diagnosis, a hypercoagulable state, or a thromboembolic state. There was nothing in the patient history or imaging to support the idea of blunt abdominal trauma. The amylase was 36 units/L, which was within normal range.

Immune disorders leading to antiphospholipid syndrome were also discounted due to the panels showing negative for antibodies. The panel for vaccine-induced thrombotic thrombocytopenia was also negative; however, this was expected as it was carried out at a considerable time after the patient's initial admission (table 1).

Atherosclerosis is weakly evidenced as causing splenic infarcts. If the patient's aetiology was not caused by Vaxzevria, then this could be considered a rare differential as was noted on radiology. It is also possible the vaccine may have interacted with the patient's atherosclerotic disease.

TREATMENT

Conservative management included therapeutic doses of dalteparin sodium, antibiotics, analgesics and antiemetics. Postsplenic infarction vaccines were administered to the patient (meningococcal, pneumococcal and *Haemophilus influenzae* vaccines). Postdischarge, phenoxymethylpenicillin (penicillin V) 250 mg two times per day has also been prescribed. She was initiated on a one-off dose of dalteparin (12 500 IU), which was then reduced to 10 000 IU/day and then reduced once more to 7500 IU/day from 9 April 2021. It was then replaced with apixaban (2.5 mg to be taken daily twice) from 11 May 2021. The patient is also being treated with amlodipine (5 mg).

OUTCOME AND FOLLOW-UP

The patient is making a very good recovery. She was counselled a few times. On 1 April, the patient received the second dose of the Vaxzevria vaccine. A follow-up CT scan has been arranged in 2 months' time after discharge from the hospital; no new abnormalities were identified. She remains under the care of consultants in haematology and general surgery.

The probable link between the vaccine and thrombosis of the splenic artery was hypothesised and discussed with the hospital's senior pharmacists. The incident, which was characterised as a life-threatening adverse drug reaction, was immediately reported to the UK Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card Scheme and by telephone.

DISCUSSION

Although this is not the first case where a link between the Vaxzevria vaccine and clotting issues has been suggested, no further cases of this exact type had been reported as of April 2021 and as of the 10th of October 2021 there were only 2 other cases identified using the keywords of splenic artery infarction and AstraZenca COVID-19 vaccine. In March 2021, there was a discussion on whether the AstraZenca vaccine and postvaccination thromboembolic events are related.¹⁵ Certain countries, such as Germany and Denmark, have suspended their AstraZenca-based vaccination programmes due to the preliminary results. On 7 April, the European Medicines Agency announced a relation between the Vaxzevria vaccine and clotting.¹⁶ On 7 April, the MHRA has also stated they had established a relation, saying that the side effect was 'extremely rare',¹⁷ contradicting their previous stance that the Vaxzevria vaccine and clotting were unrelated.¹⁸ As of 5 April, approximately 100 cases of thromboembolism had occurred within the UK population of 20,600,000 that have been vaccinated using Vaxzevria,¹⁹ meaning that this adverse reaction occurs in 0.000485% of those vaccinated. The WHO has also declared on 16 April that the type of thrombosis caused by the vaccine is a completely new type of adverse effect, and has called it thrombosis with thrombocytopenia syndrome²⁰ and was later renamed to vaccine-induced immune thrombotic thrombocytopenia.²¹⁻²³ This is a very current topic, and recent developments suggest that as the COVID-19 pandemic continues future vaccinations may be necessary for large cohorts of the population.^{24 25}

The Vaxzevria vaccine is a replication-deficient, attenuated adenovirus that expresses the SARS-CoV-2 spike protein genes

using cell organelles. This results in mass production of the external coat protein of the SARS-CoV-2 virus by host cells, this causes expansion with the systemic release of this non-replicating protein and hopefully resulting in the stimulation of the adaptive immune system. This confers long-term protection to the host.²⁶ However, in the case of some capsid proteins of viruses such as *H. influenzae*, which has a spike equivalent protein called haemagglutinin and neuraminidase, poor processing may result in small vessel thrombosis in certain individuals.^{27 28}

It is also important to highlight now that COVID-19 vaccines, although with health effects, still cumulatively offer a net positive effect to the individual and to the population and that rare adverse effects should not be a justification for avoiding vaccination. At the individual level, vaccinations have a low risk of serious adverse effects, and the risk of getting COVID-19, which has a significantly higher case fatality ratio (3.10% in the UK),²⁹ is reduced, as is the subsequent risk of being hospitalised if the individual does succumb to the virus, which means that the case fatality rate of those who have been vaccinated is also reduced.³⁰ It is also important to add that the long-term effects of COVID-19 are reduced as the patient is less likely to get this disease in the first place. At the population level, it is key to understand that through herd immunisation the R0 of the virus is reduced, leading to less transmission due to less susceptible hosts. This means that outbreaks are less likely as the chain of transmission is interrupted.³¹ This also allows for more susceptible individuals, such as those who are immunocompromised or immunosuppressed or allergic to the vaccine, to be protected as well. There are also economic and other social considerations that would imply that vaccinations are a better option as a population-wide policy due to their net benefits.³¹ So, despite having negative effects in some patients, most will have positive protective benefits from these vaccination programmes.

There are currently very few published cases of splenic artery thrombosis in *BMJ Case Reports*, showing 130 articles, while a search on 10 October 2021 of the combined terms 'splenic artery thrombosis' and 'AstraZenca COVID-19 vaccine' provided two results.^{32 33} National Institute for Health and Care Excellence guidelines are currently non-existent. Management of splenic thrombosis is currently based on treatment of the pathophysiology instigating an episode, which makes sense as it is normally a manifestation of other diseases and can be considered more a sign than a diagnosis in its own right. However, in this situation there exists a lack of guidance on how to manage a patient experiencing such an effect of a vaccination, although it is now recommended that patients in the UK do not get the second dose if they have experienced these effects.¹⁷

Atherosclerosis as an alternative differential diagnosis is weakly associated with splenic arterial thrombosis, especially at first presentation of the pathology.⁵ The fact that atherosclerosis is a especially common condition,³⁴ and with splenic infarction as the first presentation being extremely rare, makes it an unlikely diagnosis as well and would not have been considered if not for the imaging.³⁵

However, it is still important to consider the whole patient. This line of inquiry would lead to consideration of a more complex pathophysiological mechanism in this case, due to the interaction of the vaccination, or inflammatory response with the atherosclerotic intravascular plaques. Atherosclerosis has a very complex interaction with inflammation and both the innate and adaptive immune systems,³⁶ and this would warrant further research and analysis in order to have better understanding of the mechanism behind the clotting.²⁰ Unfortunately, with just this one episode at present, there is an insufficient data set to get

Patient's perspective

I received my first vaccine AstraZeneca on 13th January 2021. I did not feel ill after the injection, I did not experience any flu like symptoms. It was on 1st Feb I contacted my doctor as I had started to feel unwell, I was feeling dizzy and unbalanced and a bit confused with my memory. I went immediately to have blood tests, I attended the clinic to have them done.

I met again with my doctor on 5th Feb to discuss the results and what I thought I was told was I had a deficiency in my vitamins. I went to the chemist to collect the injections. My daughter asked what injections I was given I told her Neo-cytamen, she looked it up and explained it was a deficiency of B12 which is needed for the production of red blood cells.

During the evening of the 9th Feb I was suffering severe pains just below the waist, front, left hand side and they kept me up all night. I was in agony but decided to wait until the morning when I was due my second injection. I attended the doctors on the 10th Feb and asked to see my GP before I went in for my second injection and was told he was fully booked. When I saw the nurse she was aware of my pain and discomfort and was very concerned for my wellbeing and she called an ambulance immediately, I was taken to the hospital.

I spent a week in the hospital whilst they investigated the cause of the pain. I was kept in isolation due to them thinking I was suffering from covid. I had four covid tests and they come back negative every time. I had x rays, scans, drips, injections and tablets during that week. Due to partial hearing I was not sure what had happened to me. It was explained that I had a blood clot in an unusual place and a lung infection. I was only taking shallow breaths for a long time because of the pain and I am told this caused my lungs to be infected. I have a strong pain threshold so just got on with it.

I am 82 and not on any medications, I don't take tablets at all. I was fit and active and very independent. Since my hospital stay I have had to live with my daughter she gives me my Fragmin injections and daily tablets Amlodipine and Phenoxyethylpenicillin. I have had phone consultations with the hospital, phlebotomy nurses, my daughter discusses my health due to my hearing difficulties. The injections are Fragmin 15,000 and at first the blood tests came back normal. I had another blood test and they told me I had to lower the dose to 12,500 as my blood was too thin and another blood test after that changing the dosage. It has now been reduced to 10,000 I will return for another blood test in the next few days to see how my blood is now.

I have had close contact with the consultant and he has explained to me what actions he has taken reporting the clot to the MHRA (Medicines and Healthcare products Regulatory Agency, UK) to investigate any possible links/connection with the AstraZeneca injection and the clot suddenly appearing. He explained that the clot is in my spleen. I am truly shocked to find out the damage it has caused, I only have a third of it working now. I have been in good health all of my life and this experience has left me without my independence and I will have to be on medications for the foreseeable future. This is life changing for me I have never been on so much medication and I am back and forth for weekly blood tests, scans and consultations.

I do know the reasons for all the medications and appointments and this is to allow the doctors and nurses to get me back to better health. I am very thankful to our NHS at this unknown and worrying time for me.

Learning points

- ▶ We hypothesise a link between ChAdOx1 nCov-19 vaccine injection and a gross thrombosis of the splenic artery.
- ▶ We must be vigilant and aware of the possibility of rare complications in the context of unprecedented mass vaccination programmes, especially in patients with other systemic pathologies; however, we must acknowledge that vaccines have beneficial effects in the majority.
- ▶ Timing of admission and presentation in correlation with vaccination must be considered when discounting the possibility of vaccine-induced pathology.
- ▶ To encourage reporting of suspected adverse effects when they present, through official channels when they are the prevalent differential, and after discounting other possibilities.
- ▶ Data pertaining to such presentations should be collated and a knowledge base of how to treat such presentations should be established.

deeper and meaningful insight. Furthermore, if further studies are conducted and if this is found to be the cause, it would help identify at-risk groups who may be worth monitoring or at least as safety-netting for adverse effects as further vaccination programmes continue.

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Contributors AA reviewed the literature, wrote the draft and contributed to subsequent revisions of the manuscript. MS wrote part of the paper. KS revised the first version of the manuscript. RL hypothesised a link between vaccination and splenic artery thrombosis, conceived the paper, wrote a draft and contributed to subsequent revisions of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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