

Extensive thrombosis after COVID-19 vaccine: cause or coincidence?

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SUMMARY

A 62-year-old Caucasian female patient presented with abdominal pain, vomiting and fever 1 day after administration of COVID-19 vaccine. Bloodwork revealed anaemia and thrombocytosis. Abdominal CT angiography showed a mural thrombus at the emergence of the coeliac trunk, hepatic and splenic arteries, and extensive thrombosis of the superior and inferior mesenteric veins, splenic and portal veins, and the inferior vena cava, extending to the left common iliac vein. The spleen displayed extensive areas of infarction. Aetiological investigation included assessment of congenital coagulation disorders and acquired causes with no relevant findings. Administration of COVID-19 vaccine was considered a possible cause of the extensive multifocal thrombosis. After reviewing relevant literature, it was considered that other causes of this event should be further investigated. Thrombosis associated with COVID-19 vaccine is rare and an aetiological relationship should only be considered in the appropriate context and after investigation of other, more frequent, causes.

BACKGROUND

During the COVID-19 pandemic, the pharmaceutical industry is under immense pressure to develop effective and safe vaccines, and as such clinical trials have been expedited in order to make them available to help fight this health crisis. In this context, timely communication between health-care institutions and regulatory entities is especially important.

Reports of thrombosis due to administration of these vaccines have been causing an important discussion in the scientific community as well as social alarm. However, it is important to note that this is a rare complication and more frequent causes of extensive arterial and venous thrombosis should be considered and investigated.¹

CASE PRESENTATION

A 62-year-old Caucasian female patient, with personal history of obesity (body mass index of 30 kg/m²), asthma and rhinitis, presented to the emergency department with abdominal pain, nausea, vomiting and fever (38°C) 1 day after administration of the first dose of COVID-19 vaccine (from AstraZeneca). On physical examination, she presented epigastric and left iliac fossa tenderness as the only abnormal finding. The patient denied recent epistaxis and gastrointestinal or genitourinary blood loss.

INVESTIGATIONS

Blood tests revealed microcytic hypochromic anaemia (haemoglobin 7 g/L), thrombocytosis (780 × 10⁹/L), increased levels of inflammatory parameters (leucocytes 13 × 10⁹/L; C reactive protein 31.07 mg/dL) and slightly increased levels of liver enzymes and function (AST 36, ALP 126 U/L, GGT 72 U/L, LDH 441 U/L, total bilirubin 1.3 mg/dL, direct bilirubin 0.5 mg/dL). The patient was tested for COVID-19 with nasopharyngeal PCR tests at admission and on the fifth day of hospitalisation. Both tests were negative. Abdominal CT angiography (CTA) showed a mural thrombus at the emergence of the coeliac trunk, with total occlusion (figure 1), as well as at the hepatic and splenic arteries. There was also extensive thrombosis of the superior and inferior mesenteric veins and its tributaries, splenic and portal veins, including the splenoportal confluent (figure 2). There was a fili-form thrombus at the distal portion of the inferior vena cava, extending to the left common iliac vein, non-occlusive (figure 3). Spleen presented extensive areas of infarction (figure 1). Coeliac trunk occlusion due to paradoxical embolism was excluded by trans-thoracic echocardiogram. No interatrial communication was detected. Re-evaluation CTA 5 days after the diagnosis was identical.

Aetiological investigation included assessment of congenital coagulation disorders and acquired causes. Regarding congenital disorders, personal and family history of important thrombotic events, thrombosis in unusual sites and abortions were assessed with no relevant findings. Molecular testing for factor V Leiden mutation and prothrombin gene 20210 G/A mutation were both negative.

Acquired causes of a coagulation disorder, such as neoplastic, infectious and autoimmune disorders, like antiphospholipid syndrome (APS), were also investigated. Thorax, abdomen, pelvic and brain CT did not detect any suspicious lesions. Tumour biomarkers—carcinoembryonic antigen, alpha fetoprotein, carbohydrate antigen 19-9, cancer antigen 125, cancer antigen 15-3, neuron-specific enolase and chromogranin A—were negative. The patient refused to undergo upper digestive endoscopy and colonoscopy. Despite increased levels of inflammatory parameters at admission (leucocytosis and C reactive protein), these values decreased during the hospitalisation period. Blood and urine cultures were also negative. Anticardiolipin IgG and IgM and ant beta-2-glycoprotein IgG and IgM were negative, excluding APS.

DIFFERENTIAL DIAGNOSIS

In the presence of venous and arterial thrombosis, the aetiological investigation should include



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Figure 1 CT angiography arterial phase, axial image: a mural thrombus is observed at the coeliac trunk emergence, with total occlusion. Splenic parenchyma without enhancement after contrast administration can also be observed, translating to extensive infarct areas.

assessment of congenital and acquired coagulation disorders, as well as the presence of interatrial communication that could explain the coeliac trunk occlusion due to paradoxical embolism.

As previously stated, these aetiological factors were assessed with no specific findings, with the exception of digestive endoscopic study, which was refused by the patient. In this context, and given the fact that the presentation took place 1 day after administration of the first dose of COVID-19 vaccine, we hypothesise that the vaccine might be the cause of the extensive arterial and venous thrombosis. This case was immediately reported to INFARMED, the Portuguese authority for drugs and health products.

Vaccine-induced thrombotic thrombocytopenia (VITT) was also considered a differential diagnosis. However, the patient did not present with thrombocytopenia, which is a key criteria for VITT, and therefore the presence of this syndrome was unlikely.

COVID-19 tests at admission and on the fifth day of hospitalisation were negative; however, she was not tested prior to the onset of the event and therefore it was not possible to exclude

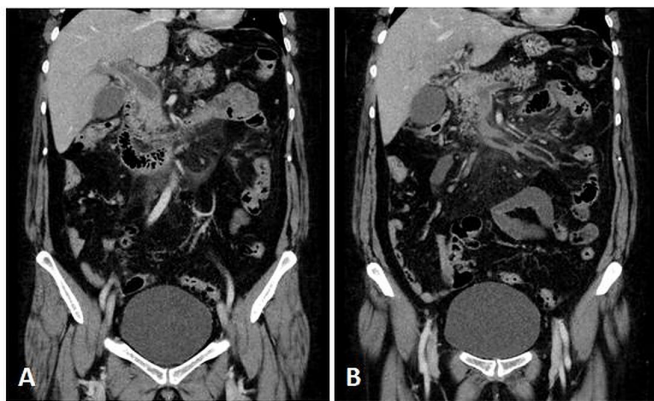


Figure 2 CT angiography portal phase, coronal image: portal vein thrombosis (A) extending to the splenoportal confluence (B) can be observed.



Figure 3 CT angiography portal phase, coronal image: a non-occlusive filiform thrombus at the distal portion of the inferior vena cava can be observed, extending to the left common iliac vein.

recent COVID-19 infection, which may predispose to thrombosis, even during the convalescent phase.

TREATMENT

At presentation, there were no signs of organ ischaemia that required revascularisation procedure or intestinal resection. Considering the anaemia, the patient was not a candidate for fibrinolysis. The treatment was empiric endovenous antibiotic therapy and transfusion of two units of red blood cells. Anticoagulation with low molecular weight heparin (LMWH) 1 mg/kg two times per day was initiated and maintained during hospitalisation, with monitoring of anti-Xa levels. After hospitalisation, in an outpatient setting, the patient was initiated on edoxaban.

OUTCOME AND FOLLOW-UP

Re-evaluation CTA 28 days after presentation revealed a portal vein with a filiform calibre, with a cavernomatous transformation. There was only permeability of the left branch of the portal vein, with venous collateralisation in the hepatic hilum. Coeliac trunk was still occluded, with permeability of the gastroduodenal artery and the right hepatic artery, and apparent occlusion at the emergence of the left hepatic artery, although with distal repermeabilisation. Partial thrombus persisted in the lumen of the left common iliac vein and inferior infrarenal vena cava.

At the follow-up consultation, 1 month after discharge, the patient was clinically asymptomatic.

DISCUSSION

Venous and arterial thrombotic disorders have long been considered separate pathophysiological entities due to their anatomical differences and distinct clinical presentations. In particular, arterial thrombosis is seen largely as a phenomenon of platelet activation, whereas venous thrombosis is mostly a matter of activation of the clotting system.²

There is increasing evidence regarding a link between venous and arterial thromboses. These two vascular complications share several risk factors, such as age, obesity, diabetes mellitus, blood

hypertension, hypertriglyceridaemia and metabolic syndrome.³ Moreover, there are many examples of conditions accounting for both venous and arterial thromboses, such as APS, hyperhomocysteinaemia, malignancies, infections and use of hormonal treatment.³ In this case, in accordance with the literature, the patient is 62 years old and obese, with no other findings. Hyperhomocysteinaemia and digestive tract malignancies were not excluded.

Recent studies have shown that patients with venous thromboembolism are at a higher risk of arterial thrombotic complications than matched control individuals. Therefore, it is speculated that the two vascular complications may be simultaneously triggered by biological stimuli responsible for activating coagulation and inflammatory pathways in both the arterial and the venous system.³

The modified adenovirus vector COVID-19 vaccines (ChAdOx1 nCoV-19 by Oxford/AstraZeneca and Ad26.COV2.S by Johnson & Johnson/Janssen) and mRNA-based COVID-19 vaccines (BNT162b2 mRNA by Pfizer/BioNTech and mRNA-1273 by Moderna) have shown both safety and efficacy against COVID-19 in phase III clinical trials and are now being used in global vaccination programmes.⁴

Rare cases of postvaccine-associated cerebral venous thrombosis (CVT) from use of COVID-19 vaccines which use a viral vector, including the mechanism of VITT, have emerged in real-world vaccination.⁴ On the other hand, the incidence and pathogenesis of CVT after mRNA COVID-19 vaccines remain unknown. However Fan *et al*⁴ presented three cases and Dias *et al*⁵ reported two cases of CVT in patients who took an mRNA vaccine (BNT162b2 mRNA by Pfizer/BioNTech). In both cases, causality has not been proven.

In a recent editorial, three independent descriptions of persons with a newly described syndrome, VITT, were highlighted, characterised by thrombosis and thrombocytopenia that developed 5–24 days after initial vaccination with ChAdOx1 nCoV-19 (AstraZeneca), a recombinant adenoviral vector encoding the spike protein of SARS-CoV-2.⁶ VITT is also characterised by the presence of CVT, thrombosis in the portal, splanchnic and hepatic veins, as well as acute arterial thromboses, platelet counts of $20\text{--}30 \times 10^9/\text{L}$, high levels of D-dimers and low levels of fibrinogen, suggesting systemic activation of coagulation.⁶

In our case, similarities were found with VITT regarding thrombosis in the portal, splanchnic and hepatic veins, as well as acute arterial thromboses and high levels of D-dimers. On the other hand, timing of the event (1 day after vaccination), high levels of fibrinogen and absence of thrombocytopenia, which is a key criteria for VITT, point to a different direction. Moreover, the presence of thrombocytosis allowed for a safe use of LMWH for anticoagulation, with monitoring of anti-Xa levels.

Most of the cases reported so far of venous and arterial thrombosis as a complication of AstraZeneca's COVID-19 vaccine have occurred in women under the age of 60 years, associated with thrombocytopenia, within 2 weeks of receiving their first dose of the vaccine.⁷ As for the mechanism, it is thought that the vaccine may trigger an immune response leading to an atypical heparin-induced thrombocytopenia-like disorder. In contrast with the literature, our patient presented with thrombocytosis, not thrombocytopenia.⁷

Smadja *et al*⁸ reported that between 13 December 2020 and 16 March 2021 (94 days), 361734967 people in the international COVID-19 vaccination data set received vaccination and 795 venous and 1374 arterial thrombotic events were reported in Vigibase on 16 March 2021. Spontaneous reports of thrombotic events are shared in 1197 for Pfizer/BioNTech's COVID-19 vaccine, 325 for Moderna's COVID-19 vaccine and 639 for AstraZeneca's COVID-19 vaccine.⁷ The reporting rate for cases of venous (VTE) and arterial (ATE) thrombotic events during this time period

among the total number of people vaccinated was 0.21 cases of thrombotic events per 1 million person vaccinated-days.⁷ For VTE and ATE, the rates were 0.075 and 0.13 cases per 1 million persons vaccinated, respectively, and the timeframe between vaccination and ATE is the same for the three vaccines (median of 2 days), although a significant difference in terms of VTE was identified between AstraZeneca's COVID-19 vaccine (median of 6 days) and both mRNA vaccines (median of 4 days).⁸

The first paper addressing this issue was published in the *New England Journal of Medicine* and described 11 patients, 9 of them women.⁹ Nine patients had cerebral venous thrombosis, three had splanchnic vein thrombosis, three had pulmonary embolism and four had other thromboses. All 11 patients, as well as another 17 for whom the researchers had blood samples, tested positive for antibodies against platelet factor 4 (PF4). These antibodies are also observed in people who develop heparin-induced thrombocytopenia. However, none of the patients had received heparin before their symptoms started.⁹

Our patient did not present thrombocytopenia, so anti-PF4 antibodies were not tested. Thus, considering the anaemia, thrombocytosis and thrombosis diagnosed 1 day after the first dose of COVID-19 vaccine, it seems prudent to continue investigation for other causes of this event, such as haematological malignancies or others.

Learning points

- ▶ This is a rare case of extensive abdominal arterial and venous thrombosis with special relevance due to its diagnosis 1 day after administration of COVID-19 vaccine, which has been associated with thrombosis.
- ▶ A multidisciplinary team approach was necessary to achieve appropriate aetiological investigation and treatment.
- ▶ During the COVID-19 pandemic, a time of rapid technology development, communication between healthcare institutions and regulatory entities is of utmost importance.
- ▶ Despite being a sensible topic, thrombosis associated with AstraZeneca's COVID-19 vaccine is rare and should only be considered as a cause of the event in the appropriate clinical context and after investigation of other, more frequent, causes.

Contributors MS and MJA observed and initiated the diagnostic procedures and treatment of the patient in the emergency department of the hospital. LLG and BC observed and treated the patient at the intermediate care unit and at the general surgery ward. BC is the doctor who follows the patient after discharge, in an outpatient setting. Conception and design of the case were mainly defined by BC and LLG. LLG and MJA were responsible for data acquisition and drafting the article. MS and BC made an important contribution to the analysis and interpretation of data, as well as revising it critically for intellectual content. The final version of the manuscript was approved by all authors before submission. It was agreed among the authors that all were accountable for the article regarding its accuracy and integrity.

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REFERENCES

- 1 Burch J, Enofe I. Acute mesenteric ischaemia secondary to portal, splenic and superior mesenteric vein thrombosis. *BMJ Case Rep* 2019;12:e230145.
- 2 Singer DE, Albers GW, Dalen JE, *et al*. Antithrombotic therapy in atrial fibrillation: American College of chest physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:546S–92.
- 3 Ageno W, Becattini C, Brighton T, *et al*. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation* 2008;117:93–102.
- 4 Fan BE, Shen JY, Lim XR, *et al*. Cerebral venous thrombosis post BNT162b2 mRNA SARS-CoV-2 vaccination: a black Swan event. *Am J Hematol* 2021. doi:10.1002/ajh.26272. [Epub ahead of print: 16 Jun 2021].
- 5 Dias L, Soares-Dos-Reis R, Meira J, *et al*. Cerebral venous thrombosis after BNT162b2 mRNA SARS-CoV-2 vaccine. *J Stroke Cerebrovasc Dis* 2021;30:105906.
- 6 Cines DB, Busse JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med* 2021;384:2254–6.
- 7 AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. Available: <https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood> [Accessed Apr 2021].
- 8 Smadja DM, Yue Q-Y, Chocron R, *et al*. Vaccination against COVID-19: insight from arterial and venous thrombosis occurrence using data from VigiBase. *Eur Respir J* 2021;58:2100956.
- 9 Wise J. Covid-19: rare immune response may cause clots after AstraZeneca vaccine, say researchers. *BMJ* 2021;373:n954.

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