Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Successful treatment of acute spleno-porto-mesenteric vein thrombosis after ChAdOx1 nCoV-19 vaccine. A case report

Michele Umbrello a,⁎, Nicola Brenab, Ruggero Vercelic, Riccardo Alessandro Foac, Marco Femiac, Umberto Rossid, Gian Marco Podda c, Francesca Cortellarob, Stefano Muttinina

a SC Anestesia e Rianimazione II, Ospedale San Carlo Borromeo, ASST Santi Paolo e Carlo – Polo Universitario, Milano, Italy
b Sc Pronto Soccorso e Degenza Breve, Ospedale San Carlo Borromeo, ASST Santi Paolo e Carlo – Polo Universitario, Milano, Italy
c SSD UO a Direzione Universitaria di Radiologia Vascolare ed Interventistica, Ospedale Galliera, Genova, Italy
d SC Radiologia I, Ospedale San Carlo Borromeo, ASST Santi Paolo e Carlo – Polo Universitario, Milano, Italy
e SC Medicina Generale II, Ospedale Paolo, ASST Santi Paolo e Carlo – Polo Universitario, Milano, Italy

⁎ Corresponding author at: U.O. Anestesia e Rianimazione II, Ospedale San Carlo Borromeo, ASST Santi Paolo e Carlo – Polo Universitario, Via Pio II, 3, 20153 Milano, Italy.
E-mail address: Michele.umbrello@asst-santipaolocarlo.it (M. Umbrello).

A R T I C L E   I N F O

Keywords:
COVID-19 vaccine
Splanchnic thrombosis
Thrombocytopenia
Ultrasound-enhanced thrombolysis
VITT

A B S T R A C T

Several cases of deep venous thrombosis in people who had recently received Vaxzevria (previously known as COVID-19 Vaccine AstraZeneca) have recently been reported, mainly presenting as cerebral vein/cerebral venous sinus thrombosis. This syndrome has been termed “vaccine-induced immune thrombotic thrombocytopenia (VITT)”. Acute spleno-porto-mesenteric vein thrombosis is an uncommon but serious condition with potential sequelae, such as small-bowel gangrene and end-stage liver failure. We describe a case of concomitant thrombosis of portal, superior mesenteric and splenic veins in a young female patient with no other risk factors who received Vaxzevria (previously ChAdOx1 nCoV-19 vaccine, AstraZeneca) 17 days before. The diagnostic workup and the successful endovascular treatment and systemic anticoagulation management is reported.

© 2021 Elsevier Inc. All rights reserved.

1. Background

Vaccination is considered as the critical weapon in the battle against COVID-19. In March 2021, several cases of deep venous thrombosis in people who had recently received Vaxzevria (previously known as COVID-19 Vaccine AstraZeneca) have been reported, mainly presenting as cerebral vein/cerebral venous sinus thrombosis. This syndrome has been termed vaccine-induced immune thrombotic thrombocytopenia (VITT). We present a case of a 36-year-old woman who developed a spleno-porto-mesenteric vein thrombosis few days after vaccination with Vaxzevria.

2. Case presentation

A previously healthy, Caucasian Italian 36-year-old female patient presented to the Emergency Department with a 10-day history of upper abdominal pain. 17 days before she received her first dose of Vaxzevria COVID-19 Vaccine. A few days after the vaccination she suffered from a short course of fever, asthenia and diffuse osteoarticular pain. She was not taking oral contraceptives, nor did she report a personal or familiar history of venous thromboembolism or thrombophilia.

On admission she was normotensive, vital parameters and physical examination were normal. Bloods showed a mild thrombocytopenia (133 × 10^3/μL, normal values 150–350), while the remaining tests were normal. The nasopharyngeal swab ruled out SARS-COV-2 infection. Chest X-ray was negative, her electrocardiogram showed sinus rhythm 98 b/min. Emergency US and a subsequent abdominal CT with contrast showed complete thrombosis of splenic, superior mesenteric and portal vein (Fig. 1), with abdominal and pelvic free fluid. A continuous infusion of unfractioned heparin was started and the patient was admitted to the ICU for close monitoring of her disease course and adverse events. Considering the thrombotic burden, on the following day the patient underwent trans-hepatic portal vein venography via right internal jugular vein access that confirmed the complete thrombosis of splenic, superior mesenteric and portal vein (Fig. 2A). Thrombus aspiration with a Penumbra catheter was performed (Fig. 2B). A porto-systemic shunt was performed between the right suprhepatic and the right portal vein. Venous pressure measures are reported in Table 1. Ultrasound-accelerated thrombolysis was performed with two EkoSonic ultrasound-enhanced infusion catheters inserted through the right internal jugular vein. A 1 mg/h rtPA infusion was started and continued for 24 h. The results of coagulation tests are reported in Table 2.

Serum and urine protein electrophoresis excluded a myeloproliferative disorder. Given the findings of anti-heparin PF4 antibodies, the continuous infusion of heparin was discontinued and a continuous infusion of argatroban 2 μg/kg/min, with a target aPTT of 45″, was started. A

https://doi.org/10.1016/j.jcrc.2021.05.021
0883-9441/© 2021 Elsevier Inc. All rights reserved.
diagnosis of an autoimmune HIT was suggested, and a 5-day course of 0.4 g/kg intravenous Immunoglobulin was started.

During the second day of ICU stay, the patient developed melena and the haemoglobin levels dropped to 5.6 g/dl; her BP dropped to 90/60 mmHg and heart rate rose to 130 b/min. Three units of packed red blood cells were transfused, with normalisation of blood pressure and heart rate. Urgent esophagogastroduodenoscopy was performed and several vascular lesions at greater curvature and gastric fundus were found, which were treated with local epinephrine injection with no further evidence of bleeding.

The patient stayed in the ICU for 6 further days. Her clinical conditions remained stable. A mesenteric angiography was repeated on the 7th day. The superior mesenteric, portal and splenic veins were patent, and a partial reperfusion right intrahepatic portal vein branches (Fig. 3). Venous pressures are reported in Table 1. The patient was then eventually discharged from the ICU and transferred to a gastroenterology unit in good conditions. Long-term anticoagulation with apixaban was started. At 5 weeks of follow up no relapse had occurred.

### 3. Discussion

We report the case of a young, healthy, female patient in whom total spleno-porto-mesenteric thrombosis developed few days after Vaxzevria (previously COVID-19 Vaccine AstraZeneca), associated with thrombocytopenia and antiPF4 antibodies with no prior history of heparin exposure.

As of late March 2021, >20 million people in Europe and the UK had received the Vaxzevria vaccine. Cases of thrombosis and thrombocytopenia, mainly presenting as cerebral vein/cerebral venous sinus thrombosis, have been reported in persons who had recently received the vaccine, mostly within 14 days after vaccination. In some of these cases, mainly in women under 55, a combination of thrombosis and thrombocytopenia and bleeding, was described and attributed to an autoimmune form of Heparin-induced thrombocytopenia (HIT), which was termed vaccine-induced immune thrombotic thrombocytopenia (VITT) [1].

During the review process of this report, several other papers [2-7] described cases of a new syndrome characterized by thrombocytopenia and deep thrombosis, which developed 5 to 24 days after administration of ChAdOx1 nCoV-19, a recombinant chimpanzee adenoviral-
We found antibodies against PF4, which induce massive platelet activation despite not having previously received heparin. **HIT** antibody-induced platelet activation, leading to rapid platelet count recovery. Although the role of heparin in the pathogenesis of VITT is uncertain, to date there is no evidence that heparin dislodges PF4 bound to endothelium and other cellular surfaces also in VITT, thus increasing anti-PF4/heparin antibodies. Thus, according to ISTH recommendations [18] non-heparin anticoagulants are recommended. We chose argatroban for its short half-life in a patient with high bleeding risk.

As far as the specific treatment for the spleno-portal-mesenteric vein thrombosis is concerned, there is not a universally accepted protocol for management and treatment [13]. Systemic anticoagulation has shown a decreased benefit compared with sequential compression devices and inferior outcomes with regard to quality of life and cost-effectiveness [19]. Intravenous immunoglobulin and aggressive anticoagulation with argatroban was started as suggested [9], with the aim of interrupting HIT antibody-induced platelet activation, leading to rapid platelet count recovery. Although the role of heparin in the pathogenesis of VITT is uncertain, to date there is no evidence that heparin dislodges PF4 bound to endothelium and other cellular surfaces also in VITT, thus increasing anti-PF4/heparin antibodies. Thus, according to ISTH recommendations [18] non-heparin anticoagulants are recommended. We chose argatroban for its short half-life in a patient with high bleeding risk.
six-month recanalization rate of about 50%, as well as a failure rate of 10% [19]. Local infusion of thrombolytic therapy, given via a transjugular route, was shown effective to provide recanalization [12]. Adjunctive endovascular techniques have recently been developed to reduce thrombolytic drug exposure, and improve efficacy compared with standard thrombolysis [20,21], which include balloon angioplasty, thrombectomy devices, ultrasound–accelerated thrombolysis, aspiration thrombectomy and TIPS creation. Ultrasound–accelerated thrombolysis involves the simultaneous endovascular delivery of low-intensity ultrasound and thrombolytic agent. In in vitro studies, this technique proved effective in accelerating clot lysis by increasing clot permeability and penetration of the thrombolytic agent, exposing additional plasminogen receptor sites to the thrombolytic agent [22]. In a multicentre, retrospective report, this technique was shown to be associated to a reduced drug infusion time, with a greater incidence of complete lysis and a reduction in bleeding rates [23]. In the case reported, effective venous recanalization was achieved; however, a major haemorrhagic complication occurred. Gastric bleeding, despite potentially associated with splenic vein thrombosis [24], is most likely a major complication of the systemic anticoagulation and the regional thrombolysis. In our centre, the EkoSonic ultrasound-enhanced thrombolysis system is routinely used in cases of intermediate-high risk pulmonary embolism. The decision to use the device in this case of splanchic thrombosis, as well as the prolonged duration of the rtPA infusion, was empiric and based on our previous experience, as well as on the significant thrombotic burden. Given the only recent description of VITT, no data are available for the risk of recurrence. Hence, long-term duration of anticoagulant therapy is still an open issue.

4. Conclusion

While the vaccination campaign to progress, further studies will be required to allow for a better understanding of the real incidence and the exact pathogenesis, as well as the optimal treatment of this condition. In the meantime, we suggest that (1) consider spleno–porto-mesenteric thrombosis in the differential diagnosis of epigastric abdominal pain, (2) perform a complete thrombotic work-up to elucidate abnormalities that could be contributing to a pro-thrombotic state and (3) initiate aggressive endovascular and systemic measures in order to avoid decompensation and a significant adverse outcome.

Declarations of interest

None.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Cines DB, Busse JB. SARS-CoV-2 vaccine–induced immune thrombocytopenia. N Engl J Med. 2021. https://doi.org/10.1056/NEJMMe2106315.
[2] Greinacher A, Theile T, Warkentin TE, Weisser K, Kyrlle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021. https://doi.org/10.1056/NEJMoa2104882.
[3] Schultz NH, Sorvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021. https://doi.org/10.1056/NEJMoa2105385.
[4] Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. N Engl J Med. 2021. https://doi.org/10.1056/NEJMMe2105860.
[5] Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021. https://doi.org/10.1056/NEJMoa2105385.
[6] Thaler J, Ay C, Gleixner KV, Hauswirth AW, Cacioppo F, Graefeneder J, et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). J Thromb Haemost. 2021. https://doi.org/10.1111/jth.15346.
[7] Wolf ME, Luz B, Niehaus L, Bhogal P, Banzet H, Henkes H. Thrombocytopenia and intracranial venous sinus thrombosis after “COVID-19 Vaccine Astrazeneca” exposure. J Clin Med. 2021;10(8). https://doi.org/10.3390/jcm10081599.
[8] Agency EM. Astrazeneca’s COVID-19 vaccine: benefits and risks in context. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-benefits-risks-context. (accessed April 23rd 2021).
[9] Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. J Thromb Haemost. 2017;15(11):2099–114. https://doi.org/10.1111/jth.13813.
[10] Oldenburg J, Klamaroth R, Langer F, Alibisetti M, von Auer C, Ay C, et al. Diagnosis and management of vaccine-related thrombosis following Astrazeneca COVID-19 vaccination: guidance statement from the GHT. Hamartosaseologie. 2021. https://doi.org/10.1002/a-1469-7481.
[11] Battistelli S, Coratti F, Gori T. Porto-spleno-mesenteric venous thrombosis. Int Angiol. 2021;30(1):1–11.
[12] Ponziani FR, Zocco MA, Campanale C, Rinninella E, Tortora A, Di Maurizio L, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol. 2010;16(2):143–55. https://doi.org/10.3748/wjg.v16.i2.143.
[13] Russell CE, Wadhera RK, Piazza G. Mesenteric venous thrombosis. Circulation. 2015;131(18):1599–603. https://doi.org/10.1161/CIRCULATIONAHA.114.012871.
[14] Liu FY, Wang MQ, Fan QS, Duan F, Wang ZJ, Song P. Interventional treatment for symptomatic acute-subacute portal and superior mesenteric vein thrombosis. World J Gastroenterol. 2009;15(40):5028–34. https://doi.org/10.3748/wjg.v15.5028.
[15] Rajesh S, Mukund A, Arora A. Imaging diagnosis of splanchic venous thrombosis. Gastroenterol Res Pract. 2015;2015:101029. https://doi.org/10.1155/2015/101029.
[16] Emile SH. Predictive factors for intestinal transmural necrosis in patients with acute mesenteric ischemia. World J Surg. 2018;42(8):2364–72. https://doi.org/10.1007/s00268-018-4503-3.
[17] Connors JM. Thrombophila testing and venous thrombosis. N Engl J Med. 2017;377(12):1177–87. https://doi.org/10.1056/NEJMra1700365.
[18] Haemostasis ISoTa. Statement from the ISTH on reports indicating blood clots associated with the Astrazeneca vaccinehttps://www.isth.org/news/559981/; ; 2021. https://doi.org/10.1056/NEJMoa2105869.
[19] Parikh S, Shah R, Kapoor P. Portal vein thrombosis. Am J Med. 2010;123(2):117–9. https://doi.org/10.1016/j.amjmed.2009.05.023.
[20] Ferro C, Rossi UG, Bovio G, Dahamane M, Centanaro M. Transjugular intrahepatic portosystemic shunt, mechanical aspiration thrombectomy, and direct thrombolysis in the treatment of acute portal and superior mesenteric vein thrombosis. Cardiovasc Intervent Radiol. 2007;30(5):1070–8. https://doi.org/10.1007/s00270-007-9137-2.
[21] Rossi UG, Rollandi GA, Dalatana R, Cariati M. Mechanical aspiration thrombectomy in the treatment of acute infraumbilical artery thrombosis. Cardiovasc Revasc Med. 2010;29(4):344–6. https://doi.org/10.1016/j.carrev.2018.04.009.
[22] Braaten JV, Goss RA, Francis CW. Ultrasound reversibly deaggregates fibrin fibers. Thromb Haemost. 1997;78(3):1063–8.
[23] Parikh S, Motarjeme A, McNamara T, Raabe R, Hagspiel K, Benenati JF, et al. Ultrasound-accelerated thrombolysis for the treatment of deep vein thrombosis: initial clinical experience. J Vasc Interv Radiol. 2008;19(4):521–8. https://doi.org/10.1016/j.jvir.2007.11.023.
[24] Paramythiotis D, Papavramidis TS, Giavoglou K, Potsi S, Girtovits F, Michelopoulos A, et al. Massive variceal bleeding secondary to splenic vein thrombosis successfully treated with splenic artery embolization: a case report. J Med Case Reports. 2010;4:139. https://doi.org/10.1186/1752-1947-4-139.