



Thromboembolic events following mRNA vaccines for COVID 19: a case series

Alessandra Serrao¹ · Roberta Agrippino¹ · Mattia Brescini¹ · Rosaria Mormile¹ · Antonio Chistolini¹

Accepted: 25 December 2021 / Published online: 3 February 2022

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

To the Editor,

In response to the SARS-COV-2 pandemic, different types of vaccines have been developed: mRNA vaccines, non-replicative vector vaccines, inactivated and subunit vaccines [1]. By late December 2020, mass vaccination campaigns have started all around the world. Thromboembolic events have been reported after SARS-COV-2 vaccines [2], in particular after ChAdOx1 n COV-19 vaccine (Oxford-AstraZeneca) [3] and the Ad26.COV2.S (Johnson Johnson/Janssen) [4]. In these cases, a particular severe syndrome has been described (VITT) characterized by thrombosis, particularly at unusual sites including cerebral/splanchnic thrombosis, mild to severe thrombocytopenia and positive PF4-heparin ELISA and platelet activation assays [3, 5]. Despite the excellent safety profile of mRNA vaccines, some cases of venous thromboembolism (VTE) related to this type of vaccination have been recently reported in literature [6–8], including cerebral vein thrombosis [9–11]. Herein, we described our single centre experience of 15 cases of VTE following mRNA vaccination. From May 2021 to September 2021, 112 patients were admitted to our Institute for VTE. Among them, fifteen patients were admitted for the onset of a thromboembolic event occurred after the administration of mRNA vaccines. Nine were male and 6 were female. The median age was 51 years (range 29–74 years), with 13 patients younger than 60 years old. Overall, 11 patients received Comirnaty BNT 162b2 Pfizer/BioNTech vaccine while 4 the Spikevax 1273 Moderna vaccine.

The median time from vaccination to the thromboembolic event was 12 days (range 1–30 days).

In particular, a median of 18 days (range 4–30 days) occurred from the administration of BNT 162b2 and 1, 4,

12 and 22 days respectively from the administration of Spikevax 1273.

The VTE onset was documented either after the first (n = 9) or the second dose (n = 6) of vaccine. Among the BNT162b2 vaccinated population, 7 patients (63.6%) experienced thrombosis after the first dose and 4 (36.4%) after receiving the second dose. Among the Spikevax 1273 vaccinated population, 2 experienced thrombosis after the first dose and 2 after the second one. Overall, we observed 10/15 deep-vein thrombosis (DVT), in two cases complicated by pulmonary embolism and in a single case involving the cerebral circle (transverse and sigmoid sinus). In the other 5/15 cases a superficial-vein thrombosis (SVT) was documented, affecting the lower limbs (n = 2) or the upper limbs (n = 2); one case among these latter was associated to pulmonary embolism (PE).

The different sites affected by thrombosis are specified in Table 1.

All patients denied familiar history of VTE, trauma, recent surgery. They were investigated to exclude solid or hematologic malignancy and for the presence of congenital and acquired thrombophilia. Overall, 3/15 patients (20%) had no pro-thrombotic risk factors. Conversely, 3 patients were on treatment with estroprogestinic therapy, respectively from 5, 6 and 8 years; one of them also exhibited the presence of prothrombin G20210A heterozygous. Two other patients reported a previous history of superficial venous thrombosis (SVT). In 2 patients elevated homocysteine levels were detected (41 and 50 $\mu\text{mol/L}$). In a single case there was a mild congenital thrombophilia (factor V Leiden heterozygous). In another single case there was a previous diagnosis of essential thrombocythemia (ET), not requiring treatment, and thoracic outlet syndrome (TOS). Two patients presented a chronic venous disease one associated to obesity; one patient had smoking habit. Regarding the treatment administered for VTE, 10/15 patients who presented DVT/EP received low molecular weight heparin (LMWH) or fondaparinux and subsequently oral anticoagulation: 8 were

✉ Antonio Chistolini
antonio.chistolini@uniroma1.it

¹ Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Via Benevento 6, 00161 Rome, Italy

Table 1 Characteristics of the patients and of the thromboembolic events

Patient	Age (years)	Sex	Vaccine	VTE risk factors	VTE site	Vaccine to VTE onset (days)	VTE therapy
1	59	Female	Comirnaty	Obesity, chronic venous disease	SVT	21	Fondaparinux
2	51	Male	Comirnaty	Hyperhomocysteinemia	Cephalic vein, right pulmonary embolism	10	LMWH, apixaban
3	30	Female	Comirnaty	Estroprogestinic therapy	Common femoral vein, right external iliac vein	19	LMWH, apixaban
4	59	Male	Comirnaty	Hyperhomocysteinemia	Left common femoral vein, right pulmonary embolism	20	Fondaparinux, apixaban
5	39	Female	Comirnaty	Estroprogestinic therapy, FIIG20210A heterozygous, hyperhomocysteinemia	Popliteal, superficial femoral vein	4	LMWH, apixaban
6	29	Male	Comirnaty	JAK2 V617F, TOS	Venous circulation upper right limbs	18	Dabigatran
7	57	Male	Spikevax	Previous SVT	Left great saphenous vein	1	LMWH
8	60	Male	Spikevax	F V Leiden heterozygous	Common femoral vein, superficial femoral vein, common iliac vein	22	LMWH, apixaban
9	73	Female	Comirnaty	Chronic venous disease	SVT	4	Fondaparinux
10	46	Female	Comirnaty	Estroprogestinic therapy	Transverse and right sigmoid sinus	30	Warfarin
11	50	Female	Spikevax	Smoking	SVT	12	LMWH
12	74	Male	Spikevax	None	Left popliteal femoral vein, right pulmonary embolism	4	LMWH, rivaroxaban
13	45	Male	Comirnaty	None	Right popliteal femoral vein	20	Fondaparinux, apixaban
14	54	Male	Comirnaty	Previous SVT	Left popliteal femoral vein	10	Fondaparinux, apixaban
15	44	Male	Comirnaty	None	Left popliteal vein	7	LMWH, apixaban

treated with apixaban, 1 patient with rivaroxaban, 1 with dabigatran. The patient affected by cerebral venous thrombosis was treated with the vitamin K antagonist, warfarin. The others 4/15 patients, who presented SVT, were treated with fondaparinux or EBPM for 45 days. The patient who presented EP and SVT of the arm was treated with LMWH and subsequently apixaban. Moreover, among patients who experienced thrombosis after the first dose of the vaccine, 5/9 did not complete the scheduled vaccination with the second dose because of patient's decision. Conversely, 4/9 patients (44.4%) received the second dose with the same type of vaccine during anticoagulant therapy and after a median time of 61 days (range 14–111 days) from the onset of thrombosis. Importantly, none of them experienced recurrence of thrombosis nor worsening of the clinical status. None of the patients required hospitalization. It is known that thromboembolic events are part of the clinical manifestations of COVID-19 [12] and even if rare, VTE could complicate the administration of vaccines. This is particularly true for the ChAdOx1 n COV-19 vaccine [3]. Regarding

the mRNA vaccines, there are few reported cases of venous thrombosis including those of the cerebral district [9, 10]. Their incidence is lower than expected and the current evidences do not suggest a causal relationship. We described our single centre experience of 15 patients presenting VTE after the administration of BNT162b2 vaccine or Spikevax 1273 vaccine. Although temporal relationship suggests that the vaccine may have caused thrombotic events, it could be coincidental as some patients presented additional risk factors for thrombosis. For instance, 1 patient had a history of ET and congenital TOS. In 2 patients we found a mild congenital thrombophilia; in 2 cases we found high levels of homocysteinemia. Three patients were on estroprogestinic treatment for many years. It is not possible to document a clear association between these thromboembolic events and the mRNA vaccines. There is the probability that these events may correspond to a normal incidence of VTE among general population. Even though the temporal linkage between the thromboembolic complications and anti-COVID vaccination is strongly suggestive for a correlation,

mRNA vaccines are considered safe and must still be used. In fact, the reported incidence of thrombosis after COVID-19 vaccines is 0.21 (95% CI 0.19–0.22) cases per million person vaccinated-days, while the frequency of venous thromboembolism during COVID-19 infection was 14.7% (95% CI 12.1–17.6%) [13]. Interestingly, no recurrence of thrombosis occurred after the second dose administration in patient who experimented VTE after the first vaccination. The thromboembolic complications do not represent a contraindication to complete the vaccination cycle; indeed, many our patients completed the vaccination scheduled. The vaccination for SARS-Cov-2 is essential to overcome the pandemic, therefore it is important to continue to be vigilant for possible complications emerging during the campaign. Systematic safety monitoring of COVID-19 vaccines is essential to ensure that benefits are superior to risks. A longer follow up is needed to clarify and to document this relationship between VTE and mRNA vaccines. The limitations of this study include the monocentric and retrospective nature that can't permit to calculate the real incidence of thromboembolic complications in the vaccinated population compared to the general population.

Author contributions A.S. analyzed the data and participated in the writing the manuscript; M.B. collected and analyzed the data; R.M. performed laboratory tests; A.C. analyzed, supervised and interpreted the data and wrote the manuscript.

Funding Funding is not applicable.

Data availability The data are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors declare no relevant conflict of interest.

References

- Centers for Disease Control and Prevention. COVID-19 Vaccines. Available 17 from: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html>

- Kantarcioglu B, Iqbal O, Walenga JM, Lewis B, Lewis J, Carter CA, Singh M, Lievano F, Tafur A, Ramacciotti E, Gerotziakas GT, Jeske W, Fareed J (2021) An update on the pathogenesis of COVID-19 and the reportedly rare thrombotic events following vaccination. *Clin Appl Thromb Hemost* 27:10760296211021498
- Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S (2021) Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 384(22):2092–2101
- Muir KL, Kallam A, Koepsell SA, Gundabolu K (2021) Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. *N Engl J Med* 384(20):1964–1965
- Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, Wiedmann M, Aamodt AH, Skattør TH, Tjønnfjord GE, Holme PA (2021) Thrombosis and thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 384(22):2124–2130
- Dias L, Soares-Dos-Reis R, Meira J, Ferrão D, Soares PR, Pastor A, Gama G, Fonseca L, Fagundes V, Carvalho M (2021) Cerebral venous thrombosis after BNT162b2 mRNA SARS-CoV-2 vaccine. *J Stroke Cerebrovasc Dis* 30(8):105906
- Andraska EA, Kulkarni R, Chaudhary M, Sachdev U (2021) Three cases of acute venous thromboembolism in females following vaccination for COVID-19. *J Vasc Surg Venous Lymphat Disord*
- Carli G, Nichele I, Ruggeri M, Barra S, Tosetto A (2021) Deep vein thrombosis (DVT) occurring shortly after the second dose of mRNA SARS-CoV-2 vaccine. *Intern Emerg Med* 16(3):803–804
- Zakaria Z, Sapiai NA (2021) Ghani ARI cerebral venous sinus thrombosis 2 weeks after the first dose of mRNA SARS-CoV-2 vaccine. *Acta Neurochir* 163(8):2359–2362
- Fan BE, Shen JY, Lim XR, Tu TM, Chang CCR, Khin HSW, Koh JS, Rao JP, Lau SL, Tan GB, Chia YW, Tay KY, Hameed S, Umaphathi T, Ong KH (2021) Prasad BMRV cerebral venous thrombosis post BNT162b2 mRNA SARS-CoV-2 vaccination: a black swan event. *Am J Hematol* 96(9):E357–E361
- Krzywicka K, Heldner MR, Sánchez van Kammen M, van Haaps T, Hiltunen S, Silvis SM, Levi M, Kremer Hovinga JA, Jood K, Lindgren E, Tatlisumak T, Putaala J, Aguiar de Sousa D, Middeldorp S, Arnold M, Coutinho JM, Ferro JM (2021) Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European Medicines Agency. *Eur J Neurol*. <https://doi.org/10.1111/ene.15029>
- Allegra A, Innao V, Allegra AG, Musolino C (2020) Coagulopathy and thromboembolic events in patients with SARS-CoV-2 infection: pathogenesis and management strategies. *Ann Hematol* 15:1–13
- Konstantinides SV (2021) Thrombotic complications of vaccination against SARS-CoV-2: what pharmacovigilance reports tell us—and what they don't. *Eur Respir J* 58(1):2101111

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.