Received: 9 April 2023 | Revised: 19 May 2023 | Accepted: 25 May 2023

DOI: 10.1002/ccr3.7468

CASE REPORT

Clinical Case Reports Open Access WILEY

# Covishield vaccination and pulmonary thromboembolism: A coincidence or a causal association?

**Rijal Divas**[1] | **Rijal Prabhat**[2] | **Raina Rohit**[2] | **Chaudhari Ashish Sanjay**[2] | **Homagain Sushan**[1] | **Rawol Bijaya**[1]

[1]Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Maharajgu, Kathmandu, Nepal

[2]Department of Internal Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

**Correspondence**
Rijal Divas, Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Maharajgunj Medical Campus, Maharajgunj 44600, Kathmandu, Nepal.
Email: rijaldivas@gmail.com

**Key Clinical Message**

With the eruption of COVID pandemic, many cases of thromboembolic events in association with the COVID infection were reported suggesting the prothrombotic state associated with the infection. After a few years, eventually some of the COVID vaccines came into implementation. With the discovery and implementation of COVID vaccinations, a very few cases have been reported to have developed thromboembolic events, including pulmonary thromboembolism. Different types of vaccines have been associated with different rates of thromboembolic events. Covishield vaccine is rarely associated with thrombotic complications. In the case report below, we present a case summary of a young married female, who presented with shortness of breath a week after the Covishield vaccination and presented to our tertiary care center with further worsening of symptoms during a course of 6 months. On detailed workup, she was diagnosed to have a large pulmonary thrombus affecting the left main pulmonary artery. Other possible etiologies of the hypercoagulable states were ruled out. Though COVID vaccines are known to induce prothrombotic state in the body, we could not be sure if it was the actual cause for the pulmonary thromboembolism or just a coincidence.

**KEYWORDS**

COVID infection, COVID vaccine, Covishield, pulmonary thromboembolism

## 1 | INTRODUCTION

Covishield is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 spike(S) glycoprotein. After vaccination, the genetic material of the virus is expressed, which mounts an immune response leading to its protective efficacy. Its dosing schedule includes two doses, which are administered at a gap of 12–16 weeks. It also includes various different ingredients that increase the stability, as well as potentiate the immune response following vaccination. Apart from the adverse reactions like fever, malaise, and allergic reactions, it rarely is associated with thrombotic events with an incidence of less than 1 per 1 lakh vaccinated individual.[1] In our case, the lady presented with pulmonary thromboembolism associated with Covishield vaccination. Despite having mild symptoms in the initial few days following vaccination, she came to our tertiary care center after 6 months

of vaccination. We aim to sensitize the physicians toward the possibility of occurrence of such incidents following COVID vaccination, though rare in frequency.

## 2 | CASE REPORT

A 32-year-old female without any known comorbidities and addictions, mother of two children, presented to us with insidious onset shortness of breath for 6 months, which developed 5 days after the second dose of Covishield vaccination. Shortness of breath was present only on exertion (MMRC Grade II) in the initial days and gradually progressed in severity to MMRC Grade III over the duration of past 2 weeks. She underwent evaluation and treatment in different local clinics for her symptoms. Despite the treatment, her symptoms progressed in severity and she ultimately presented to our institute 6 months after her symptoms started. It was not associated with chest pain, cough, syncope, orthopnea, paroxysmal nocturnal dyspnea, or bilateral lower limb swelling. There is no history of fever, joint pain, rashes, hair fall, photosensitivity, oral ulcers, impaired consciousness, skin thickening, bluish discoloration of fingers, difficulty swallowing, restricted mouth opening, or fetal losses. Bowel and bladder habits were normal. On examination, the patient had loud P2 and pansystolic murmur of grade 3/6 over the tricuspid area, prominent on inspiration, and associated with right parasternal heave. Routine blood investigations did not reveal significant abnormality. Chest X-ray showed cardiomegaly with prominent right descending pulmonary artery. ECG showed features of pulmonary hypertension and right ventricular strain pattern (Figure 1). Echocardiography showed severe pulmonary artery hypertension (PAH) with severe tricuspid regurgitation (TR) with right ventricular systolic pressure (RVSP) of 110 mm of Hg (Figure 2). CT pulmonary angiography was done that showed evidence of left main pulmonary artery thrombosis extending to its branches (Figures 3 and 4) (Table 1). The patient did not give consent for thrombolysis or any surgical interventions. The patient was started on unfractionated heparin (UFH) infusion, and the dose was titrated based on 6 hourly activated partial thromboplastin time (APTT) values with target range of 60–70 s. Serial monitoring of complete blood counts was also done to look for the possibility of heparin-induced thrombocytopenia (HIT). Sildenafil was started at a low dose in view of pulmonary hypertension. The antinuclear antibody (ANA) report was positive; however, the extractable nuclear antigen (ENA) panel came out to be negative (Tables 2 and 3). Protein C, protein S, and homocysteine were within normal limits, and the antiphospholipid antibody panel was also negative. However, a detailed thrombophilia panel could not be sent due to the resource-limited setting and the cost of the test being far beyond the affordability of the patient. Deep vein thrombosis was ruled out by bilateral lower limb venous Doppler. The patient was switched to oral rivaroxaban in maintenance dose after stopping the UFH infusion; repeat echocardiography was done after 7 days that showed only minimal reduction in RVSP to 100 mm of Hg. The patient denied any surgical and catheter-guided intervention and hence discharged on oral medications with advice for follow-up. But she is lost to follow up at the time of preparing this manuscript 6 months after discharge.

## 3 | DISCUSSION

Pulmonary embolism (PE) as a consequence to COVID infection is a known fact. COVID infection leads to a

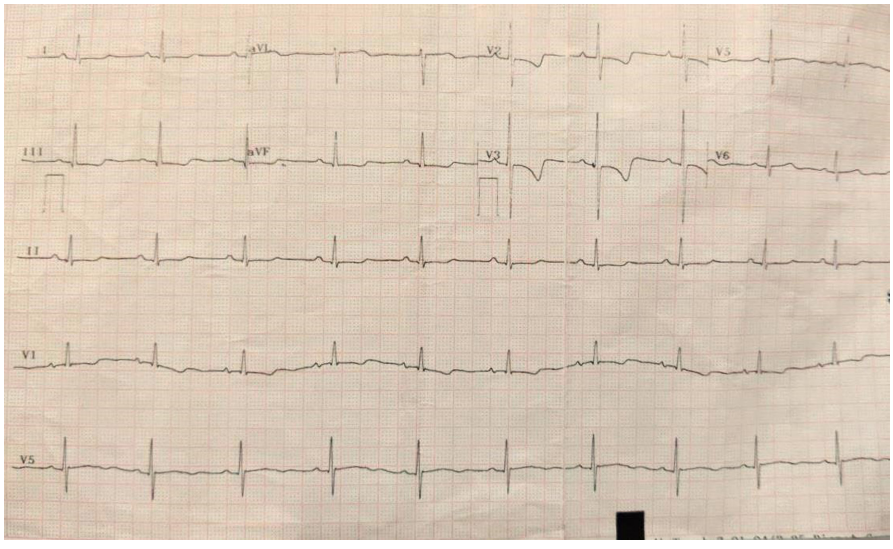


**FIGURE 1** ECG showing right ventricular hypertrophy with strain pattern.

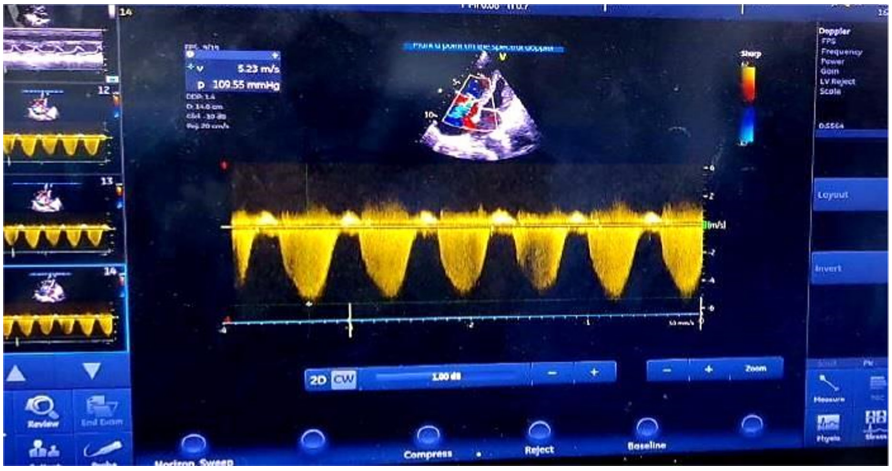


**FIGURE 2** Echocardiography imaging showing measurement of right ventricular systolic pressure.

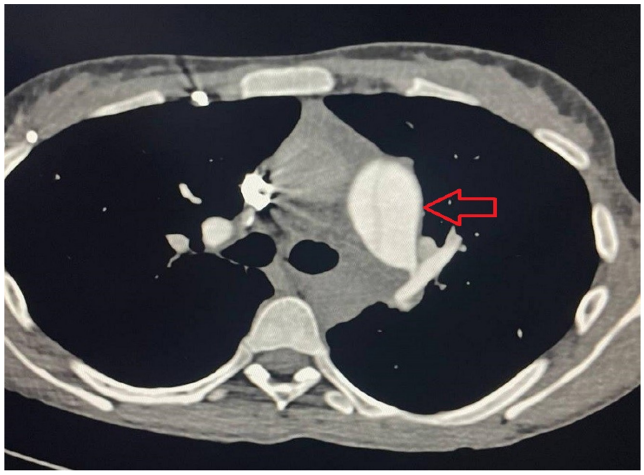

**FIGURE 3** CT pulmonary angiography showing normal contrast opacification of the main pulmonary trunk (as in arrow).

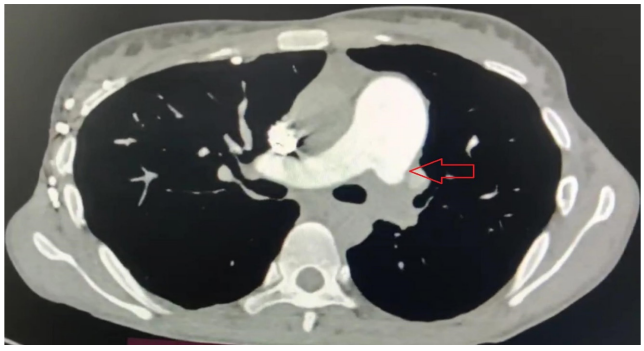

**FIGURE 4** CT pulmonary angiography showing contrast cutoff in the left pulmonary artery (as in arrow).

state of hypercoagulability, endothelial dysfunction, hypoxia-related blood viscosity, and dysregulation of hypoxia-inducible transcription factor-dependent signaling pathway important in thrombus formation. On the contrary, COVID vaccine also has led to unprovoked pulmonary embolism in a few instances.[2] Smadja et al. presented an analysis of thrombotic events across the globe in association with three major COVID vaccines, namely Pfizer-Biotech (BTN162b2), Moderna (mRNA-1273), and Oxford AstraZeneca (ChAdOx1 nCoV-19). The study confirmed the rarity of possible thrombotic complications in association with COVID-19 vaccination, reporting only 0.21 cases of thrombotic events per million person vaccinated days.[3] However, the reported incidences are as high as 14.7% in a meta-analysis by Tan et al.[4,5]

In a review of 40 reported cases of thrombotic complication following COVID vaccination, female-to-male ratio was 2.1 with median age of 40.5 years and pulmonary embolism was present in 23.1%.[6] Similar results were obtained in a meta-analysis by Clio Bilotta et al.[7] analyzing the thrombotic complications AstraZeneca vaccine with high female prevalence and duration of symptoms onset of about 9 days after vaccination. Two cases of isolated pulmonary embolism following COVID vaccination were reported by Nwosu Ifeanyi et al.[8] in which the patient presented with symptoms of pulmonary embolism 8 days and 4 weeks after the COVID vaccination. In our case scenario, our patient presented to us 6-month postvaccination; however, she had mild symptoms since the fifth day of vaccination. Viktoria Muster et al. presented a case who presented with shortness of breath, fatigue, and cough 8 days after the ChAdOx1 nCoV-19 vaccination. On investigating, she was diagnosed to have central pulmonary embolism with right ventricular dysfunction.[9]

The term vaccine-induced thrombotic thrombocytopenia was used to represent those patients with thrombotic phenomenon with thrombocytopenia.[10] Polyanions including the nucleic acids and other components of bacterial cell wall, due to their negative charge, promote binding to positively charged platelet factor-4, leading to the formation of anti-PF-4 antibodies.[11] Anti-PF-4 ab thus formed cause pan

**TABLE 1** Imaging studies.

| Imaging modality | Findings |
|---|---|
| CT pulmonary angiography | Pulmonary thromboembolism involving the left main pulmonary artery and its superior and inferior branches (Figures 3 and 4); Mild cardiomegaly with dilated main pulmonary artery and right ventricle |
| Ultrasonography abdomen | No significant abnormality detected |
| Echocardiography (first study) | Severe tricuspid regurgitation, severe pulmonary artery hypertension, RVSP: 110 mm of Hg, D-shaped left ventricle, normal left ventricle function (Figure 2) |
| Echocardiography (repeat study after 7 days) | Severe pulmonary artery hypertension with RVSP 100 mm of Hg |
| Bilateral lower limb venous Doppler | No evidence of deep vein thrombosis |

**TABLE 2** ANA profile.

| Investigations | Result |
|---|---|
| ANA(IFA) | 4+ |
| Primary dilution | 1:80 |
| Pattern | Homogenous pattern |
| End dilution | 1:640 |

**TABLE 3** Extractable nuclear antigen (ENA) profile.

| Antibodies | Status |
|---|---|
| Anti-Smith antibody | Negative |
| U1SM/RNP antibodies | Negative |
| SS-A antibodies | Negative |
| RO-52 antibodies | Negative |
| SS-B antibodies | Negative |
| Antihistone antibodies | Negative |
| Anticentromere antibodies | Negative |
| Abs to extractable nuclear antigen: SCL-70 | Negative |
| Abs to extractable nuclear antigen: JO-1 | Negative |
| Anti-dsDNA | Negative |

Abbreviations: Abs, Aantibodies; dsDNA, double- stranded Ddeoxyribonucleic Aacid; JO-I, histidyl tRNA synthetase; SCL-70, Ttopoisomerase I; SS-A, Sjogren Ssyndrome-A; SS-B, Sjogren Ssyndrome B; U1RNP, U1 Rribonucleoprotein.

cellular activation (platelets, coagulation cascade, and endothelial cells) leading to high risk of thrombosis.[11]

Therapeutic anticoagulation is the treatment of choice unless contraindicated along with high-dose intravenous immunoglobulin (IVIG) with rapid improvement as reported.[12,13] Plasma exchange and immunosuppression are options in refractory cases.[14,15] Our patient received UFH during hospital stay and was discharged on rivaroxaban.

## 4 | CONCLUSION

Though rare, physicians must be watchful for one of the dreaded complications of the COVID vaccine, that is, pulmonary embolism. High degree of suspicion and immediate workup can help diagnose and start treatment at the earliest. Pulmonary embolism is one of the causes that when treated can lead to complete reversal of pulmonary artery hypertension.

## AUTHOR CONTRIBUTIONS

**Divas Rijal:** Conceptualization; formal analysis; investigation; resources; supervision; writing – original draft; writing – review and editing. **Prabhat Rijal:** Conceptualization; methodology; resources; software; writing – review and editing. **Rohit Raina:** Resources; supervision; writing – review and editing. **Ashish Sanjay Chaudhari:** Conceptualization; resources; writing – original draft; writing – review and editing. **Sushan Homagain:** Conceptualization; investigation; methodology; supervision; writing – review and editing. **Bijaya Rawol:** Resources; software; writing – original draft.

## FUNDING INFORMATION

None.

## CONFLICT OF INTEREST STATEMENT

The author does not possess any conflict of interest.

## DATA AVAILABILITY STATEMENT

Available from the corresponding author on reasonable request.

## CONSENT

Informed written consent signed by the patient and attached with the original files.

## ORCID

*Rijal Divas* https://orcid.org/0000-0002-8265-2293
*Rijal Prabhat* https://orcid.org/0000-0001-9332-2786
*Homagain Sushan* https://orcid.org/0000-0002-8767-6112

## REFERENCES

1. Kulkarni PS, Padmapriyadarsini C, Vekemans J, et al. A phase 2/3, participant-blind, observer-blind, randomised,

controlled study to assess the safety and immunogenicity of SII-ChAdOx1 nCoV-19 (COVID-19 vaccine) in adults in India. *EClinicalMedicine*. 2021;42:101218.
2. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099.
3. Smadja DM, Yue QY, Chocron R, Sanchez O, Lillo-Le LA. Vaccination against COVID-19: insight from arterial and venous thrombosis occurrence using data from VigiBase. *Eur Respir J*. 2021;58(1):2100956. doi:10.1183/13993003.00956-2021
4. Tan BK, Mainbourg S, Friggeri A, et al. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. *Thorax*. 2021;76(10):970-979.
5. Konstantinides SV. Thrombotic complications of vaccination against SARS-CoV-2: what pharmacovigilance reports tell us – and what they don't. *Eur Respir J*. 2021;58(1). doi:10.1183/13993003.01111-2021
6. Franchini M, Liumbruno GM, Pezzo M. COVID-19 vaccine-associated immune thrombosis and thrombocytopenia (VITT): diagnostic and therapeutic recommendations for a new syndrome. *Eur J Haematol*. 2021;107(2):173-180.
7. Bilotta C, Perrone G, Adelfio V, et al. COVID-19 vaccine-related thrombosis: a systematic review and exploratory analysis. *Front Immunol*. 2021;12:729251.
8. Ifeanyi N, Chinenye N, Oladiran O, David E, Mmonu C, Ogbonna-Nwosu C. Isolated pulmonary embolism following COVID vaccination: 2 case reports and a review of post-acute pulmonary embolism complications and follow-up. *J Community Hosp Intern Med Perspect*. 2021;11(6):877-879.
9. Muster V, Gary T, Raggam RB, Wölfler A, Brodmann M. Pulmonary embolism and thrombocytopenia following ChAdOx1 vaccination. *Lancet*. 2021;397(10287):1842.
10. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med*. 2021;384(22):2092-2101.
11. Greinacher A, Selleng K, Palankar R, et al. Insights in ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia. *Blood*. 2021;138(22):2256-2268.
12. Bourguignon A, Arnold DM, Warkentin TE, et al. Adjunct immune globulin for vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med*. 2021;385(8):720-728.
13. Uzun G, Althaus K, Singh A, et al. The use of IV immunoglobulin in the treatment of vaccine-induced immune thrombotic thrombocytopenia. *Blood*. 2021;138(11):992-996.
14. Pavord S, Scully M, Hunt BJ, et al. Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. *N Engl J Med*. 2021;385(18):1680-1689.
15. Rock G, Weber V, Stegmayr B. Therapeutic plasma exchange (TPE) as a plausible rescue therapy in severe vaccine-induced immune thrombotic thrombocytopenia. *Transfus Apher Sci*. 2021;60(4):103174.

**How to cite this article:** Divas R, Prabhat R, Rohit R, Sanjay CA, Sushan H, Bijaya R. Covishield vaccination and pulmonary thromboembolism: A coincidence or a causal association? *Clin Case Rep*. 2023;11:e7468. doi:10.1002/ccr3.7468