ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–5
https://doi.org/10.1093/ehjcr/ytad353

CASE REPORT
Heart failure

Acute pulmonary hypertension due to microthrombus formation following COVID-19 vaccination: a case report

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Received 5 January 2023; revised 10 July 2023; accepted 25 July 2023; online publish-ahead-of-print 26 July 2023

Background Several side effects have been reported after mRNA COVID-19 vaccinations. Nonetheless, the risk of pulmonary hypertension (PH) is rarely reported. Most cases with acute PH following vaccination were due to macropulmonary embolism secondary to deep vein thrombosis. However, acute PH due to microthrombus formation after COVID-19 vaccination has not been reported before, although a microthrombus has been considered to lead to the dysfunction of multiple organs, particularly in patients infected with COVID-19.

Case summary A 63-year-old woman without any past medical history presented to our hospital with facial and bilateral pedal oedema and progressive dyspnoea on exertion. Her symptoms began the day after her second COVID-19 vaccination and developed gradually, which prompted her to seek consultation in our hospital 6 weeks later. An echocardiogram revealed substantially elevated right heart pressure, and cardiac catheterization revealed high pulmonary artery pressure (mean PAP, 30 mmHg). Contrast-enhanced computed tomography and venous echography revealed no apparent thrombus, and ventilation/perfusion (V/Q) scintigraphy revealed no V/Q mismatch. However, elevated D-dimer indicated the presence of a coagulation–fibrinolysis system in her body; thus, heparin therapy was initiated intravenously on Day 3 for 4 days, followed by direct oral anticoagulants ended on Day 16. Her symptoms substantially improved as her D-dimer level decreased, and a follow-up cardiac catheterization on Day 14 revealed a decline in mean PAP (15 mmHg).

Discussion Our case suggests that the presence of acute PH is likely due to microangiopathy. Further studies are required to reveal the relationship between immune responses and microthrombus formation after COVID-19 vaccination.

Keywords COVID-19 vaccines • Pulmonary hypertension • Microthrombus • Immune-mediated thrombus • Case report

ESC curriculum 9.5 Pulmonary thromboembolism • 9.6 Pulmonary hypertension

Learning points

- Acute pulmonary hypertension (PH) due to pulmonary microvascular thrombosis should be suspected in cases of acute PH following COVID-19 vaccination even after ruling out macrothrombosis by imaging.
- Heparin therapy can be effective in treating PH due to pulmonary microvascular thrombosis after COVID-19 vaccination, in the absence of macrothrombi.

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Handling Editor: Edgar Francisco Carrizales Sepulveda
Peer-reviewers: Dan Octavian Nistor; Dmitry Duplyakov
Compliance Editor: Abdelsalam Bensaaud

Introduction

As of December 2022,[1] ~13 billion COVID-19 vaccine doses have been administered globally, and they had been widely used as a pandemic containment strategy. However, the first mRNA COVID-19 vaccine has been reported to cause various side effects. According to the Vaccine Adverse Event Reporting System (VAERS), pulmonary hypertension (PH) is one of the side effects of the COVID-19 vaccine, but its occurrence is rare compared with the occurrence of other adverse effects such as myocarditis and pericarditis.[2] In the VAERS database, there have been 216 reports of PH following COVID-19 vaccination as of 9 December 2022.[3] The most common cause of PH was thrombosis [pulmonary thromboembolism (PE) secondary to deep vein thrombosis[3]] and left heart failure secondary to cardiomyopathy and myocardial infarction.[3] Conversely, PH due to microthrombus formation following COVID-19 vaccination has not been previously reported, although a microthrombus has been considered to cause dysfunction of various organs, particularly in patients with COVID-19 infection.[4] Herein, we report a case with acute PH and systemic coagulopathy in the absence of macrothrombi by multiple imaging modalities, indicating the presence of acute PH due to microangiopathy following COVID-19 vaccination.

Summary figure

August		Received the 1st COVID-19 vaccine Pedal edema was noted on the day after vaccination, resolved on its own within few days.
September	3 weeks after the 1st shot	Received the 2nd COVID-19 vaccine Pedal edema appeared again on the day after the 2nd shot
	3 weeks after the 2nd shot	The pedal edema persisted, and the patient visited her home doctor.
	6 weeks after the 2nd shot	Facial edema and progressive dyspnea was appeared
October	7 weeks after the 2nd shot	Came to our hospital: echocardiography showed severe pulmonary hypertension. D-dimer: 9.0 μg/ml.
	Day 2	Right heart catheterization demonstrated elevated mean pulmonary artery pressure (PAP, 30mmHg) with normal pulmonary artery wedge pressure (11 mmHg).
	Day 3	Initiated heparin intravenously
	Day 7	The Six-minute Walk Test : 120m
	Day 11	Echocardiography showed remarkable improvement of right ventricular pressure.
	Day 12	The Six-minute Walk Test : 335 m
	Day 14	The Six-minute Walk Test : 405 m Follow-up right heart catheterization at day 14 showed decreased mean PAP (15 mmHg) suggesting improvement in pulmonary hypertension D-dimer dropped to 2.8 μg/ml
	Day 16	The symptom was disappeared. Discharge.

Case presentation

A 63-year-old Japanese woman presented to our hospital with facial and bilateral pedal oedema and progressive dyspnoea on exertion. She had no past medical history, family history, and allergies, and was previously healthy until she received her COVID-19 vaccinations. The oedema emerged the day following her first COVID-19 vaccination (Pfizer-BioNTech COVID-19 Vaccines, Pfizer, New York, NY, USA) but resolved on its own. The bilateral leg oedema occurred again after her second COVID-19 vaccination (Pfizer-BioNTech COVID-19 Vaccines), and dyspnoea on exertion gradually developed. As the oedema and dyspnoea did not improve and facial oedema was newly developed, the patient visited our hospital 6 weeks following her second vaccination. On admission, her physical examination revealed a jugular venous distention with bilateral lower extremity pitting oedema. Echocardiography revealed substantially elevated right heart pressure with a D-shaped left ventricle and a high tricuspid regurgitation peak gradient (TRPG, 57 mmHg) (*Figure 1A* and *B*). Enhanced computed tomography (CT) revealed no apparent thrombus in the pulmonary arteries or lower extremity veins (*Figure 2*). Venous echography of the lower extremities also showed no evidence of thrombi. Electrocardiogram revealed right-axis deviation, incomplete right bundle branch block, an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III (*Figure 3A* and *B*). On the Day 2 of admission, right cardiac catheterization revealed elevated mean pulmonary artery pressure (mean PAP, 30 mmHg) with normal pulmonary artery wedge pressure (11 mmHg). Ventilation/perfusion (V/Q) scintigraphy on Day 3 revealed no V/Q mismatch (see Supplementary material online, *Figure S1*). Blood tests revealed no sign of collagen or malignant illness, but D-dimer level was 9.0 μg/mL and mildly elevated (normal range: <0.4 μg/mL). The C-reactive protein level (normal range: 0.8–1.0 mg/dL) and white blood cell count (normal range: 4.5–11.0 × 10^3/μL) were both within the normal range (*Figure 4*). Because neither enhanced CT scan nor V/Q scintigraphy illustrated evidence of a thrombus, the elevated D-dimer level suggested the involvement of microthrombi; thus, intravenous heparin therapy (infusion rate: 1.5 mL/h) was initiated on Day 3 and it continued until Day 7. Her symptoms improved substantially as her D-dimer levels dropped, and we began edoxaban treatment at 30 mg following heparin (*Figure 5*) on Day 8. Edoxaban treatment ended on Day 16. Her 6 min walk test results improved from 120 m on Day 7 to 405 m on Day 14, and echocardiography on Day 11 showed decreased TRPG (20 mmHg; *Figure 5A*, Supplementary material online, *Video 1*). Follow-up right heart catheterization on Day 14 showed decreased mean PAP (15 mmHg) indicating improvement in PH. As the symptoms substantially improved, the patient refused all the medications, including anticoagulants, and she was discharged on Day 16. A 1 month follow-up echocardiogram revealed normal right heart pressure, no tricuspid valve regurgitation, and a normal D-dimer level (*Figure 5B*, Supplementary material

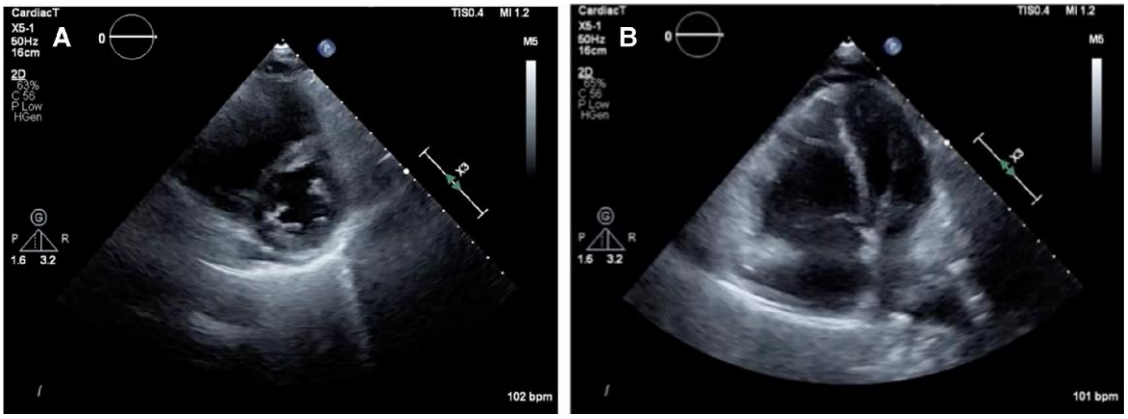

Figure 1 Echocardiography on the day of admission. Left sternal border short-axis view (*A*) and apical four-chamber echocardiographic view (*B*) demonstrate a D-shaped left ventricle and high tricuspid regurgitation peak gradient (TRPG, 57 mmHg). TRPG, tricuspid regurgitation peak gradient.

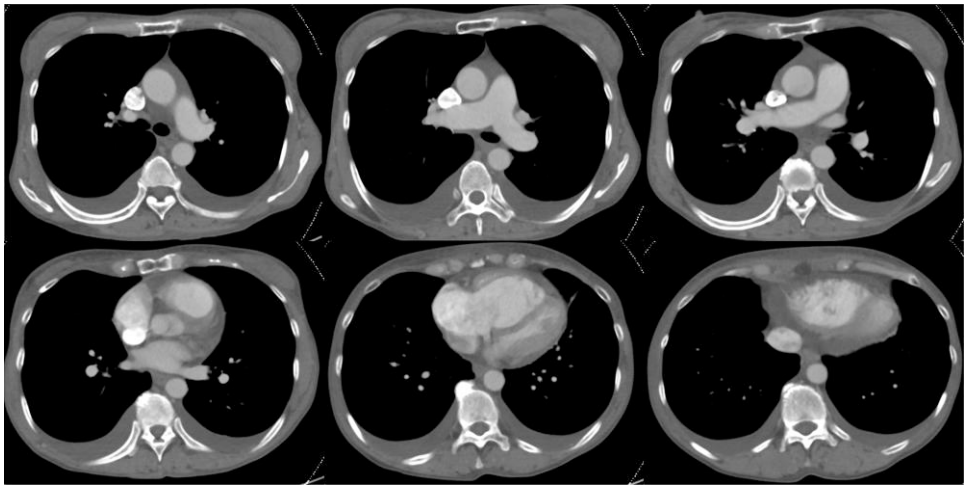

Figure 2 Contrast-enhanced computed tomography on the day of admission. There is no evidence of thrombi in pulmonary arteries.

online, *Video 1*). The patient has been asymptomatic at the 8 month follow-up.

Discussion

In the current case, the patient developed PH, which developed from an unknown cause after receiving the COVID-19 vaccination, and was successfully treated with anticoagulant therapy. We initiated heparin intravenously for 4 days, followed by direct oral anticoagulants for 9 days. Although there is no consensus on the duration and types of anticoagulants for patients with thrombosis caused by COVID-19 vaccination, we followed previous studies for patients with PE caused by COVID-19 infection[5,6]

There were no signs of macrothrombi observed by commonly used image modalities such as contrast-enhanced CT, venous echography, and V/Q scintigraphy. In addition, all the possible diseases that could cause acute PH were ruled out.[7] Because elevated D-dimer levels indicated systemic activation of coagulation/fibrinolysis, we diagnosed that the cause of acute PH in the current case was microvascular thrombosis. Although onset of the symptom next day after vaccination was faster than the average onset of thrombotic complication following COVID-19 vaccination (4.8 days),[8] the rapid diminution of the symptom after heparin initiation supported our diagnosis. Previous pathological analyses of patients infected with COVID-19[9] have revealed that microthrombi in the lung microvasculature are common. The current case is the first case report of acute PH due to microthrombus formation after COVID-19 vaccination.

Recent studies have suggested that COVID-19 vaccines may cause immune-mediated thrombosis,[10] leading to intravascular thrombus formation. The angiotensin-converting-enzyme (ACE) 2 receptor-binding spike protein expressed by mRNA COVID-19 vaccination induces

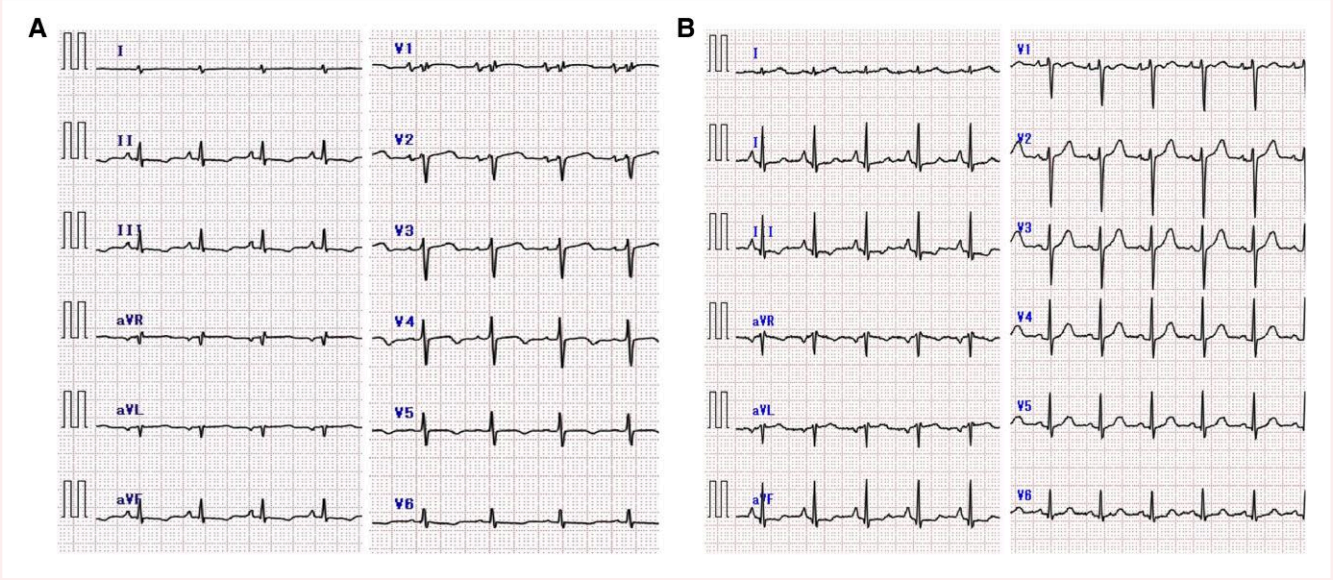

Figure 3 Electrocardiogram on the day of admission and 1 month after discharge. (*A*) Electrocardiogram on the day of admission reveals right-axis deviation, incomplete right bundle branch block, an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III but a normal Q wave in lead III. (*B*) Electrocardiogram 1 month after discharge demonstrates almost normal electrocardiogram.

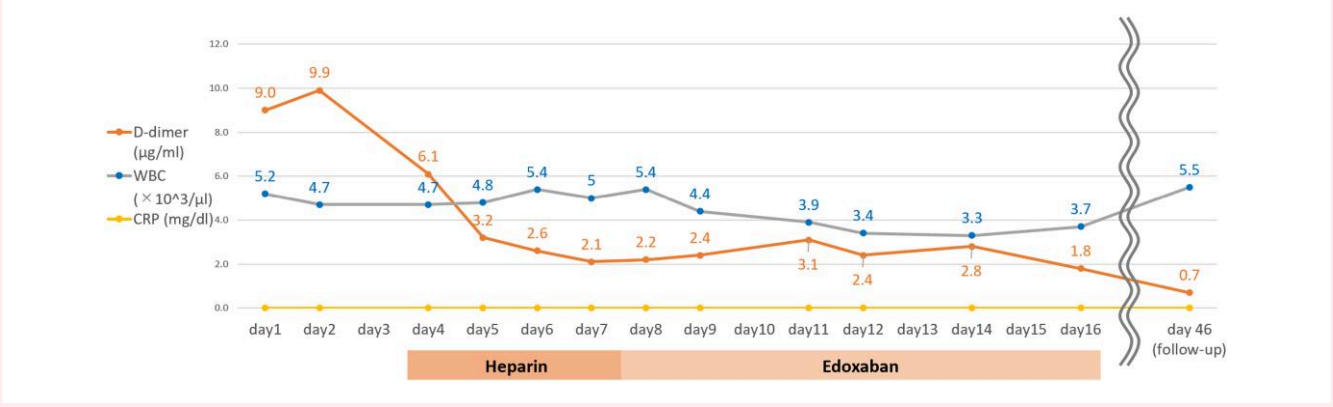

Figure 4 Time course of blood tests and treatments during admission. The D-dimer levels are elevated in the beginning, but C-reactive protein and white blood count levels remain normal. Normal ranges for D-dimer, C-reactive protein, and white blood count levels are <0.4 μg/mL, 0.8–1.0 mg/dL, and 4.5–11.0 × 103/μL, respectively.

endothelial damage.[10] Various cells express spike proteins after mRNA COVID-19 vaccines induce anti-Spike protein antibodies.[10] These antibodies occasionally stimulate anti-idiotypic antibodies to interact with ACE2-like spike protein on functionally damaged vascular endothelial cells.[10] Because of fluid dynamics,[11] flowing platelets instantly adhere to damaged endothelial cells,[12] resulting in the formation of thrombi in microvessels. These antibodies are suggested to increase with multiple inoculations of vaccines.[10]

Conclusion

We reported a case with acute PH that could have been caused by a microthrombus in the lungs as an adverse reaction to COVID-19 vaccination. Heparin therapy was effective in the case even in the absence of macrothrombi. Further studies are required to understand the relationship between immune responses and microthrombus formation after COVID-19 vaccination.

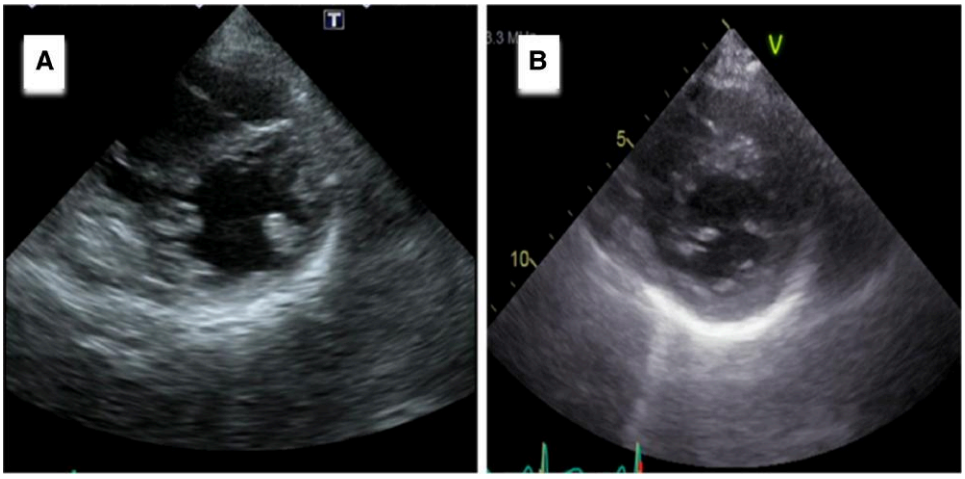

Figure 5 Changes in echocardiographic findings of short-axis view. Serial changes in the short-axis view on Day 10 (*A*) and after a month following discharge (*B*).

Lead author biography

She is currently in her final year at Tokai University School of Medicine, Japan. She will begin a two-year junior residency programme in Japan upon graduation.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Consent: The authors confirm that written consent for the submission and publication of this case report, including images and associated text, was obtained from the patient in line with COPE guidelines.

Conflict of interest: None declared.

Funding: None declared.

Data availability

The data underlying this article are available in the main text and its online *supplementary material*.

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