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Acute Pulmonary Embolism Following Moderna mRNA-1273 SARS-CoV-2 Vaccination – A Case Report and Literature Review

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Key Words: Anti-PF4 antibody • Moderna vaccine • Pulmonary embolism • SARS-CoV-2 • Vaccine-induced immune thrombotic thrombocytopenia (VITT)

INTRODUCTION

In the era of the novel coronavirus (SARS-CoV-2) pandemic, vaccination has become an important and urgent need worldwide. Despite the development of vaccines, their safety is still a common concern among the public. Thromboembolism is a safety concern with these vaccines, especially adenovirus (AstraZeneca) vaccines. However, although not rarely reported, mRNA vaccines have also been associated with the risk of thromboembolism, especially in East Asian populations. Herein, we describe a previously asymptomatic patient who presented with acute pulmonary embolism shortly after receiving the Moderna mRNA-1273 SARS-CoV-2 vaccine.

CASE

This case was a 70-year-old East Asian male, a current smoker, with a past medical history of hypertension and an old cerebrovascular accident, with independent activities of daily living. He received the first dose of the Moderna mRNA-1273 vaccine 5 weeks prior to this episode. He presented to our emergency department with progressive shortness of breath for 5 days. A physical examination revealed blood pressure of 120/70 mmHg, heartbeat of 102 beats per min, and SpO2 around 90%. Resting 12-lead electrocardiography revealed sinus tachycardia and a typical S1Q3T3 pattern. Laboratory data showed normal platelet count, hemoglobin and fibrinogen levels. A SARS-CoV-2 polymerase chain reaction was negative. The D-dimer level was 4895 ng/mL, and chest computed tomography angiography showed bilateral saddle pulmonary embolism (Figure 1).

To further survey the pulmonary embolism, we conducted examinations in order to verify the possible etiology, including autoimmune disease markers (including antinuclear antibody, C3, C4, lupus anticoagulant, anticardiolipin immunoglobulin), tumor markers (including CEA, alpha-fetal protein, CA199, and PSA), coagulant function tests (including protein C function, antithrombin III, prothrombin time, partial thromboplastin time), all of which were within normal limits. Protein S function was 25.4% (normal value 62.6-150.4%) and the anti-platelet factor 4 (PF4) antibody titer was 50.01 ng/ml (cutoff value of 50 ng/ml) with an optical density of 0.424 units (weakly positive, cutoff value of 0.4 units). Left popliteal vein thrombosis was found by peripheral Doppler sonography (Figure 2).

He was initially treated with low molecular weight heparin (enoxaparin sodium) for the first 3 days, and direct oral anticoagulants (dabigatran 110 mg twice daily) was added thereafter because vaccine-induced immune thrombotic thrombocytopenia (VITT) was highly suspected. The symptoms gradually improved, and he was discharged 7 days later uneventfully. He is still asymptomatic 3 months after the episode with regular follow-up at the outpatient department and direct oral anticoagulant treatment.

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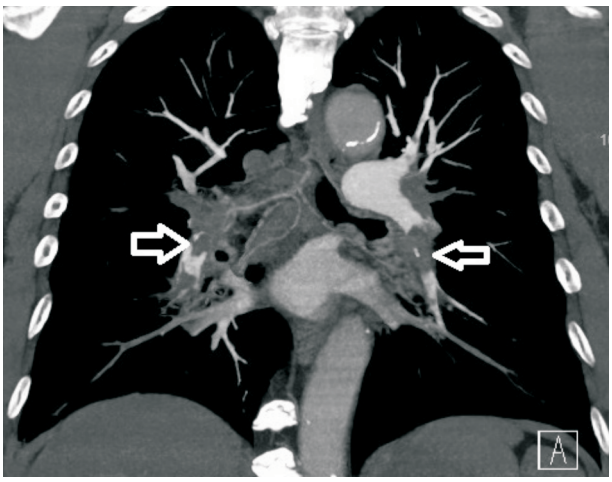

Figure 1. *Bilateral pulmonary embolism noted on computed tomography angiography (white open arrows).*

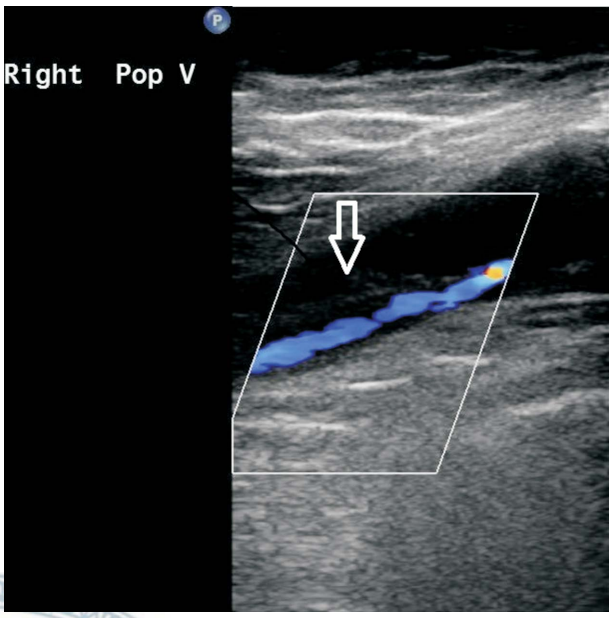

Figure 2. *Peripheral Doppler revealed probable thrombus with partial occlusion at the right popliteal vein (white open arrow).*

DISCUSSION

In this report, a previously healthy East Asian patient without known risk factors for thromboembolic disorder presented with acute pulmonary embolism 5 weeks after receiving the Moderna mRNA-1273 vaccine. After a series of studies, we found that the possible etiology for left popliteal deep vein thrombosis and bilateral pulmonary embolism was VITT, which was confirmed by weakly positive anti-PF4 antibodies and protein S deficiency.

In previous reports of thromboembolic events after mRNA vaccines, a large self-controlled case series study in England reported increased risks of both hematological and thromboembolic events within 2 to 3 weeks after ChAdOx1 nCoV-19 and BNT162b2 mRNA vaccines.[1] Venous thromboembolism has seldom been reported with the BNT162b2 mRNA vaccine. Moreover, these risks are much lower compared to those with SARS-CoV-2 infection based on a recent meta-analysis.[2] However, in our case, acute pulmonary embolism developed more than 5 weeks after vaccination. A possible explanation is the thromboembolism originated from left popliteal vein thrombosis initially after vaccination, and then the thrombus gradually migrated into bilateral pulmonary trunk 2 to 3 weeks later.

The most common mechanism of VITT is a heparin-induced thrombocytopenia-like pathway related to anti-PF4 antibodies. This mechanism has also been reported in adenovirus vector and RNA vaccines,[3,4] however it has also been reported in mRNA vaccines.[5] The mechanism by which the immune response after vaccination leads to the formation of anti-PF4 antibodies is poorly understood. A recently published case series showed no strong correlations between the levels of PF4-heparin antibodies and anti-SARS-CoV-2 IgG antibodies. In addition, no significant difference in the level of anti-SARS-CoV-2 IgG antibodies has been found between patients with and without thrombus formation.[6]

It is currently unclear how long pathogenic anti-PF4 antibodies persist. In a study involving 35 patients with serologically confirmed VITT, levels of anti-PF4 antibodies were found to gradually decline but could exist for more than 12 weeks in some cases.[7] In our case, the level of anti-PF4 antibodies was only weakly elevated at the diagnosis of pulmonary embolism, which may be related to a decline in anti-PF4 antibodies due to the time interval from vaccination (5 weeks).

Interestingly, one case report reported a relationship between vaccination and autoimmune disorders, in which positive antiphospholipid antibodies and lupus anticoagulants were demonstrated.[8] A similar phenomenon has been observed in patients with COVID-19 infection.[9] Nevertheless, in our patient, protein S deficiency was observed with normal antiphospholipid antibodies and lupus anticoagulants. This has never been reported

in other studies, and the relationship between protein S and COVID-19 vaccine is unknown. We hypothesize that a COVID-19 vaccine may be the trigger for thrombosis in a patient with protein S deficiency.

For patients with vaccine-induced thrombosis, the use of direct oral anticoagulants has been recommended in order to avoid initial heparin therapy which may aggravate VITT. The administration of high-dose intravenous immunoglobulin or dexamethasone may also be helpful.[10] We immediately switched enoxaparin sodium to dabigatran in our case after excluding other etiologies. However, the duration of anticoagulant therapy is not well understood. Whether it should be treated as unprovoked pulmonary embolism is still under debate, and further studies are needed to guide treatment.

LEARNING POINTS FOR PHYSICIANS

1. Thromboembolic events can occur in patients after SARS-CoV2 mRNA vaccination.
2. The pathophysiology of SARS-CoV2 vaccine-related thromboembolic events may be caused by anti-PF4 antibodies, but is probably multifactorial.
3. How long pathogenic anti-PF4 antibodies persist and the correlations between levels of PF4-heparin antibodies and anti-SARS-CoV-2 IgG antibodies are not currently well understood.
4. Direct oral anticoagulants are recommended as the anticoagulation strategy for such patients, however a tailored strategy is necessary.

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None.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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