American Journal of Medical Case Reports, 2021, Vol. 9, No. 11, 527-531
Available online at http://pubs.sciepub.com/ajmcr/9/11/2
Published by Science and Education Publishing
DOI:10.12691/ajmcr-9-11-2

COVID-19 Vaccine and Potentially Related Thromboembolic Events: Case Series

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Received May 22, 2021; Revised June 28, 2021; Accepted July 08, 2021

Abstract The advent of multiple COVID vaccinations over the past year through an accelerated vaccine development process has led to concerns over its safety. The United States approved for emergency use the BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (Oxford-AstraZeneca), and the Ad26.COV2.S (Janssen/Johnson & Johnson) vaccines. Although these vaccines have had a high safety profile, rare but serious adverse events have been reported including pulmonary embolism (PE) and cerebrovascular thrombosis. In this case series, we identified three patients admitted to Beaumont Hospital with new onset of pulmonary thromboembolism shortly after receiving the Pfizer-BioNTech vaccine. Clinical and laboratory data were obtained and reviewed from the Epic charting system. The three patients included two male and one female patient. All were older than the age of 40, obese with a BMI > 30 $kg/m^{2,}$ and had underlying vascular disorders including hypertension, coronary artery disease, and/or a history of a cerebrovascular accident. One patient was a current cigarette smoker, one had quit over 27 years ago, and the third patient never smoked. Two patients developed pulmonary embolism after the second dose of the Pfizer-BioNTech vaccine, while the third patient developed pulmonary embolism after the first dose. This case series illustrates a possible association between the Pfizer-BioNTech vaccine and the potential development of pulmonary thromboembolism, particularly in middle-aged, obese adults with underlying vascular disease. This is not surprising as recent research has seen higher incidence of thrombosis with other COVID-19 vaccinations including Moderna, Oxford-AstraZeneca, and Janssen/Johnson & Johnson. Identifying this possible association is crucial in early diagnosis and patient management, but more importantly in educating higher risk adults to avoid modifiable risk factors for venous thromboembolism including immobility, certain medications, and possibly postponing elective surgeries. Further prospective or retrospective cohort studies are warranted to assess this association.

Keywords: *Pfizer-BioNTech vaccine, pulmonary embolism, deep venous thrombosis, safety*

Cite This Article: Eman EL-Sawalhy, Essa Kadiri, Eiman Elhouderi, Mohammed Abdelhalim, Marwa Sokrab, Jamila Asif, Maher Khadra, Khansae Nowir, Ayman Daoud, and Faisal Musa, "COVID-19 Vaccine and Potentially Related Thromboembolic Events: Case Series." *American Journal of Medical Case Reports*, vol. 9, no. 11 (2021): 527-531. doi: 10.12691/ajmcr-9-11-2.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first reported in December of 2019 and rapidly evolved into a worldwide pandemic. Currently, COVID-19 has affected over 33 million individuals in the United States with a case-fatality ratio of 1.8 % [1]. It has a wide range of clinical manifestations from asymptomatic to critical illness. Symptoms can include fever, cough, malaise, myalgia, sore throat, diarrhea, nausea, anorexia, anosmia, ageusia, and shortness of breath [2]. COVID-19 can precipitate a severe inflammatory response resulting in acute respiratory distress syndrome (ARDs), prothrombotic states, multiorgan failure, and death.

Vaccinations remain a critical tool in reducing the number of cases and preventing the further spread of COVID-19. In December of 2020, the Food and Drug Administration (FDA) approved emergency use authorization (EUA) for two mRNA-type vaccines manufactured by Pfizer-BioNTech and Moderna [3]. In late February of 2021, a viral vector protein vaccine manufactured by Janssen/Johnson & Johnson, similar to the AstraZeneca vaccine authorized by the European Medicine Agency was also approved for EUA in the United States [3].

As of May 31, 2021, approximately 50% of the US population or 165 million individuals have received at least one vaccination dose [4]. Several cases of vaccine-induced immune thrombotic thrombocytopenia (VITT), and both arterial and venous thrombosis with thrombocytopenia,

were linked to both the Johnson & Johnson and Oxford-Astra Zeneca vaccines [5,6].

Here we present three cases of pulmonary embolism after receiving the Pfizer-BioNTech vaccine.

2. Case Presentation

2.1. Case 1

A 68-year-old female with well controlled hypertension and obesity with a BMI of 43.9 kg/m^2 presented to the hospital with complaints of sudden onset chest pain associated with dyspnea. She had received her second dose of Pfizer-BioNTech vaccine five days prior. She had no history of tobacco smoking, recent trauma, hospitalizations, or surgery, personal or family history of thrombophilia, underlying malignancy, prior confirmed COVID-19 infection, and was not any hormone replacement therapy.

Initial vitals were stable on room air and the physical exam was unremarkable. Blood work was significant for mildly elevated creatinine at 1.30 mg/dl, mildly elevated troponin (max 0.13 ng/ml), and elevated D-dimer of 4,071 ng/ml, otherwise electrolytes, cell blood count, PT/INR, and liver function tests were all within normal limits. An EKG showed normal sinus rhythm with no acute ischemic changes. Computed tomography angiography (CTA) of the chest was done which showed filling defects in the distal main pulmonary arteries, segmental upper and lower lobe branches bilaterally, and subsegmental right middle lobe and lingula branches compatible with acute pulmonary embolism (Figure 1). It also showed straightening of the intra-articular septum and right-left ventricular ratio greater than 1, compatible with right heart strain. Lower extremities venous doppler ultrasound showed no evidence of deep vein thrombosis (DVT).

She was diagnosed with acute pulmonary embolism and started on a heparin infusion. She subsequently received thrombolysis the following day and her symptoms improved. She was transitioned to apixaban (Eliquis) and discharged with instructions to follow up with hematology and oncology specialist for possible hypercoagulable workup and age-appropriate cancer screening. After few weeks, the patient had a hypercoagulable workup done including anticardiolipin antibody, beta 2 glycoprotein antibody, protein C, S, and activated protein C resistance that were negative.

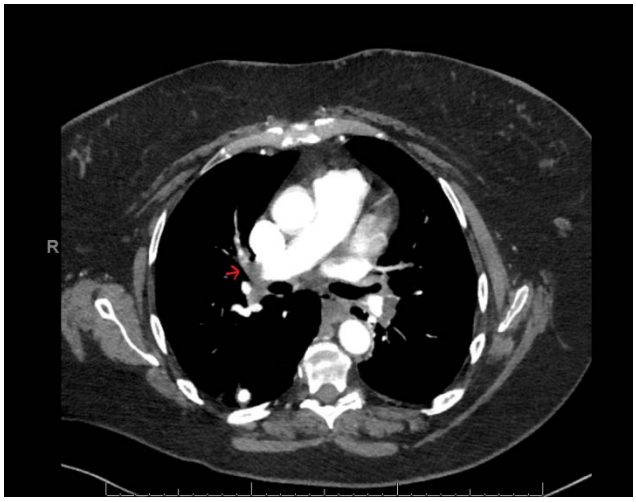

Figure 1. CTA of the chest showing filling defects in the distal main pulmonary artery and segmental branches compatible with acute PE

2.2. Case 2

A 48-year-old male with coronary artery disease, heart failure with reduced ejection fraction resulting in ICD implantation, uncontrolled hypertension, hyperlipidemia, and current cigarette smoking (25-pack-year history) presented to the hospital with a 1-day history of intermittent aching substernal chest pain associated with exertional dyspnea and left upper extremity (LUE) paresthesia. He had received his first dose of Pfizer-BioNTech vaccine three weeks prior and noted progressive right upper extremity edema (RUE) and ecchymosis since being vaccinated. He had no recent trauma, hospitalizations, or surgery, personal or family history of thrombophilia, underlying malignancy, prior confirmed COVID-19 infection, and was not any hormone replacement therapy.

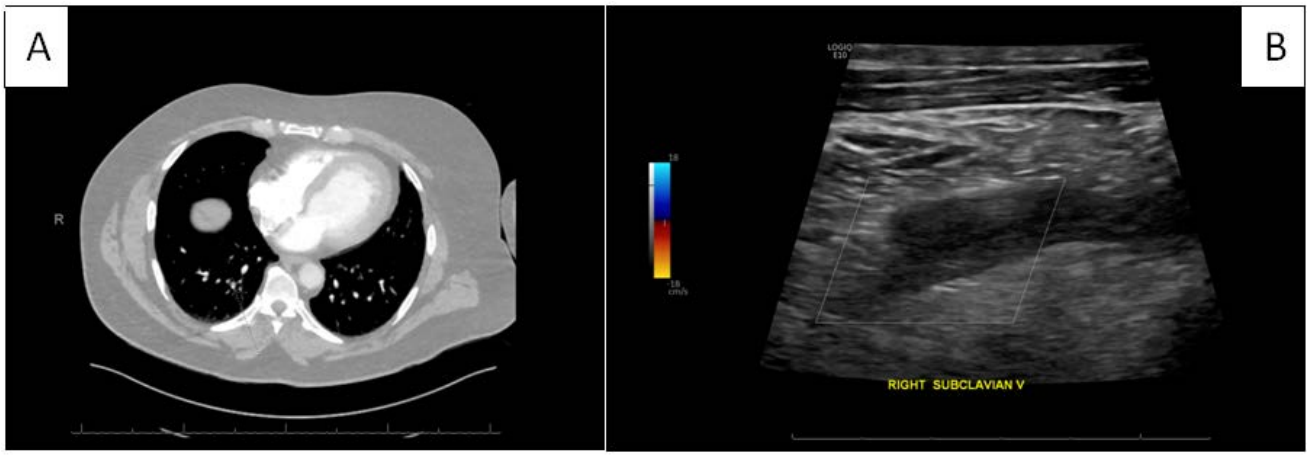

Figure 2. CTA of the chest showing small right lower lobe segmental pulmonary artery embolus (A). Venous doppler ultrasound of the right upper extremity showing an occlusive thrombosis of the right subclavian (B)

Initial vitals were stable on room air and physical exam was remarkable for proximal RUE edema with ecchymosis. Blood work was significant for up trending serial troponin 2.65->5.57->8.71 ng/ml and elevated D-dimer at 1,326 ng/ml, otherwise electrolytes, cell blood count, PT/INR, aPTT, and liver function tests were all within normal limits. An EKG showed normal sinus rhythm with no acute ischemic changes. Computed tomography angiography (CTA) of the chest showed a small right lower lobe segmental pulmonary artery embolus (Figure 2). Venous doppler ultrasound of the right upper extremity showed an occlusive thrombosis in the right subclavian, basilic, and cephalic veins (Figure 2). He was diagnosed with acute pulmonary embolism and non-ST segment elevation myocardial infarction (NSTEMI).

He was started on heparin infusion and taken for a cardiac catheterization the next day where he underwent percutaneous coronary intervention with drug eluting stent placement to the mid left anterior descending artery due to a 70% stenosis. His symptoms improved and he was transitioned to rivaroxaban (Xarelto). He was discharged with instructions to follow up with hematology and oncology specialist for possible hypercoagulable workup and age-appropriate cancer screening. After few weeks, the patient had a hypercoagulable workup done including anticardiolipin antibody, beta 2 glycoprotein antibody, protein C, S, and activated protein C resistance, prothrombin and Factor V mutation that were negative.

2.3. Case 3

An 80-year-old male with diabetes, congestive heart failure, and hyperlipidemia presented to the hospital with complaints of exertional dyspnea associated with chest pain and right leg edema. He had received his second dose of Pfizer-BioNTech vaccine four weeks prior. He has a 30 pack-year history of cigarette smoking, however, he quit at the age of 53. He had no recent trauma, hospitalizations, or surgery, personal or family history of thrombophilia, underlying malignancy, prior confirmed COVID-19 infection, and was not on any hormone replacement therapy.

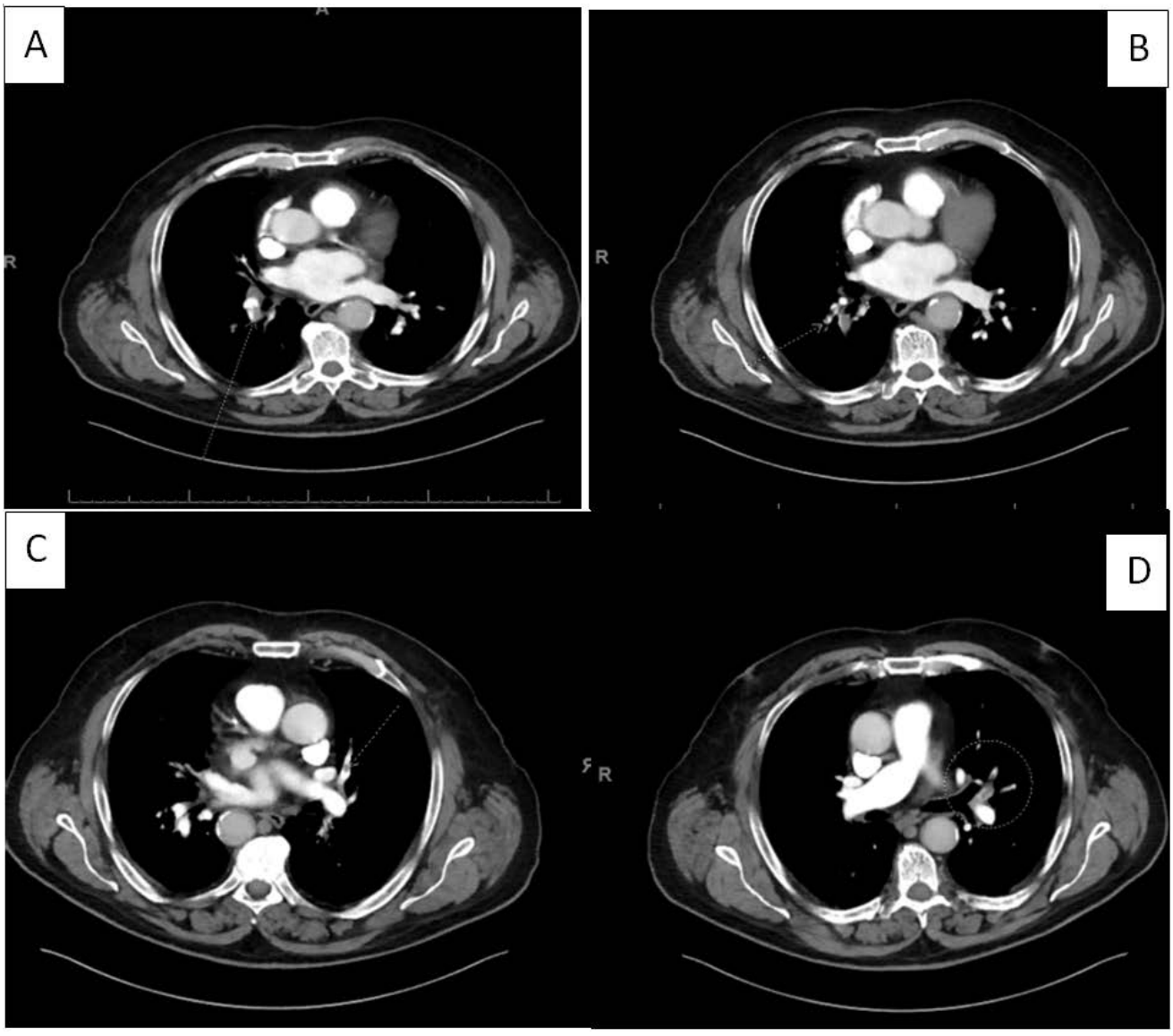

Figure 3. CTA of the chest showing bilateral pulmonary embolism

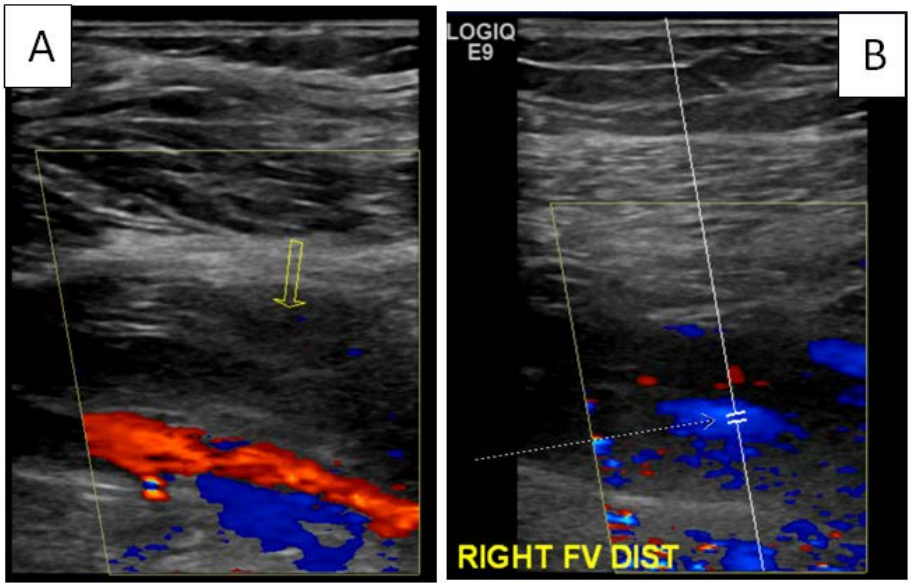

Figure 4. Venous doppler ultrasound of the right lower extremity showed deep venous thrombosis of the right popliteal vein (A) and involving the right femoral vein (B)

Initial vitals were stable on room air and the physical exam was unremarkable. Blood work was significant for slightly elevated creatinine at 1.32 mg/dl, otherwise, electrolytes, cell blood count, PT/INR, aPTT, serial troponins, and liver function tests were all within normal limits. D-Dimer was not performed. An EKG showed normal sinus rhythm with no acute ischemic changes. Computed tomography angiography (CTA) of the chest showed bilateral pulmonary embolism with no signs of right heart strain (Figure 3). Venous doppler ultrasound of the right lower extremity showed deep venous thrombosis involving the right femoral vein and right popliteal vein (Figure 4). He was diagnosed with acute pulmonary embolism and right lower extremity deep vein thrombosis.

He was started on heparin infusion and his symptoms improved. He was transitioned to rivaroxaban (Xarelto) and discharged with instructions to follow up with hematology and oncology specialist for possible hypercoagulable workup and age-appropriate cancer screening.

3. Discussion

As of May 31, 2021, with a little over a year since the COVID-19 pandemic began, there have been an estimated 568,965 deaths from COVID-19 in the United States alone. According to the CDC, over 50% of the United States' population have received at least one dose of the vaccine, while over 40% are fully vaccinated[5]. The CDC has found that 65-90% of individuals who are fully vaccinated with any of the three authorized vaccines are protected against symptomatic, laboratory-confirmed COVID-19 infection, while those who get infected, have reduced and less severe symptoms [4]. It is also noteworthy to point out that the vaccines have demonstrated a high efficacy (≥89%) in preventing COVID-19 infections, that are severe enough to require hospitalization. In addition, a growing body of evidence suggests that the vaccines also reduce asymptomatic infection and transmission [4].

This case series identified three patients who developed pulmonary embolism after receiving the Pfizer-BioNTech vaccine. Although all three of the patients were obese with a BMI > 30 kg/m^2 and had underlying cardiovascular disease, none had any obvious risk factors for venous thromboembolism, history of thrombophilia, or prior confirmed COIVD-19 infection. To our knowledge as of to date, there has been only one reported case of deep venous thrombosis associated with the Pfizer-BioNTech vaccine in a 66-year-old woman with no underlying medical conditions, a normal BMI, and no history of thrombophilia [7].

Since the introduction of COVID-19 vaccinations, there has been a growing number of cases of COVID-19 vaccine induced thrombosis associated with thrombocytopenia and in some cases bleeding, particularly with Janssen and AstraZeneca vaccines [8,9,10]. These reported cases occurred mostly in women under the age of 60, within 2-3 weeks of receiving the vaccine. Thromboses occurred in unusual sites, including cerebral venous sinus, splanchnic veins, and arteries accompanied by thrombocytopenia and bleeding [8,9,10]. The exact mechanism of thrombi formation is currently under investigation. Some hypothesize it to be related to an immunological response against platelet factor 4 leading to clotting formation and platelet consumption, similar to the mechanism of heparin-induced thrombocytopenia [8,9,10,11]. A recent study comparing the risk of cerebral thrombosis from COVID-19 infection and after vaccination with Pfizer-BioNTech or Moderna vaccines demonstrated an incidence of 39 per million in patient's diagnosed with COVID-19 versus 4.1 per million in the vaccinated population [10]. The incidence of cerebral thrombosis in the general population is estimated between 2 to 5 per million, however recent evidence suggests that may be as high as 20 per million [12,13].

In our case series, the three patients had no laboratory evidence of thrombocytopenia, coagulation abnormalities, bleeding, or prior COVID infection. This leads us to consider an alternative mechanism by which the

Pfizer-BioNTech vaccine might cause thromboses, different from the J Janssen/Johnson & Johnson and AstraZeneca vaccines.

4. Conclusion

This case series demonstrates a possible, albeit rare, likely association between the Pfizer-BioNTech vaccine and the development of venous thromboembolism. Further investigations are required to better elucidate this association and identify an underlying mechanism.

Conflict of Interest

None of the authors have any conflict of interest to declare.

Disclosure of Funding

None of the authors have any source of funding to declare.

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