CLINICAL VIGNETTE

Rare Saddle Pulmonary Embolus Following COVID Vaccine

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A 77-year-old male with a prior medical history of hypertension, hypercholesterolemia, and type-two diabetes mellitus, presented to the emergency department (ED) because of shortness of breath. The patient received his third COVID vaccine (Pfizer bivalent) booster eleven days prior. This was associated with constitutional symptoms including self-limited body aches and low-grade fevers. About four days after receiving the COVID vaccine booster, he started having mild exertional shortness of breath. Shortly thereafter, he took a commercial plane flight from Los Angeles to the Mid-West. Unfortunately, his exertional shortness of breath intensified and after returning home, he was dyspneic with minimal exertion. In the emergency department he denied lower extremity swelling, cough, dizziness, chest pain, palpitations, orthopnea, or paroxysmal nocturnal dyspnea. He did not report a personal or family history of blood clots or any symptoms associated with hypercoagulability. He denied any alcohol or illicit drug use and had been compliant in taking his medication which included valsartan-hydrochlorothiazide 320/25 mg daily, Bisoprolol 10 mg daily, Ezetimibe 10 mg PO daily, Metformin 1000 mg PO twice daily, Empagliflozin 10 mg po daily, and Pravastatin 40 mg per day. His family history was significant for heart disease in both parents and his sister as well as a daughter with Crohn's disease. On physical exam his vital signs were significant for sinus tachycardia, oxygen saturations of eighty six percent on room air but normotensive. He was awake and alert in mild distress with jugular venous distention to thirteen centimeters on the right side of his neck. His cardiac exam was most remarkable for a loud pulmonary component of his second heart sound over the second left intercostal space. His lungs were clear to auscultation bilaterally, with no crackles or wheezing. Extremities exam revealed one to two plus pitting edema over his lower extremities, left worse than right, but no cyanosis or clubbing.

The initial lab work in the ED was significant for a normal white cell count and hemoglobin but a platelet count of 185×10^9/L which decreased to 154×10^9/L on day 2 of hospitalization and reached a nadir of 112×10^9/L by day 5. His troponin, lactic acid, coagulation studies and BNP were all within normal range. His d-dimer was significantly elevated at 7556 mg/L FEU. (Normal < 0.5 mg/L FEU), Prothrombin time, partial thromboplastin time, fibrinogen, creatinine, electrolytes, aspartate aminotransferase, alanine aminotransferase, and high-sensitivity troponin T were within normal range. He did have a negative Anti-PF4 Antibody test; this result took several days to be reported. SARS-CoV-2 RT-PCR on a nasopharyngeal swab was negative. His chest x-ray was unremarkable and his electrocardiogram (ECG) was significant for sinus tachycardia with and heart rate of 120 beats per minute with no acute ST or T-wave changes.The patient was admitted to telemetry and placed on placed on oxygen via nasal cannula. A Computed Tomography Angiogram (CTA) of his chest with intravenous contrast was significant for a massive (saddle) pulmonary embolus as well as multiple pulmonary emboli filling the branch points of the left main and right pulmonary arteries extending into all lobar branches.(see Figure 1.) The clot burden was high with radiographic evidence of right ventricular (RV) strain. A venous doppler of lower extremities was significant for a deep vein thrombosis in the left popliteal and gastrocnemius veins and his echocardiogram revealed a reduced left ventricular ejection fraction of thirty-four percent and moderately increased right ventricular pressure. The patient was started on a Heparin drip and transferred to the intensive care unit for optimization followed by urgent mechanical pulmonary thrombectomy. The procedure was complicated by acute pulmonary edema that resolved with diuresis and supplemental oxygen administration. His symptoms began to improve, and he was weaned off supplemental oxygen by hospital day three. Heparin drip was discontinued 72 hours after thrombectomy, and he was started on full anticoagulation with apixiban. Follow-up imaging showed evidence of moderate right pulmonary infarct. Platelet counts over the course of his hospitalization suggests the development and resolution of thrombocytopenia: Baseline platelets from one year earlier: 255×10^9/L Admission → Day 0: 185×10^9/L → day 2: 154×10^9/L → day 4: 149×10^9/L → day 5: $\underline{112}\times 10^9$/L → day 8: 167×10^9/L → Day 9: 199×10^9/L and finally →at two week follow up: 357×10^9/L.

Discussion

This case illustrates the development of a deep vein thrombosis and subsequent large saddle pulmonary embolus in a patient with risk factors for deep vein thrombosis. To what extent the COVID Bivalent vaccine contributed to the events was discussed and debated at length with the team taking care of the patient and provides excellent context to review the clinical reasoning during his hospital stay and our report summarizes the most recent data and relevant clinical evidence when caring for patients with the triad of recent COVID vaccination, objective thrombosis and thrombocytopenia. Heparin Induced

Thrombocytopenia (HIT) was also high on the initial differential diagnosis, but this was deemed less likely temporally as the patient did not receive any heparin until he was in the emergency department. At this point his platelet count had decreased to 185× 10^9/L from a baseline of 255× 10^9/L. He also had an Anti-PF4 Ab which was negative but this information was not available till day 6 of hospitalization. Vaccine-induced immune thrombotic thrombocytopenia (VITT)[1] was high on the differential, with his clinically significant thrombosis presenting before thrombocytopenia seen on complete blood count (CBC). The syndrome is caused by antibodies that bind platelet factor 4 (PF4)[2] which in turn cause platelet activation (and possibly other cells such as neutrophils). This in turn revs up the coagulation cascade leading to clinically significant thromboembolic events. The mechanism(s) by which the implicated vaccines cause antibody formation is still unclear. Expert speculation favors a two-hit process: Vaccine injection causes new antigen formation (first hit), this in turn leads to systemic inflammatory response (second hit), with both catalyzing the activation of circulating anti-PF4 antibodies. This process also activates monocytes, neutrophils, and endothelial cells and increases circulating tissue factor.[3] Typically, venous thromboembolism such as pulmonary embolism or deep vein thrombosis (DVT) in the leg, as in our patient, are seen. Unusual sites such as the splanchnic (splenic, portal, mesenteric) veins, adrenal veins (risk for adrenal failure), and the cerebral and ophthalmic veins can also be seen. Very rarely, arterial thrombosis is a manifestation. Two adenoviral vector-based vaccines are most associated with causing VITT, the ChAdOx1 nCoV-19 (AstraZeneca, University of Oxford) and Ad26.COV2.S (Janssen; Johnson & Johnson). A case of possible VITT related to the mRNA-1273 (Moderna) vaccine has been published, but closer examination of that case suggests heparin induced thrombocytopenia was the most likely culprit.[4] Of note and relevant to our patient, the BNT162b2 (Pfizer-BioNTech) vaccine which he received four days before his trip, do not manifest with an increased risks of thrombosis based on multiple population-based analyses from around the globe.[5] What is known about the incidence of VITT is that it is exceedingly uncommon, with only a handful of cases reported despite tens of millions of vaccines administered. The risk factors for VITT are also unknown. Female sex and younger age (<55) have been suggested but not enough data to draw definitive conclusions. What is known is that VITT tends to resemble heparin-induced thrombocytopenia (HIT) in its clinical presentation beginning 5 to 10 days after the vaccination with patients presenting between 5 to 30 days post-vaccination as in our patient. Some also develop a flu-like syndrome (as in our patient) concurrent with the decrease in platelets or when presenting with thrombosis, suggesting an enhanced inflammatory response.[6] As awareness of the syndrome has increased, less-typical presentations have emerged such as thrombosis without thrombocytopenia or thrombocytopenia without thrombosis. A study published in the New England Journal of Medicine recently,[7] reviewed over 200 probable or confirmed cases of VITT. In these the patients, the age range at presentation was 18 to 79 years (median 48). There was a slight female preponderance. The time elapsed since vaccination range was 5 to 48 days (median 14 days). The most common sites of thrombosis were in descending order, the deep veins of the leg, cerebral veins, pulmonary arteries, and splanchnic vein, however, in keeping with the systemic inflammatory nature of the condition, fifty percent had thrombosis in more than one site. The laboratory manifestations from this case series are shown in Table 1.

The American Society of Hematology has published the following five criteria for making a definitive diagnosis of VITT and all five must be met to confirm the diagnosis of VITT: COVID vaccine 4 to 42 days prior to symptom onset, any venous or arterial thrombosis, platelet count less than 150 x 10^9/L, positive PF4 Elisa (Commercial PF4/polyanion ELISA test must be ordered not the PF4/heparin antibody test used to diagnose Heparin Induced Thrombocytopenia) and finally, an elevated D-dimer greater than four times upper limit of normal.[8] Our patient satisfied four of the five criteria but had a negative Anti PF4 Antibody test. When true VITT is diagnosed the clinician should be aware that disseminated intravascular coagulation (DIC) is a frequent association. This can lead to severe thrombocytopenia, or a significant decrease from the individual's baseline platelet count (as seen in our patient), elevated D-dimer, reduced fibrinogen to fifty percentage points below normal and a normal to slightly increased prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (PTT). All patients suspected of having definitive or probable VITT must be treated with systemic anticoagulation. This should be started unless contraindications such as intracerebral hemorrhage exists. The use of unfractionated or low molecular weight heparin has evolved over time. Initial observations seemed to show worsening of the condition and it was viewed as a variant of Heparin Induced Thrombocytopenia (HIT). More recently with a better understanding of the pathophysiology of VITT it seems heparin is a reasonable first choice assuming HIT has been ruled out.[9] The decision on first line anticoagulation should also consider the need for invasive procedures, the risk of bleeding and the patients overall clinical status. Guidelines suggest anticoagulants be used in the following order for stable patients: First line, a direct oral anticoagulant (DOAC), then, dabigatran or fondaparinux, a parenteral direct thrombin inhibitor e.g., argatroban would be third especially while waiting to definitively exclude HIT. The duration of anticoagulation is unknown but a reasonable approach for VITT with thrombosis would be to continue anticoagulation for three months after normalization of the platelet count. On discharge from the hospital, changing to a DOAC is prudent for ease of dosing. Vitamin K antagonists (VKA) like warfarin generally have no role in long term management unless the platelet count is normal and a DOAC is contraindicated. If VKA's are used, appropriate bridging therapy with heparin is needed. High-dose intravenous immune globulin (IVIG) is recommended along with anticoagulation in all definite VITT cases who are clinically severely ill and slow to respond to anti-coagulation. Therapeutic plasma exchange (TPE) and immunosuppression have also been used for successfully for refractory disease or for patients with concerning features such as multiple throm-

boses with evidence of excessive platelet activation (platelet count <30,000× 10^9/L).[10] Platelet transfusion can be used if severe bleeding accompanies the clinical picture. Any case of VITT that satisfies all five diagnostic criteria should be reported to the national agency on vaccine adverse events.

This case demonstrated several key learning points in managing patients with low platelets and objective evidence of thromboses in the post COVID vaccination window. Based on the clinical guideline he satisfied four of five clinical criteria for VITT. However, his commercial airline flight and his negative anti PF4 Antibody ELISA made 'economy class syndrome' the more likely diagnosis.

Table 1.

Test	Range	Median Value
D-Dimer	5000 to 80,000 fibrin equivalent units (FEU)	24,000 FEU
Fibrinogen	0.3 to 4.4 mg/dL	2.2 g/L (220 mg/dL)
Platelet Count	6000 to 344,000× 10^9/L	47,000× 10^9/L *

*The typical platelet count range of patients with definite VITT is ranges from 10,000 × 10^9/L and 100,000× 10^9/L, with a median platelet count of 20,000× 10^9/L to 25,000× 10^9/L.

Figures

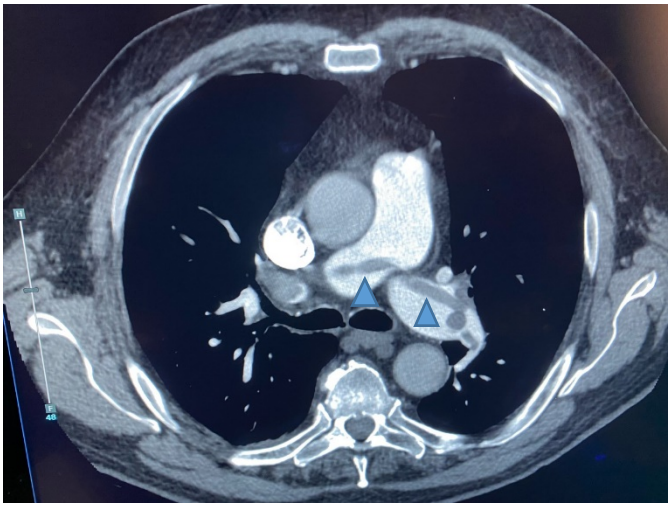

Figure 1. CT Angiogram of chest demonstrating "saddle" pulmonary embolus (arrows in blue)

REFERENCES

1. **Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S**. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med*. 2021 Jun 3;384(22):2092-2101. doi: 10.1056/NEJMoa2104840. Epub 2021 Apr 9. PMID: 33835769; PMCID: PMC8095372.
2. **Singh A, Toma F, Uzun G, Wagner TR, Pelzl L, Zlamal J, Freytag V, Weich K, Nowak-Harnau S, Rothbauer U, Althaus K, Bakchoul T**. The interaction between anti-PF4 antibodies and anticoagulants in vaccine-induced thrombotic thrombocytopenia. *Blood*. 2022 Jun 9;139(23):3430-3438. doi: 10.1182/blood.2021013839. PMID: 35679071; PMCID: PMC8949646.
3. **Huynh A, Kelton JG, Arnold DM, Daka M, Nazy I**. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. *Nature*. 2021 Aug;596(7873):565-569. doi: 10.1038/s41586-021-03744-4. Epub 2021 Jul 7. PMID: 34233346.
4. **Sangli S, Virani A, Cheronis N, Vannatter B, Minich C, Noronha S, Bhagavatula R, Speredelozzi D, Sareen M, Kaplan RB**. Thrombosis With Thrombocytopenia After the Messenger RNA-1273 Vaccine. *Ann Intern Med*. 2021 Oct;174(10):1480-1482. doi: 10.7326/L21-0244. Epub 2021 Jun 29. PMID: 34181446; PMCID: PMC8251935.
5. **Klein NP, Lewis N, Goddard K, Fireman B, Zerbo O, Hanson KE, Donahue JG, Kharbanda EO, Naleway A, Nelson JC, Xu S, Yih WK, Glanz JM, Williams JTB, Hambidge SJ, Lewin BJ, Shimabukuro TT, DeStefano F, Weintraub ES**. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. *JAMA*. 2021 Oct 12;326(14):1390-1399. doi: 10.1001/jama.2021.15072. PMID: 34477808; PMCID: PMC8511971.
6. **Muir KL, Kallam A, Koepsell SA, Gundabolu K**. Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination. *N Engl J Med*. 2021 May 20;384(20):1964-1965. doi: 10.1056/NEJMc2105869. Epub 2021 Apr 14. PMID: 33852795; PMCID: PMC8063883.
7. **Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, Rampotas A, Ambler G, Makris M**. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. *N Engl J Med*. 2021 Oct 28;385(18):1680-1689. doi: 10.1056/NEJMoa2109908. Epub 2021 Aug 11. PMID: 34379914.
8. **American Society of Hematology**. Vaccine-induced Immune Thrombotic Thrombocytopenia. [Internet] Available at: https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia.
9. **Kim AY, Woo W, Yon DK, Lee SW, Yang JW, Kim JH, Park S, Koyanagi A, Kim MS, Lee S, Shin JI, Smith L**. Thrombosis patterns and clinical outcome of COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A Systematic Review and Meta-Analysis. *Int J Infect Dis*. 2022 Jun;119:130-139. doi: 10.1016/j.ijid.2022.03.034. Epub 2022 Mar 24. Erratum in: Int J Infect Dis. 2022 Oct;123:166. PMID: 35339716; PMCID: PMC8942584.
10. **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 Aug;60(4):103174. doi: 10.1016/j.transci.2021.103174. Epub 2021 May 28. PMID: 34088601.