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Case Report

J Hematol. 2024;13(3):125-127

Venous Thromboembolism Following COVID-19 Vaccination in Patients With Hereditary Protein S Deficiency

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Abstract

Hereditary protein S (PS) deficiency is a rare condition associated with increased risk of venous thromboembolism (VTE). In 2020, the coronavirus disease 2019 (COVID-19) pandemic prompted development of vaccinations to protect against the virus. PS deficiency is not a contraindication to COVID-19 vaccinations, but there are no studies regarding potential adverse effects in this population. We report two cases, a 43-year-old mother and her 18-year-old son, who developed VTE shortly after their first COVID-19 vaccines. Testing confirmed hereditary PS deficiency with a previously undescribed mutation in both cases. The temporal association between COVID-19 vaccination and VTE in these patients with hereditary PS deficiency suggests a potential causal relationship. However, it is unclear if this applies to all patients with hereditary PS deficiency. This highlights the importance of reporting adverse events following COVID-19 vaccinations in this population to evaluate the risks and benefits of vaccination.

Keywords: Protein S deficiency; Venous thromboembolism; COVID-19; Vaccination

Introduction

In 2020, the coronavirus disease 2019 (COVID-19) spread rapidly worldwide creating a public health emergency. The devastating effects of the pandemic prompted quick development of vaccinations to provide protection against the virus. Infection with the SARS-CoV-2 virus has been reported to be associated with an increased risk of venous thromboembolism (VTE) [1]. Additionally, shortly following the start of administration of COVID-19 vaccinations, cases and concerns arose regarding vaccine-associated thrombosis. This however was found to be associated with adenoviral vector-based vaccinations and there is no convincing evidence that mRNA vaccinations are associated with increased risk of VTE [2]. For the general population, receiving a COVID-19 vaccine is still recommended and the consensus remains that the benefits of vaccination outweigh potential risks [3]. A specific population that has an increased risk of VTE are patients with inherited thrombophilias [4]. Inherited thrombophilias, such as hereditary protein S (PS) deficiency, are not listed as a contraindication to receiving a COVID-19 vaccination. However, there are no studies about the risk of VTE in these patients following COVID-19 vaccines. This poses a challenge when trying to counsel patients with thrombophilias on their specific risk-benefit ratio for receiving COVID-19 vaccinations. We describe two cases of VTE following COVID-19 vaccination in a son and mother with hereditary PS deficiency. There are currently no reported cases of family members with hereditary PS deficiency developing thrombosis following COVID-19 vaccination in the absence of thrombocytopenia.

Manuscript submitted April 14, 2024, accepted May 25, 2024
Published online June 28, 2024

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doi: https://doi.org/10.14740/jh1278

Case Report

An 18-year-old male presented to the emergency department with acute onset left-sided pleuritic chest pain and hemoptysis. He had received his first Johnson & Johnson COVID-19 vaccination 6 weeks prior. Following vaccination, the patient reported headaches but no upper extremity symptoms or lymphadenopathy. On presentation, he had no leg symptoms, provoking factors for VTE or personal or family history of VTE. On physical examination, he was afebrile and vitally stable with a normal cardiorespiratory and lower extremity exam. Bloodwork demonstrated a normal complete blood count, liver enzymes and coagulation tests. His blood cultures and heparin-platelet factor 4 (PF4) antibody were negative and he tested negative on point of care COVID-19 testing. Given his symptoms, a computed tomography pulmonary angiography (CT-PA) was completed which showed a bilateral segmental pulmonary embolism with a wedge-shaped area of infarction in the left lower lobe. Thrombophilia testing was performed after the initiation of rivaroxaban and revealed he was deficient in PS with a free PS level of 10%. He was discharged from the emergency department on rivaroxaban and with arranged outpatient hematology follow-up.

One week following his presentation, the patient's 43-year-old mother presented to the emergency department with a

6-day history of progressive left leg pain. She had received her first Pfizer COVID-19 vaccination 3 weeks prior. There was no noted upper extremity symptoms, lymphadenopathy, fevers or systemic symptoms after vaccination. On presentation, she had no symptoms of pulmonary embolism, provoking factors, or personal history of VTE. She had no symptoms of fever, respiratory symptoms or known COVID-19 infectious contacts. She was later tested for COVID-19 infection and found to be negative. She was otherwise healthy with a remote history of correction of total anomalous pulmonary venous return surgery as an infant and mild asthma. On exam, she was afebrile and vitally stable, and her left lower leg had no swelling, erythema, or signs of arterial compromise or ischemia, but there was tenderness to palpation of the calf. Bloodwork was significant for a D-dimer of 101,630 µg/L. She had a normal complete blood count and liver enzymes tests. Imaging revealed an extensive, occlusive deep venous thrombus extending from the proximal common iliac vein down to the distal popliteal vein on left leg Doppler ultrasound and a right lobar pulmonary embolism on CT-PA. She subsequently had a CT of her chest, abdomen and pelvis to investigate for malignancy which showed no neoplastic process or adenopathy. Thrombophilia testing was ordered after the initiation of unfractionated heparin and showed that she was also deficient in PS with a free PS level of 16%. She was started on rivaroxaban and arranged outpatient hematology follow-up.

In the outpatient clinic 2 months later, both patients' free PS levels were repeated while on rivaroxaban and reported to be persistently low with the son's free PS level of 13% and the mother's 21%. Genetic testing was then performed confirming hereditary PS deficiency and showed a frameshift mutation in the PROS1 gene, PROS1 c.1144_1146delins25,p.(Leu382Thrfs*20), not previously described but expected to be pathogenic. Because of the persistent risk factor of hereditary PS deficiency as well as the significant negative impact on their quality of life, both patients elected to continue lifelong anticoagulation. This was a shared decision amongst both patients and their hematologist. Given the uncertainty of their thrombotic risk with subsequent vaccinations, the decision was made to not receive further COVID-19 vaccinations. Unfortunately, these patients' situations were not recognized as a reason to avoid vaccination and as a result they experienced barriers to accessing public services during the COVID-19 pandemic.

Discussion

We describe two cases of VTE following COVID-19 vaccination in a mother and son with hereditary PS deficiency. There are currently no reported cases of family members with hereditary PS deficiency developing thrombosis following COVID-19 vaccination in the absence of thrombocytopenia. The temporal association between COVID-19 vaccination and VTE suggests a potential increased risk of VTE following COVID-19 vaccinations in patients with hereditary PS deficiency. However, it is unclear if this risk is in all patients with hereditary PS deficiency or just those with this previously undocumented mutation, since mutations with more severe alterations in secretion and function of PS carry a higher risk of thrombosis [4]. In these cases, the detection of VTE occurred within 20 - 44 days of vaccination, suggesting the risk of VTE may be highest in this period following vaccination.

Vaccine-induced immune thrombosis and thrombocytopenia (VITT) is a well-known, adverse event following adenoviral vector-based COVID-19 vaccinations, most notably the AstraZeneca and Johnson & Johnson vaccines. This condition is characterized by the development of thrombosis or bleeding 4 - 42 days following vaccination, with low platelets and evidence of thrombosis [5, 6]. The two patients' presentations are inconsistent with VITT, because both patients tested negative on point of care testing at the time of presentation, had normal platelet counts and only one patient had received an adenoviral vector-based COVID-19 vaccination.

It would be inappropriate to routinely screen patients for PS deficiency prior to vaccination due to its low prevalence and chance of false-positive results. However, physicians should consider screening patients who present with VTE following COVID-19 vaccination in the absence of any provoking factors. In patients with known hereditary PS deficiency, decisions regarding vaccination should be determined on a case-by-case basis to determine patient's individual risk-benefit ratio.

In conclusion, this case highlights the importance of reporting and evaluating adverse events following COVID-19 vaccinations in patients with hereditary PS deficiency to determine the incidence of VTE and evaluate the risk and benefit of vaccination in this population. This case was presented to the Vaccine Injury Support Program in Canada and was deemed causal, and the patients have been awarded compensation.

Acknowledgments

None to declare.

Financial Disclosure

This study was not supported by any sponsor or funder.

Conflict of Interest

The authors have no conflict of interest to declare.

Informed Consent

Written informed consent was obtained from both patients for publication of the details of their medical case and any accompanying images.

Author Contributions

Identification and management of case: KB. Literature review and manuscript writing: MR and KB.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed for this case report.

References

1. Schulman S, Hu Y, Konstantinides S. Venous thromboembolism in COVID-19. Thromb Haemost. 2020;120 (12):1642-1653. doi pubmed pmc
2. Nicholson M, Goubran H, Chan N, Siegal D. No apparent association between mRNA COVID-19 vaccination and venous thromboembolism. Blood Rev. 2022;56:100970. doi pubmed pmc
3. Sharif-Kashani B, Shafaghi S, Naghashzadeh F, Mohamadnia A, Rahdar M, Hajimoradi M, Noorali S. COVID-19 and vaccine-induced thrombosis. Tanaffos. 2022;21(4):413-418. pubmed pmc
4. ten Kate MK, van der Meer J. Protein S deficiency: a clinical perspective. Haemophilia. 2008;14(6):1222-1228. doi pubmed
5. Mele F, Tafuri S, Stefanizzi P, A DA, Calvano M, Leonardelli M, Macorano E, et al. Cerebral venous sinus thrombosis after COVID-19 vaccination and congenital deficiency of coagulation factors: Is there a correlation? Hum Vaccin Immunother. 2022;18(6):2095166. doi pubmed pmc
6. American Society of Hematology. Vaccine-induced immune thrombotic thrombocytopenia. Available from: https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia (Accessed October 23, 2023).