



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



COVID-19 vaccine (Ad26.COV2.S), an unlikely culprit of portal vein thrombosis in a middle-aged man

Dariusz Uczkowski^{*}, Arunabh Sekhri

Overlook Medical Center, Atlantic Health System, USA

ABSTRACT

While vaccination is the single most effective intervention to prevent spread of COVID-19, rare thromboembolic events have been reported following vaccination with COVID-19 vaccines ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2-S (Johnson & Johnson/Janssen). We present here a case of one such patient who received Ad26.COV2-S (recombinant) JanssenCOVID_19 vaccine.

A 55-year-old male presented with a two week history of abdominal pain, nausea, vomiting, and distention. He received the Ad26.COV2-S (recombinant) JanssenCOVID_19 vaccine, one month before onset of symptoms. On presentation, lab results revealed hyponatremia, lactic acidosis, and leukocytosis. CT abdomen and pelvis with contrast revealed moderate circumferential bowel wall thickening, prominent mesenteric vessels present, and a portal vein thrombus extending to the superior mesenteric and splenic veins. An extensive hypercoagulable workup was negative. Patient's history revealed he was a frequent airline passenger but was otherwise negative. Additional etiologies were examined before associating the COVID-19 vaccine with thrombosis and the penultimate diagnosis was only reached by exclusion of other causes after initial evaluation and further outpatient follow up.

1. Introduction

The mechanism behind natural COVID-19 infection related thrombosis is a pathophysiologic process of which the medical community's knowledge is ever expanding. Current evidence suggests an important relationship between Interleukin-6 (IL-6) elevation, RNAemia and fibrinogen levels leading to unregulated activation of the coagulation cascade and proinflammatory cytokines responsible for coagulopathy. More specifically, angiotensin-converting enzyme-2 receptor-mediated pulmonary and vascular endothelial injury lead to a pro-thrombotic environment ripe for thrombosis. The complement pathway can also become activated during the cytokine induced storm which is seen in COVID-19 patients and will accompany with it, a hypofibrinolytic state in the alveolar spaces leading to endothelial cell activation triggered by Interleukin-1 (IL-1), IL-6 and a hypoxic state leading to coagulopathy. The most common topography of venous thromboembolism in these patients is classically pulmonary embolism, but arterial manifestations such as stroke and acute coronary syndromes have also been reported. In contrast, Vaccination Induced Thrombosis is an entity with vastly different pathophysiologic mechanisms and topographic preferences and will be later described in this case report.

2. Case presentation

A 55-year-old male presented to the hospital with two weeks history of abdominal pain, nausea, vomiting, and distension. He reports that his last bowel movement was two weeks prior. On arrival, blood pressure was 143/89, HR 90, SpO2 94% on room air, and temperature 97.9F. The abdomen was diffusely tender but worse in the left upper quadrant with decreased bowel sounds. Lab exams were significant for a WBC of 11.99/nL, Hgb 14.7 g/dL, PLTs 381/nL, Na 130 mmol/L, glucose 231 mg/dL, BUN 11 mg/dl, Creatinine 0.69 mg/dL, Lactate 2.2 mmol/L. COVID-19 PCR was negative.

CT abdomen and pelvis with contrast revealed loops of jejunum demonstrating moderate circumferential bowel wall thickening, bowel wall edema, prominent mesenteric vessels, and a portal vein thrombus extending to the superior mesenteric, and splenic veins (Fig. 1A–E). Etiology was unclear; therefore, further interviewing to determine risk factors and deduce culpability was pursued. The patient was notably not a smoker, had no personal history of malignancy, had an unremarkable colonoscopy five years prior and had no prior history of thrombotic events. Notably, his mother had clots in the past, but it was unclear if the instances were arterial or venous in origin. His father had a history of leukemia and skin cancer.

Finally, one month before presentation, the patient reported that he was vaccinated with the Janssen Ad26.COV2-S COVID-19 vaccine.

^{*} Corresponding author. 99 Beauvoir Avenue, Summit, NJ, USA.

E-mail address: dariusz.uczkowski@atlantichalth.org (D. Uczkowski).

Further workup included INR of 1.7 seconds, aPTT of 24.3 seconds and lower extremity dopplers which were negative for deep venous thrombosis bilaterally. Vascular venous ultrasound of the abdomen showed portal hypertension, occluded superior mesenteric vein, splenomegaly, a prominent hepatic artery, midline collaterals and a dilated left gastric vein.

Hypercoagulability workup was initiated after initiation of IV heparin due to extensive clot burden and risk for further clinical worsening and clot propagation. Factor V Leiden gene mutation (G1691A),

Prothrombin gene mutation, Cardiolipin antibodies, Protein C activity, Protein S activity, Lupus anticoagulant, Beta-2 Glycoprotein 1 antibodies, JAK2 V617F Mutation, Anti thrombin III activity and flow cytometry for paroxysmal nocturnal hemoglobinuria were all obtained and further detailed below (Table 1). All tested hypercoagulable labs were unremarkable except for a few notable exceptions including a weakly positive JAK2 mutation with a low allele burden (0.07%) and Antithrombin III levels which were low, but could have been related to the therapeutic heparin the patient received prior. While treatment

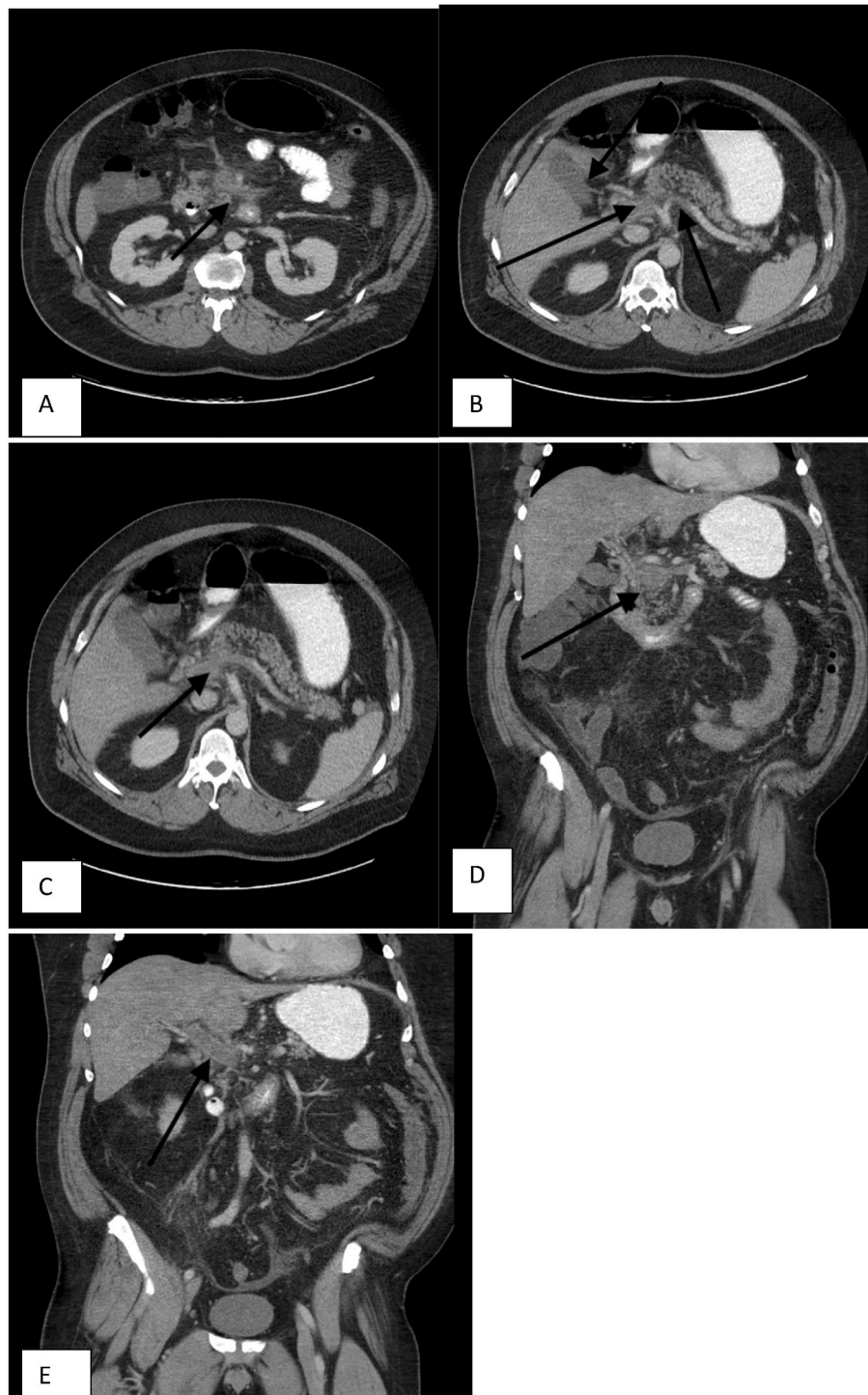


Fig. 1. A: Expanded Superior Mesenteric Vein with decreased contrast enhancement signifying thrombosis. B: CT abdomen and pelvis demonstrating extensive mesenteric portal vein thrombosis. C: Additional thrombosis cutoff. D: Coronal view of SMV occlusion with fat stranding and ischemic changes. E: Coronal view of Portal Vein occlusion with thrombus.

Table 1
Hypercoagulable Studies.

Laboratory parameter	Value	Normal
INR	1.7 sec (prior to heparin)	0.9-1.1 sec (seconds)
Activated Partial Thromboplastin Time (aPTT)	24.3 seconds (prior to heparin)	25-37 sec
aPTT Mix 1:1	52 seconds (on heparin)	25-37 seconds (on heparin)
Fibrinogen equivalent (FEU)	10,462 ng/mL	<500 ng/mL
Thrombin time(Bovine)	>300 seconds	15.8-24.9 sec
Protein C activity	72%	70-150%
Protein S activity	97%	65-160%
Antithrombin III activity	55%	80-120%
Lupus anticoagulant: dilute Russell's viper venom time (DRRVV), Reptilase Time	DRVVT: 1.12 ratio Reptilase: 25.7 sec	<1.20 ratio 14-23.9 sec
JAK 2 mutation	0.07%, low allele burden	Normal
Cardiolipin antibodies (IgA,IgM, IgG)	IgA 1.4, IgM 6.2, IgG 1.7	IgA: <12 APL (-), >20 (+), 12-20 indeterminate IgM: <12.5 MPL (-), >20 (+), 12.5-20 indeterminate IgG: <15 GPL negative, >20 (+), 15-20 indeterminate
Beta-2 Glycoprotein 1 antibodies (IgA, IgM, IgG)	IgA,IgM,IgG: <2.0 U/mL	<20 antibody not detected, >20 or (=): antibody detected
Factor V Leiden activity	Normal	Normal
Prothrombin time	18.5 seconds (on heparin)	9.4-12.5 seconds
PT Mix 1:1	12.9 seconds (on heparin)	9.4-12.5 seconds

consisted of IV heparin initially, a trans jugular intrahepatic portosystemic shunt was attempted but was unsuccessful due to extensive clot burden. A bowel regimen was also initiated with relief of the patient's constipation. The patient was transitioned to rivaroxaban 15mg BID for 21 days and then 20mg daily with the improvement of his symptoms over time.

Outpatient follow-up was notable for thrombocytopenia of 128/ μ L 3 months after discharge, with a continual downtrend to a nadir of 63/ μ L. Repeat JAK 2 testing was performed and found to be negative, effectively excluding myeloproliferative neoplasm and repeat B2 glycoprotein 1 antibodies were also negative. The patient continued to tolerate full-dose rivaroxaban 20mg daily for the duration of his treatment course. On repeat ultrasound 6 months after discharge, clot burden was unappreciable but portal hypertension remained. Persistent thrombocytopenia not present on hospitalization would not recover until the end of the 6 month's anticoagulation course. Repeat hypercoagulability labs were planned off anticoagulation, but the patient changed residences due to work related purposes and subsequently followed up with medical care elsewhere.

3. Discussion

Although this case meets only three of five criteria during hospitalization, the clinical picture overall until now has not been explained by other factors and therefore has been attributed to a diagnosis of exclusion. The exclusion being a phenomenon more clearly defined in the literature as Vaccine-Induced Thrombotic Thrombocytopenia [VITT] associated with SARS-CoV-2 vaccines, particularly the Adenovector vaccines [1,2]. Initially, VITT was poorly understood, but now, definitive diagnosis can be established with the following five criteria: (i) A 5–30 days prior history of Covid-19 vaccine administration or <42 days in patients with isolated deep venous thrombosis or pulmonary

embolism, (ii) presence of thrombosis (often cerebral or abdominal), (iii) Thrombocytopenia <150 per cubic millimeter, (iv) Positive Anti-Platelet factor 4 antibodies (PF4) by ELISA (Enzyme-linked immunosorbent assay) and (v) a markedly elevated D-Dimer level (>4000 Fibrinogen-equivalent unit) [3,4]. This case was treated before the improved understanding of the pathophysiology, and therefore Anti-PF4 antibodies were not obtained and as a result, it does not fit all five criteria for VITT. Therefore, in the absence of Anti-PF4 and thrombocytopenia, this case would be considered possible VITT, but not definitive, given the aforementioned workup.

The incidence of thrombosis from VITT is estimated to be 1 in 100,000 based on several reports, but data are not sufficient [5]. Most of the initially reported cases of VITT involved females with suspicions that a preponderance was likely. Although, after a prospective cohort in the United Kingdom involving 294 patients with 170 definitive VITT and 50 probable was evaluated, the findings did not show a skew for either male or female sex [4].

The mechanism for which the SARS-CoV2 virus causes thrombosis is fundamentally different from the vaccines and is likely due to the high circulating levels of RNA (RNAemia) causing a cascade effect in immune activation and hypercoagulability [6,7]. Vaccines using adenovirus vectors are theorized to trigger an autoimmune response toward PF4, creating anti-PF4 antibodies. PF4 is essentially a heparin-binding protein and the target of autoimmunity in HIT (Heparin-Induced Thrombocytopenia). The negative charge of DNA in adenovector Vaccines and the positive charge of PF4 form DNA-PF4 complexes contributing to autoantibody development [8]. High titers of autoantibodies against PF4 lead to an exaggerated immune response, including platelet and neutrophil activation with increased platelet consumption and thrombosis [6].

The unusual topography associated with VITT originates from areas of high microbiota/viral venous drainage basins, such as, the cavernous cerebral venous sinus and the portal circulation which are responsible for clearing respiratory tissue barriers and gastrointestinal barriers, respectively [5,9]. The viruses and microbiota from these areas can harbor PF4. While in normal innate immunity, PF4 would contribute to the clearance of these organisms, the presence of high titers of PF4 autoantibodies second to PF4-DNA complexes from Adenovector vaccines would cause high levels of complex formation. This leads to B cell migration to the area and a similar platelet/neutrophil activation with increased platelet consumption and thrombosis as HIT [10].

The recommendations for treatment of VITT are based on management of HIT and non-heparin-dependent autoimmune thrombotic thrombocytopenia [11]. It is unknown whether use of heparin can exacerbate this condition, therefore its best to avoid heparin or low molecular weight heparin (LMWH) anticoagulation in these patients. Prompt recognition and treatment with anticoagulation would be the mainstem of therapy [4]. Non heparin products such as parenteral direct thrombin inhibitors (argatroban or bivalirudin), direct oral anticoagulants (apixaban, edoxaban or rivaroxaban), Fondaparinux or Danaparoid should be chosen based on clinical status of the patient [11]. Use of IVIG (1 g/kg daily for two days) should be considered as a disease modifying therapy. Patients with low fibrinogen or bleeding associated with VITT, should still be treated with anticoagulation as long as platelets are above 20×10^9 10^{11} . Replacing fibrinogen in patients with low values should be considered to ensure the levels do not drop below 1.5 g/L¹². Platelets transfusion should be considered only for life threatening situations and plasma exchange can be considered in severe and resistant cases [12]. Finally, the use of complement inhibitors such as Eculizumab to inhibit the complement pathway and decrease further coagulopathic progression can be considered in patients who progress despite the use of anticoagulation and IVIG [11,13].

In conclusion, the hypercoagulable workup of this case was specifically challenging due to the need to immediately start therapeutic anticoagulation with emergent trans jugular intrahepatic portosystemic shunt attempted to reduce the risk of further thrombus propagation,

morbidity and mortality. On presentation, the patient was at risk of bowel necrosis and decompensation and therefore the urgent need to begin treatment was prioritized in the emergency department. Classically, Protein C, S and Anti Thrombin III activity can all be interfered with while on therapeutic anticoagulation. Therefore, the hypercoagulability work up may have been altered due to the administration of heparin. However, in this patient with no previous history of Deep venous thrombosis, no known malignancies with age appropriate screening completed, no recent surgery or prolonged immobility, no known exogenous hormone use, normal coagulation factor times prior to anticoagulation and a known inciting factor being recent Covid-19 Ad26.COVS2 vaccination, the case was attributed to a exclusion diagnosis of possible VITT in light of the negative hypercoagulable workup in the setting of anticoagulation. Outpatient follow up months later revealed a persistent thrombocytopenia not present on hospitalization which would not recover until the end of the 6 month's anticoagulation course and to date, no further explanations were found for this extensive thrombotic event and nor were there any further thrombotic events.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] N.H. Schultz, I.H. Sorvoll, A.E. Michelsen, et al., Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination, *N Engl J Med* 384 (2021) 2124–2130.
- [2] D.B. Cines, J.B. Bussel, SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia, *N Engl J Med* 384 (2021) 2254–2256.
- [3] A. Greinacher, T. Thiele, T.E. Warkentin, K. Weisser, P.A. Kyrle, S. Eichinger, Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination, *N Engl J Med* 384 (2021) 2092–2101.
- [4] S. Pavord, M. Scully, B.J. Hunt, et al., Clinical features of vaccine-induced immune thrombocytopenia and thrombosis, *N Engl J Med* 385 (2021) 1680–1689.
- [5] E. Mahase, Covid-19: unusual blood clots are "very rare side effect" of Janssen vaccine, says EMA, *BMJ* 373 (2021) n1046.
- [6] D. McGonagle, G. De Marco, C. Bridgewood, Mechanisms of immunothrombosis in vaccine-induced thrombotic thrombocytopenia (VITT) compared to natural SARS-CoV-2 infection, *J Autoimmun* 121 (2021), 102662.
- [7] L. Nicolai, A. Leunig, S. Brambs, et al., Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy, *Circulation* 142 (2020) 1176–1189.
- [8] L. Rauova, J.D. Hirsch, T.K. Greene, et al., Monocyte-bound PF4 in the pathogenesis of heparin-induced thrombocytopenia, *Blood* 116 (2010) 5021–5031.
- [9] I. Torjesen, Covid-19: risk of cerebral blood clots from disease is 10 times that from vaccination, study finds, *BMJ* 373 (2021) n1005.
- [10] J. Sadoff, K. Davis, M. Douoguih, Thrombotic thrombocytopenia after Ad26.COVS2. S vaccination - response from the manufacturer, *N Engl J Med* 384 (2021) 1965–1966.
- [11] J.B. Bussel, J.M. Connors, D.B. Cines, Vaccine-induced Immune Thrombotic Thrombocytopenia, American Society of Hematology (ASH), 2022.
- [12] G. Rock, V. Weber, B. Stegmayr, Therapeutic plasma exchange (TPE) as a plausible rescue therapy in severe vaccine-induced immune thrombotic thrombocytopenia, *Transfus Apher Sci* 60 (2021), 103174.
- [13] A. Islam, M.S. Bashir, K. Joyce, H. Rashid, I. Laher, S. Elshazly, An update on COVID-19 vaccine induced thrombotic thrombocytopenia syndrome and some management recommendations, *Molecules* 26 (2021).