Vascular Specialist International
pISSN 2288-7970 • eISSN 2288-7989
(2022) 38:40

Case Report

Deep Vein Thrombosis after COVID-19 mRNA Vaccination in a Young Man with Inferior Vena Cava Anomaly Leading to Recurrent Deep Vein Thrombosis

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Severe side effects of adenoviral-vectored-DNA COVID-19 vaccines such as thrombosis have been reported. Herein, we report a case of sudden massive deep vein thrombosis (DVT) in a young man with inferior vena cava anomaly 20 hours after the second dose of the mRNA vaccine for COVID-19. There was recurrence of iliofemoral DVT after one year, despite complete resolution and administration of prophylactic anticoagulants. We suggest that the sudden episode was triggered by the vaccine rather than the venous anomaly, which can be associated with recurrence due to inadequate venous return through the small and tortuous infrarenal veins or increased venous pressure and stasis. There are no standard guidelines for the management of DVT following mRNA vaccination. However, we highlight the importance of initial workups, regular follow-ups, and standard treatment options, including the continuous administration of prophylactic anticoagulants which should be considered to prevent recurrence.

Key Words: Deep vein thrombosis, mRNA COVID-19 vaccination, Inferior vena cava anomaly

Received October 7, 2022
Revised November 8, 2022
Accepted December 9, 2022
Published on December 30, 2022

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Cite this article; Vasc Specialist Int 2022. https://doi.org/10.5758/vsi.220045

INTRODUCTION

The COVID-19 pandemic has been deemed to have a significant global impact. COVID-19 vaccines, which received full approval, showed high efficacy (65%-95%) against symptomatic laboratory-confirmed COVID-19 in adults aged ≥18 years. The COVID-19 vaccine is considered the most important and effective strategy to prevent infection, and is safe and efficacious [1]. However, with the emergence of the COVID-19 vaccine, severe adverse effects such as venous thromboembolism (VTE) and vaccine-induced thrombotic thrombocytopenia (VITT) after the administration of adenoviral-vectored-DNA vaccines of AstraZeneca ChAdOx1 nCoV-19 (AstraZeneca, Cambridge, UK) and Janssen Ad26.COV2.S (Janssen, Beerse, Belgium) have been reported [2]. Compared with the administration of adenovector vaccines, there are few reports on the possible association between VTE and the mRNA vaccine of BNT162b2 mRNA COVID-19 vaccine (Pfizer, New York, NY, USA) and Moderna COVID-19 mRNA-1273 vaccine (Moderna, Cambridge, MA, USA) [3-6].

Herein, we present the case of a young healthy patient who presented with acute massive deep vein thrombosis (DVT) after Pfizer vaccine administration. Upon further evaluation, he was found to have an inferior vena cava

anomaly (IVCA). However, there were no previous DVT episodes. This case links Pfizer vaccines with sudden onset of massive DVT. It also serves as a means of raising awareness of the importance of early detection of rare and unknown etiologies of sudden pain and edema of the lower extremities, proper treatment, and prophylactic management to prevent VTE recurrence. Informed consent has been obtained from the patient for this case report. This study was approved by the Institutional Review Board of the Armed Forces Capital Hospital (IRB no. 2021-12-003-002). This study conducted in accordance with the principles of the Declaration of Helsinki.

CASE

A 26-year-old male, active military officer, presented to the emergency room in July 2021 with sudden cramps and edema in the right leg. He received his first dose of the Pfizer vaccine 25 days prior, without complications, and a second dose 20 h before this episode. He had no history of COVID-19 infection or underlying disease, including VTE. Additionally, the patient did not undergo surgery, trauma, hospitalization, or have a history of blood clotting disorders, familial hypercoagulable disorders, or predisposing risk factors for VTE. The patient was a social drinker and had a history of smoking one-third to half a pack of cigarettes per day. However, he did not use any illicit drugs. Initially, the patient was alert and oriented, with unremarkable systemic examinations. Homans sign was positive without motor or sensory deficits. The initial vital signs were normal, and his body mass index (BMI) was 27.5 kg/m^2

Duplex ultrasonography (DUS) of both extremities and the abdomen showed extensive thrombosis in both common iliac veins (CIVs) and right external iliac vein (EIV), extending into the common femoral vein, femoral vein (FV), popliteal vein (PV), and calf veins. The computed tomography angiography (CTA) demonstrated a large thrombus burden in the left infrahepatic inferior vena cava (IVC), both internal iliac veins (IIVs), and veins detected by DUS. However, no pulmonary embolism (PE) was detected.

Catheter-directed aspiration thrombectomy and thrombolysis were attempted via the right PV, after inserting a temporary IVC filter at the suprarenal level via the right jugular vein. However, an insufficient amount of the thrombus was extracted. With systemic heparinization, we removed the temporary IVC filter seven days later. The patient was administered edoxaban (60 mg) once a day.

The initial routine complete blood count was normal (platelet count 198,000/μL). Coagulation panel was normal, including prothrombin time and partial thromboplastin time. D-dimer level was increased to 16.09 mg/dL. Fibrinogen and plasminogen levels were above normal limits.

Initial blood tests revealed no evidence of hypercoagulable etiologies except for lupus anticoagulant (LA). These included the normal range of protein C activity, protein C antigen (Ag), protein S activity, free protein S Ag, total protein S Ag, antithrombin III, anti-Xa heparin assay, vWF Ag, factor V, factor V Leiden (FVL) mutation (negative), antiplatelet antibody (Ab) (negative), factor X, heparin platelet factor 4 (PF4) Ab, prothrombin G20210A mutation (negative), homocysteine, fluorescence anti-nuclear Ab (negative), complement C3 and C4, anti-phospholipid IgG, anti-phospholipid IgM, anti-cardiolipin IgG, anti-cardiolipin IgM, anti-cardiolipin IgA, anti-β2-GPI IgG, anti-β2-GPI IgM. The LA test was positive (1.28; normal range, 0.89-1.19), and subsequently negative (1.09) 10 weeks later. The LA confirmation test was weakly positive (1.20), and subsequently negative (1.09) after 10 weeks.

All tumor marker screening for malignancy (α-fetoprotein, carcinoembryonic antigen, prostate-specific antigen, cancer

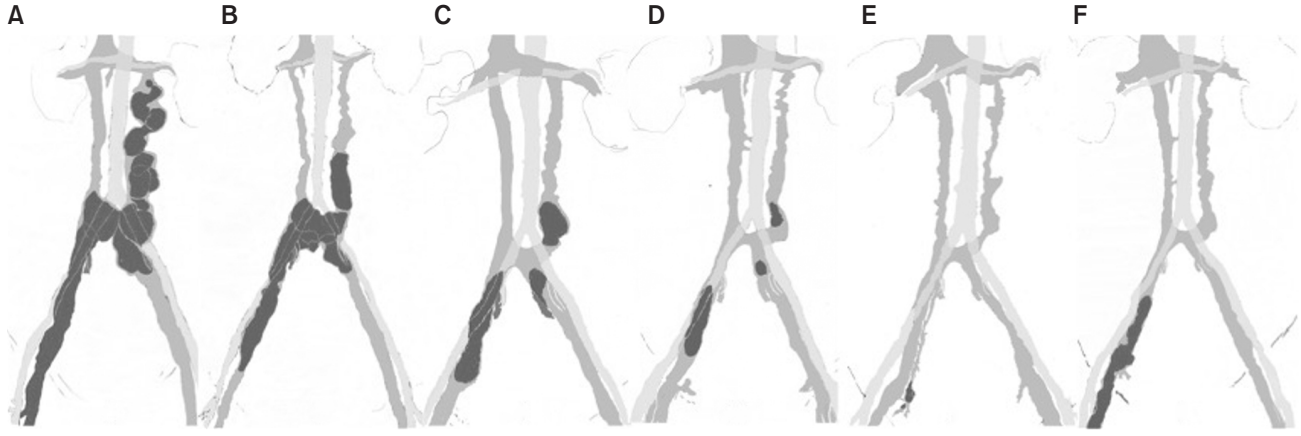

Fig. 1. Diagrams of changing patterns of deep vein thrombosis at two weeks (A), 1 month (B), 2 months (C), 4 months (D), 1 year (E) after treatment and 2 weeks after recurrence (F).

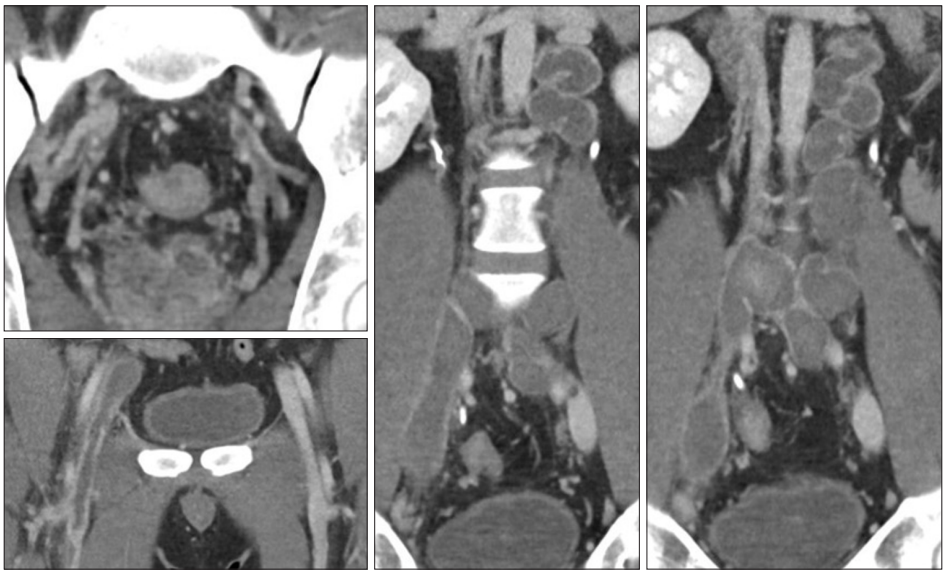

Fig. 2. Computed tomography coronal view at two weeks showed acute massive thrombosis in left inferior vena cava, both iliac veins, and right femoral to calf veins.

antigen [CA] 125, CA 19-9) were negative.

One month after the first VTE episode, brain magnetic resonance venography showed no cerebral cavernous embolism.

The differences in diameters between the right and left thighs (10 cm above the knee) and calves (10 cm below the knee) were assessed weekly. Swelling of the thigh returned to normal seven weeks later, from 54/52 cm to 50/50 cm. The leg returned to normal seven weeks later, from 44/41 cm to 41/41 cm.

The progression of thrombi was evaluated with DUS monthly. The 2-week follow-up CTA showed no demonstrable changes in the heavily burdened DVT (Fig. 1A, 2). The thrombi were markedly resolved two months after treatment (Fig. 1C, 3), and showed a further decrease in thrombosis involving the left-sided infrarenal IVC and both iliac veins four months after treatment (Fig. 1D). The patient was discharged and returned to his usual activity with 60 mg edoxaban once daily for 40 days. The 6-month follow-up DUS showed that the thrombi in the right FV were resolved, and segmental thrombi remained in the EIV. We identified a further increase in the marginal flow around the thrombi (Fig. 4). After taking edoxaban for 6 months, the drug was reduced to apixaban 2.5 mg twice daily. He gained 10 kg in six months; thus, we recommended jogging to reduce body weight to the previous healthy level. The 1-year follow-up CTA demonstrated complete recanalization of the major veins, except for new segmental thrombi in the peripheral branches of the right IIV (Fig. 1E, 5). We recommended lifelong anticoagulation (apixaban 2.5 mg bid).

However, the patient presented with sudden pain in the right leg two weeks later, despite continuous low-dose anticoagulation therapy after heavy physical exercises such as

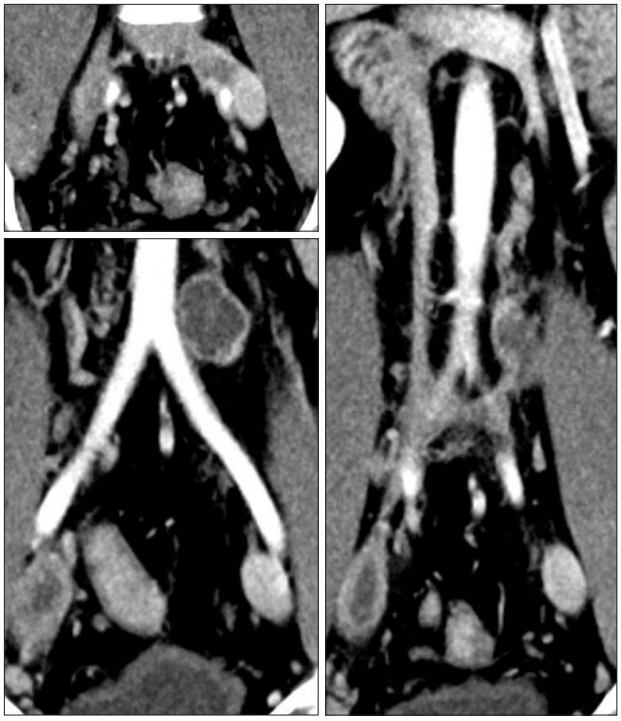

Fig. 3. Computed tomography angiography coronal view at two months showed markedly decreased deep vein thrombosis in iliac veins.

squatting, lift-ups, and jogging. At this point, CTA showed new thrombi in the right EIV and FV (Fig. 1F, 6). Therefore, apixaban 10 mg was administered twice a day for one week, followed by 5 mg twice a day, and the symptoms alleviated rapidly. During this recurrence period, he complained of a headache, sore throat, cough, and fever (38.3°C) in August 2022. The 2019-nCOV real-time reverse transcription

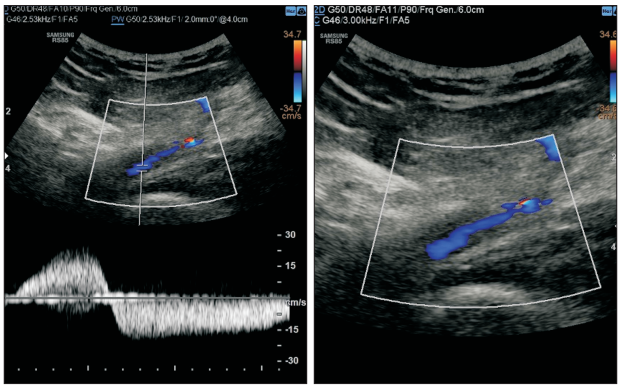

Fig. 4. Six-month follow-up duplex ultrasonography showed marginal flow around the thrombi in right external iliac vein.

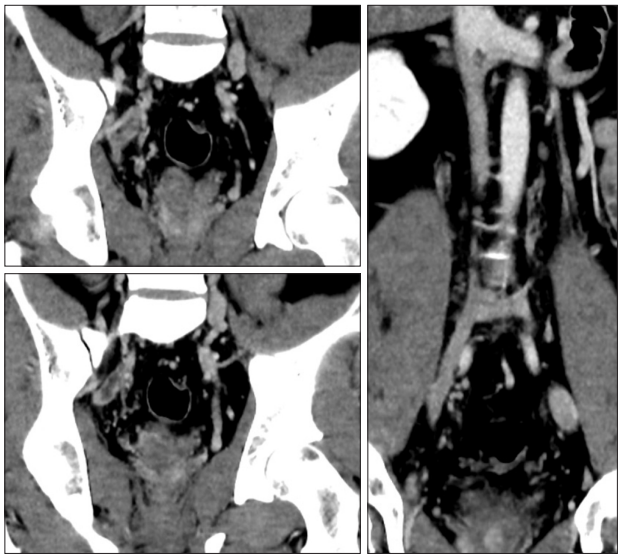

Fig. 5. Computed tomography angiography coronal view after one year showed no thrombi in major veins except new thrombi in right internal iliac vein branches.

polymerase chain reaction test was positive. The symptoms were relieved with conservative treatment for seven days after isolation.

Two months after the 1-year follow-up, CTA showed near-resolved chronic thrombosis in the right EIV and FV. The patient was followed up with anticoagulation for four months without recurrence after the second episode of VTE.

DISCUSSION

Regarding to the complication of adenovector vaccine, there have been serious concerns about the increased occurrence of DVT at unusual sites (such as the cerebral venous sinus or splanchnic vein), PE, and low levels of platelets [2]. The European Medicines Agency described them

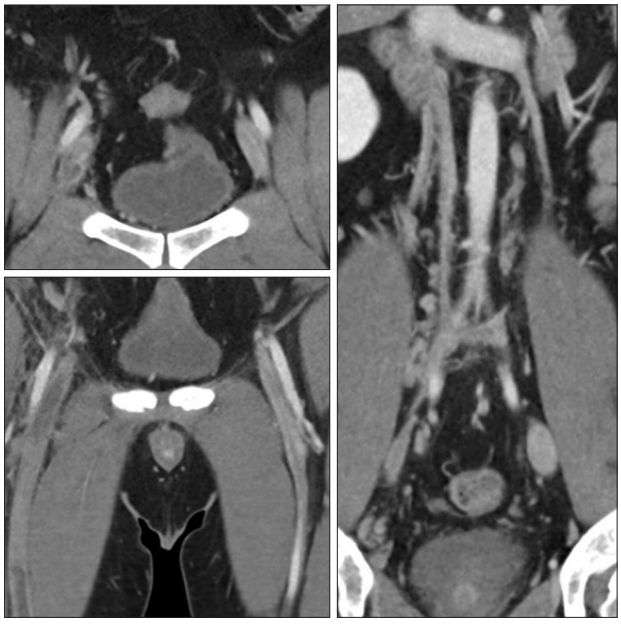

Fig. 6. Computed tomography angiography coronal view one month after recurrence showed recurent thrombosis in the right external iliac vein and femoral vein.

as a "very rare side effect," and suggested that the unusual combination of blood clots and low blood platelets is an immune response leading to a condition similar to that seen in heparin-induced thrombocytopenia (HIT) [2]. This condition was named VITT.

The Moderna Vaccine was approved in December 2020. In persons aged >16 years, a 2-dose series of Pfizer vaccines received full approval in August 2021 [1]. VTE after mRNA vaccination is rare. Carli et al. [3] reported the first case of possible association between VTE and Pfizer vaccination in April 2021. A 66-year-old woman with a heterozygous FVL mutation presented with symptoms of DVT in the leg 48 h after the second vaccination. Al-Maqbali et al. [4] reported a case of DVT with PE seven days after the first dose of Pfizer vaccine in a 59-year-old female who had a positive HIT screen in June 2021. Andrasaka et al. [5] reported three cases of VTE in females after Moderna vaccination in January 2022. The hypercoagulable panel for genetic predisposition to VTE was negative in all three patients. The first case was a 25-year-old female who presented with PE two days after the first vaccination. She had been taking an oral contraceptive pill for several years. The second case was a 77-year-old female who presented with PE and lower leg DVT three days after the first vaccination. She had a history of breast cancer. The third case was an 84-year-old female presenting with lower leg DVT without PE three days after the second vaccination. Atoui et al. [6] reported a case of PE and DVT after a second Pfizer vaccination as an acute phase reaction in a patient with thrombophilia in January

2022. A 24-year-old male experienced VTE symptoms 24 h after vaccination. Thrombophilia screening revealed a FVL G169A heterozygous mutation and a homozygous methylenetetrahydrofolate reductase (MTHFR) A1298C mutation.

Compared to other reports, our young healthy patient experienced sudden severe leg pain and edema 20 hours after the second dose. DVT in both lower extremities and iliac veins was massive and progressed rapidly.

The pathophysiological mechanisms underlying VTE remain unclear. Greinacher et al. [7] and Oldenburg et al. [8] suggested that the development of atypically located thromboses with falling platelet levels 1 to 2 weeks after AstraZeneca vaccination is an immune response, and vaccination is likely to induce the formation of antibodies against PF4-polyanion complexes as part of the inflammatory reaction and immune stimulation. These antibodies subsequently cause massive platelet activation via the Fc receptor and, in turn, contribute to coagulopathy, analogous to HIT. Atoui et al. [6] proposed that the combination of FVL heterozygous mutation leading to resistance to activated protein C, MTHFR A1298C homozygous mutation leading to increased homocysteine levels, and a severe acute inflammatory reaction after mRNA vaccination could trigger VTE.

Many studies on COVID-19, VITT, and HIT are ongoing. McGonagle et al. [9] suggested a hypothesis. Cerebral venous circulation drains the nasal sinus. It facilitates the passage of bacteria, viral products, and toxins through veins. The interaction between these elements and PF4 can cause an abnormal immune response with platelet and neutrophil activation in cases of high anti-PF4 Ab titers. Kowarz et al. [10] suggested that the major incidence of thrombosis in venous sites could be related to a non-unidirectional blood flow that does not present a valvular system, with prolonged exposure to the soluble spike protein and a high risk of binding of this protein to endothelial cells expressing angiotensin-converting enzyme-2 receptor.

IVCA are rare and can be of various types. The most frequent types are the left IVC, double IVC, circumaortic left renal vein, interruption of IVC, and absence of the infrarenal IVC [11].

In our case, the patient had no thrombophilia-related risk factors for DVT, except for infrarenal double IVC. The right and left CIVs were continuous with the right and left renal vein, respectively. Both infrarenal IVC were small in diameter, tortuous, and developed collateral venous systems. The right and left CIV join together with a bridge as a "H shape" distal to the bifurcation of aorta, at the common iliac arteries level.

Recently, IVCA has been regarded as an important risk factor for DVT in young patients. IVCA should be suspected if idiopathic thrombosis involving the iliac or proximal lower limb veins is observed in patients ≤30 years. Despite the development of collateral venous systems, inadequate blood return may increase blood pressure in the veins of the lower extremities, resulting in venous stasis and subsequent DVT [12,13]. In addition, coagulation abnormalities, which may be contributing factors, are frequently observed in patients with IVCA. Patients with both IVCA and thrombosis may be at a higher risk of thrombotic recurrence. Anticoagulation is probably required for life [12,13].

However, the safety of mRNA vaccines has not yet been investigated in patients with underlying anatomical variants that could exacerbate VTE post-vaccination. It is important to consider that the double IVC may place a patient at risk of DVT, which may not provoke acute and massive DVT without any immunological mechanism specific to the COVID-19 vaccine.

Despite thorough evaluation, we could not identify the risk factors for serologic examination and VITT was not found. The fact that the early, sudden onset of massive DVT just after mRNA vaccination is more suggestive of an association between DVT and vaccination than with IVCA. Even with continuous low-dose anticoagulation therapy, DVT recurred in the iliofemoral vein after heavy physical activity. We assumed that the causes of DVT recurrence were inadequate venous return through the small and tortuous infrarenal double IVC, or increased venous pressure and stasis followed by intense physical activities.

Unfortunately, insufficient data exists to determine the optimal therapeutic approach for VTE following COVID-19 vaccination. Oldenburg et al. [8] recommended that in addition to general measurement (exercise, fluid replacement, compression stockings), prophylactic dosages of anticoagulants such as rivaroxaban 10 mg and apixaban 2.5 mg once and twice daily, respectively, may be considered as an alternative. The duration of anticoagulant administration or prophylaxis should be discussed on a case-by-case basis. Therefore, a general consensus with the standard guideline regarding standard DVT management after COVID-19 vaccination should be reached.

In conclusion, we report a case of massive DVT in a patient with a previously unknown IVC anomaly 20 hours after the second dose of the Pfizer mRNA COVID-19 vaccine. The mRNA COVID vaccine is known to have a favorable safety profile, but in patients who have IVCA, the risk of VTE will be increased owing to the combination of these factors with an unknown immune inflammatory response to the vaccine.

FUNDING

None.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHOR CONTRIBUTIONS

Concept and design: SYN. Analysis and interpretation: SYN. Data collection: HCK. Writing the article: SYN. Critical revision of the article: SYN, KK, HR, WSY. Final approval of the article: all authors. Overall responsibility: HCK.

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