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Refractory thrombosis in a middle-aged caucasian female following recent SARS-CoV-2 infection (COVID-19): A case report and literature review

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Abstract

The short- and long-term implications following COVID-19 remain unclear. This case report includes a unique case of COVID-19 which was followed with the development of recurrent, widespread thrombosis. The treatment course consisted of a variety of anticoagulants which were adjusted and changed according to the patient's presentation at the given time. The therapies used in this case included: Rivoraxaban (Xarelto), Enoxaparin sodium (Lovenox), and Apixaban (Eliquis). A review of relevant literature was conducted to gauge how such complications arise and how they can be mitigated. This case exemplifies serious, potentially fatal clotting as an implication of COVID-19. Further studies should focus on preventing such outcomes and providing effective, optimal treatment.

Keywords: Coronavirus disease (COVID-19); Recurrent thrombosis; COVID-associated DVT; Clot pathophysiology; COVID vaccination; Case report.

Introduction

SARS-CoV-2, a novel single-stranded RNA (sRNA) virus, presented its first case in the United States on January 20, 2020, per the CDC [1]. With the virus's rapid spread, the symptoms and onset were broad and varied per case. The most common severe presentation has been pneumonia with acute respiratory distress syndrome [2]. The scope of all the short- and long-term implications following SARS-CoV-2 infection continues to be studied. This includes the high incidence of COVID-associated thrombosis involving both arterial and venous systems. This association is robust in COVID patients requiring admission to the intensive care unit [3,4]. In ambulatory patients, the association between COVID and thromboembolism is not as strong [5]. Pulmonary embolisms represent most COVID-associated venous thromboembolisms, followed by deep venous thrombosis [6]. The presence of thrombosis and abnormal coagulation studies, particularly elevated fibrin degradation products (FDPs) and D-dimer, are important factors in the prognosis of patients with COVID-19 [7].

Here, we present a case of a middle-aged Caucasian female who developed recurrent, widespread deep venous thrombus (DVT) 3 weeks following a COVID-19 diagnosis. The patient was not found to have any genetic thrombophilic disorder during testing. Furthermore, the patient did not have any other predisposing factors to clot formation - no family history, prolonged immobilization, surgery with general anesthesia, estrogen ex-

posure (oral contraceptive pills or hormone replacement therapy), recent pregnancy or puerperium, central venous catheter placement, prolonged air travel, heparin exposure while hospitalized, leg injury, acute medical illness requiring hospitalization, obesity, smoking, paralysis, or chronic medical condition (malignancy, inflammatory bowel disease, nephrotic syndrome, myeloproliferative neoplasms/PNH – paroxysmal nocturnal hemoglobinuria) [8,9]. Based on the above findings, diverse clot formation was suspected to be related to recent COVID-19 infection.

Case presentation

A 46-year-old female with no prior medical history, no medications, and no predisposing factors to clot formation presented to an outside hospital in January 2022 with fatigue, weakness, and tenderness in both calves. She tested positive for COVID-19 two weeks prior and reported continued weakness and fatigue. Before this diagnosis, there was no prior history of anticoagulation therapy. Additionally, she had not received any COVID-19 vaccination. At the time of the positive COVID-19 test, she had no respiratory symptoms upon presentation to suggest pneumonia. A chest CT done to rule out pulmonary embolism was negative.

On physical examination, the right calf measured 37.5 cm (10 cm below the knee), and the left calf measured 39.2 cm (10 cm below the knee). Pedal pulses were palpable bilaterally, with no evidence of ischemia. The remainder of the physical examination was not suggestive of any pathology. She was assigned an Eastern Cooperative Oncology Group (ECOG) performance status of 0. It was determined that she did not have any oxygen requirement. Based on the findings from the physical exam, a bilateral lower extremity venous duplex was performed. The results revealed a superficial vein thrombosis (SVT) in the right proximal-mid small saphenous vein (acute) and an SVT in the noncontinuous segments of the left proximal-mid small saphenous vein (acute). No DVT was noted in either lower extremity.

She was started on a 45-day course of Rivaroxaban 10 mg PO daily. Adequate hydration and compression stockings were recommended. The plan was to have a 2-week or sooner follow-up for a repeat bilateral lower extremity venous duplex. CT scan of chest/abdomen and pelvis was negative as a source of malignancy causing recurrent thrombosis.

Two days later, she returned to the vascular center with a chief complaint of right forearm and upper arm pain. She had blood drawn from the cephalic vein of the right arm the day prior. A right upper extremity venous duplex was performed based on the recent presentation of bilateral SVTs in the small saphenous veins. This revealed an acute DVT in the noncontinuous mid-distal brachial vein. She was then started on Enoxaparin 100 mg SC q day x 1 dose (1.5 mg/kg q day dose).

She left the office and presented again the following day with a new complaint of left lateral mid-calf pain. A limited left lower extremity venous duplex revealed acute DVT in the left anterior tibial vein. An acute DVT dose of Rivaroxaban of 15 mg PO 1-tab BID for 21 days, then 20 mg daily for the remaining treatment course, was initiated.

Following the start of the 15 mg Rivaroxaban prescription, she presented to the clinic four days later. She complained of soreness on her right neck and thought she may have slept incorrectly. A limited ultrasound of the right neck revealed a noncompressible subclavian vein at the jugular takeoff. She was put on aspirin 81 mg po 1-tab q. d. and 125% of Enoxaparin 100 mg SC q day x 1 dose (1. 5 mg/kg q day dose).

The following day, the patient was seen for recurrent thromboses. Anti-phospholipid (APLA) antibodies and Factor V/Prothrombin mutations were negative, ruling down anti-phospholipid syndrome and Factor V Leiden as etiologies of the patient's hypercoagulable state. ANA, PT, PTT, INR, CBC, and CMP tests were normal. A D-dimer was also ordered and was unremarkable (<200 ng/mL). The plan was to manage her recurrent thromboses with Apixaban 5 mg (Eliquis) 1-tab PO Q12HR and 81 mg aspirin. Nearly one month after the visit, she called the office to inform them that she was experiencing significant hair loss and bruising and wanted to come off Apixaban. She was changed to Enoxaparin 1. 5 mg/kg QD to mitigate the side effects that she may have been experiencing from the Apixaban. Aspirin was continued.

Given the patient's presentation, physical examination findings, laboratory and imaging studies, lack of predisposing factors to clotting, and continued feelings of weakness since her infection, the primary differential diagnosis was development of diverse clots secondary to an implication of her recent SARS-CoV-2 infection.

Discussion

Pathophysiology of clot formation in COVID-19 patients: Virchow's triad is an essential consideration when discussing the formation of any thrombus, and it may provide some insight into clot formation in patients diagnosed with COVID-19. Virchow's triad includes the stasis of blood flow, endothelial cell damage, and hypercoagulability. Accordingly, classic risk factors for thrombosis can include immobilization, trauma, inherited risk factors (such as Protein C deficiency or Factor V Leiden), malignancy, hypertension, among others [8,9].

COVID-19 infection could impact each component of this triad, thus making an individual more susceptible to the development of blood clots. A common symptom of COVID-19 is generalized fatigue. Although often overlooked, this may cause one to take excessive rest or more rest than usual. The prolonged bed rest or immobile time during active severe infection increases the chances of venous stasis, thereby increasing the chances for clot development [10].

Most notably, COVID-19 induces immunothrombosis through several pathways. As with many other viral infections, COVID-19 causes widespread systemic inflammation. With widespread inflammation, many cytokines and interleukins are released into the bloodstream; specifically, COVID-19 results in increased levels of IL-6, IL-8, and TNF-α [11]. An increase in these factors may cause endothelial damage and dysfunction through a cytokine storm event [11]. Additionally, the pathogenesis of SARS-CoV-2 involves downregulation of the angiotensin converting enzyme 2 (ACE2) receptor and subsequent vascular and endothelial damage [12]. The inflammation caused by COVID-19 also in-

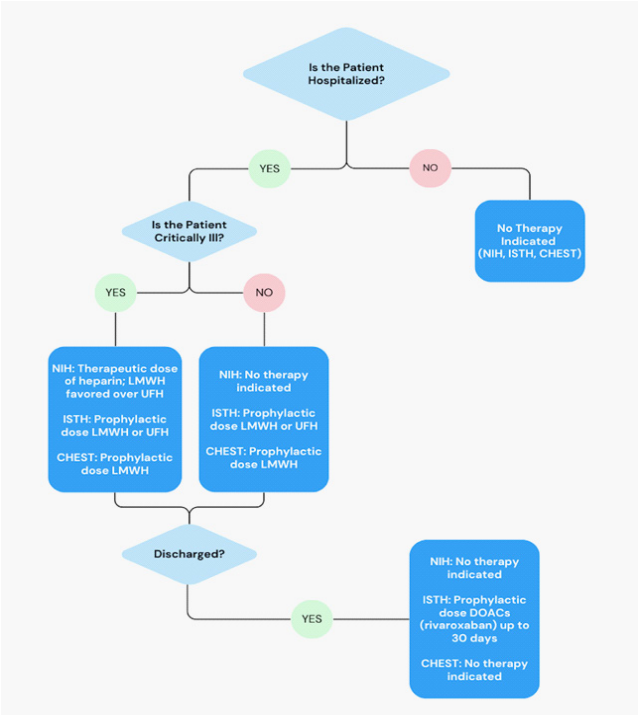

Figure 1: Thrombosis prophylaxis recommendations [21-24].

LMWH: Low Molecular Weight Heparin; UFH: Unfractionated Heparin; DOAC: Direct-Acting Oral Anticoagulants.

creases the levels of von Willebrand factor (vWF), a glycoprotein that binds to platelets and assists with clot formation [10]. Additionally, patients who are severely ill from COVID-19 have been found to have low levels of ADAMTS13, an antithrombotic factor that cleaves von Willebrand factor [11]. SARS-CoV-2 may also induce extracellular complexes known as neutrophil extracellular traps (NETs) through interactions between platelets and neutrophils, producing proinflammatory and thrombotic states that resolve post recovery [13].

Ultimately, the imbalance between prothrombotic and antithrombotic factors, widespread inflammation, and decreased mobility caused by COVID-19 increases the risk for clot development.

The acute stage of COVID-19 infection can be defined as 2-4 weeks post-infection [14]. During this period, it is found that the occurrence of venous thromboembolisms within non-hospitalized COVID-19 is higher than control, with previous vaccination demonstrating significant lowering of this risk. The patient's unvaccinated status, combined with the acute phase of her infection, elucidates the involvement of COVID-19 with her nearly simultaneous thrombotic manifestations in major veins. However, it is crucial to acknowledge that a substantially high D-dimer is characteristic of a COVID-19 induced coagulopathy [15], consequently establishing the distinctive and extraordinary nature of this case. Systemic reviews have indicated that treatment with DOACs does not influence ICU admission rates and mortality risks for COVID-19 patients [16-18], and the role and benefit of anticoagulant therapy with COVID-19 patients is still inconsistent, presenting high variability that requires further investigation [19].

Prophylaxis of VTE and thrombotic events in COVID-19 patients: A retrospective study from 2020 (n=107) including chronically anticoagulated patients prior to SARS-CoV-2 infection indicated that chronic therapeutic anticoagulation may protect against thrombotic complications and decrease disease severity. None of the patients in the study were diagnosed with a new thrombotic complication [20].

Guidelines from the National Institutes of Health (NIH), International Society of Thrombosis and Hemostasis (ISTH), and American College of Chest Physicians (CHEST) each provide different guidelines for thrombosis prophylaxis for patients who range from mildly to critically ill conditions. Figure 1 depicts the varying guidelines.

The varying recommendations from these institutions indicate the need for further research into thrombosis prophylaxis in patients with COVID-19 and no other underlying risk for clotting.

Vaccination status and clot formation in COVID-19 patients: Multiple hospital-based studies have shown an association between COVID-19 and the development of venous thromboembolisms. The incidence of VTE and PEs in hospitalized patients with COVID-19 has been shown to range from 7-17% [25,26].

However, the risk of thrombosis in the ambulatory patient population has been debated in the literature. A meta-analysis of 7 COVID-19 heterogeneous cohorts suggested no VTE risk in mild COVID-19 infections, with a relative risk of 1.18 (95% CI, 0. 79-1.77) [27]. This result can be compared to a case series that suggests a sizable increased risk of VTE post-COVID-19 infection, with a 7-fold and more than 46-fold increased risk at 1-2 weeks for DVT and PE, respectively [28]. Another cohort study involving 5 European countries showed a 90-day VTE incidence of 0.2%-0.8% among all patients with COVID-19 and as high as 4.5% in those requiring hospitalization [29].

Another study from the Augusta University Health System reported that factors such as ICU admission, elevated hemoglobin level, elevated D-dimer, and the use of psychoactive medications put patients with COVID-19 at increased risk for thrombotic events. Among the 332 patients in the study, 29 had thrombosis with a 9.4% risk of thrombosis, which is substantially higher than the 4% per 100 patient-year baseline population risk [30].

A retrospective cohort study utilizing the UK Biobank included 18,818 ambulatory patients with COVID-19 and 93,179 noninfected, propensity score-matched patients and revealed an increased VTE incidence in the former, with an HR of 21.42. When stratified for vaccine status, the risk of VTE decreased in the fully vaccinated subjects with breakthrough infection compared to partially or not vaccinated subjects (HR, 5.95; 95% CI, 1.82-19.5; interaction P=.02) [31]. Older age, male sex, and obesity were other clinical risk factors for post-COVID VTE. This study may reiterate the importance of vaccination and aid in risk stratification when discussing the need for anticoagulation in patients with COVID-19, particularly nonvaccinated patients.

Another recent study focused on analyzing pulmonary embolism risk in COVID-19 vaccinated and non-vaccinated patients. The authors found that unvaccinated patients had a significantly higher chance of pulmonary embolism (45.7%) than vaccinated patients (11.1%). Interestingly, the vaccinated patients were older and had more comorbidities than the unvaccinated group [32].

A review of adenoviral-vector COVID-19 vaccinations like those developed by AstraZeneca and Johnson&Johnson (J&J) found that the risk of Vaccine-Induced Immune Throm-

botic Thrombocytopenia (VITT) was extremely low. Between 1/26,500 persons to 1/518,181 persons experienced VITT with the AstraZeneca vaccine and 1/263,000 persons experienced VITT with the J&J vaccine [33].

The patient in this case was not vaccinated for COVID-19 prior to diagnosis. This factor could have played a significant role in the patient's disease progression and long-term prognosis, including a greater predisposition to embolisms. Additional studies, particularly of higher power, need to be completed to further assess this factor. However, vaccination status should be considered in assessing a COVID-19 patient's future embolism risk.

Conclusion

This case of diverse clot formation was managed using various anticoagulants. The main drugs used to treat this patient were Rivaroxaban, Enoxaparin, Apixaban, and low-dose aspirin. Rivaroxaban was first initiated at 10 mg PO daily following the first manifestation of acute thrombosis within both the left and right small saphenous veins. Enoxaparin at 100 mg SC q day x 1 dose was started two days after Rivaroxaban following the discovery of an upper-extremity thrombosis within the brachial vein. Dosage of Rivaroxaban was subsequently increased to 15 mg PO 1-tab BID, 3 days after the first prescription of Rivaroxaban, following the third occurrence of venous-duplex diagnoses of DVT, this time within the left anterior tibial vein. After another four days, a noncompressible subclavian vein (fourth incidence) was discovered and the patient was started on aspirin at 81 mg po 1-tab q. d. and a 125% increased dose of Enoxaparin. Within the next six months, 81 mg aspirin was continued, and Apixaban 5 mg 1-tab PO Q12HR was switched to Enoxaparin 1. 5 mg/kg QD at the one-month point. The patient's thrombotic occurrences appear to be halted only after antiplatelet therapy (aspirin) and high-dose low-molecular-weight heparin (Enoxaparin) was initiated.

The plan was to continue anticoagulant treatment for six months following the DVT diagnosis and to have routine follow-up visits with the hematologist. At her six-month follow-up, the patient was stable, had not developed any new clots, and did not have any other concerns. Her regimen of anticoagulation was subsequently halted. The patient continues to remain stable and has not developed any new clots. The isolated incidences of thrombotic episodes within close proximity of the patient's diagnosis of COVID-19 further indicates the COVID-19 associated coagulopathy.

This case suggests a need for further research into the hematological impacts of SARS-CoV-2 infection. Particularly, further research should examine recurrent thrombosis in the setting of post-COVID-19 infection and effective treatment plans to mitigate potential severe outcomes.

Declarations

Data availability: The data used to support the findings of this study are included within the article.

Conflict of interest: The authors of this case report declare that they have no conflicts of interest.

Ethics statement: This case report utilized anonymized patient information and is classified to be exempt from review from the Institutional Review Board.

Informed consent: The patient provided full written consent for the publishing of this case report.

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Dongyu Zhang: writing – review and editing

Andrew Ji: writing – review and editing

Girindra Raval: Conceptualization; investigation; methodology; project administration; resources; supervision; writing – review and editing

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