Case Report

Non-Severe COVID-19 Complicated by Deep Vein Thrombosis (DVT)

Wulyo Rajabto, Dimas Priantono

Faculty of Medicine, Universitas Indonesia - Division of Hematology-Medical Oncology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

Abstract

Background: Coronavirus Disease 2019 (COVID-19) displays various symptoms ranging from asymptomatic to life-threatening. Patients may present with typical respiratory infections or atypical symptoms. Non-severe COVID-19 encompasses mild and moderate cases, characterized by the absence of criteria for severe or critical illness, with mild cases not showing evidence of viral pneumonia or hypoxia and moderate cases maintaining SpO_2 levels of at least 90% on room air.

Case: We presented a COVID-19 case with the chief complaint of unilateral leg swelling. A 48-year-old male was admitted with the chief complaint of cramps and swelling of the left leg. He had a history of fever, cough, nausea, and vomiting. Laboratory studies showed elevated D-dimer. Doppler ultrasound shows signs of both proximal and distal deep vein thrombosis. CT pulmonary angiography excluded pulmonary embolism while the lung window image supported the diagnosis of COVID-19 pneumonia. Polymerase chain reaction (PCR) obtained from nasopharyngeal and oropharyngeal swabs confirmed COVID-19 infection.

Discussion: We treated the patient with parenteral anticoagulation followed by direct oral anticoagulant upon discharge. The swelling improved as well as the patient's clinical status. Thromboembolic complications have been credited as the culprit of high mortality in COVID-19. Systemic activation of coagulation in pulmonary and peripheral circulation contributed to life-threatening thrombotic complications. Our patient presented with COVID-19-associated proximal and distal DVT without pulmonary embolism.

Conclusion: Prompt diagnosis of COVID-19 infection and acute DVT improves patient care. The hallmark of the management of VTE in COVID-19 patients is treatment with therapeutic dose parenteral anticoagulation followed by oral anticoagulant.

Keywords: anticoagulant, DVT, non-severe COVID-19, VTE

Corresponding Author:
Dimas Priantono | Faculty of Medicine, Universitas Indonesia - Division of Hematology-Medical Oncology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia | dimas.priantono@gmail.com

Submitted: January 19th, 2022
Accepted: April 9th, 2024
Published: April 30th, 2024

J Respirol Indones. 2024
Vol. 44 No. 2: 138–43
https://doi.org/10.36497/jri.v44i2.263

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS CoV-2) which has spread rapidly throughout the world and was declared a global health problem by the WHO Emergency Committee in January 2020.[1] The WHO categorizes COVID-19 severity into critical, characterized by conditions necessitating life-sustaining therapies like mechanical ventilation, severe, marked by oxygen saturation <90% on room air or severe respiratory distress, and non-severe, where none of the criteria for severe or critical COVID-19 are met.[2]

Non-severe COVID-19 consists of mild and moderate disease. Mild disease includes symptomatic COVID-19 patients who meet the case definition but do not show evidence of viral pneumonia or hypoxia, while moderate disease exhibits pneumonia symptoms without signs of severe pneumonia, including maintaining SpO_2 levels of at least 90% on room air.[2]

According to the 4th edition of the COVID-19 Management Guidelines, jointly developed by 5 medical professional organizations in Indonesia, mild COVID-19 cases necessitate up to 10 days of self-isolation at home or in monitored facilities, plus an additional 3 days without fever and respiratory symptoms. Meanwhile, moderate cases require hospitalization in specialized COVID-19 care units.[3]

For mild cases, pharmacological treatment includes vitamin C and D supplementation along with antiviral medication such as Favipiravir, Molnupiravir, or Nirmatrelvir/Ritonavir, depending on availability, alongside symptomatic relief. Moderate cases involve intravenous vitamin C, vitamin D supplementation, and pharmacological therapy with antivirals like Remdesivir or alternatives, along with

anticoagulation and symptomatic management, considering existing comorbidities and complications.[3]

The clinical course of patients with COVID-19 may be complicated by coagulopathy leading to venous thromboembolism.[4] Current evidence revealed that COVID-19 is often complicated by a significant coagulopathy, which commonly manifests as venous thromboembolism: deep vein thrombosis (DVT) and pulmonary embolism (PE).[5]

D-dimer levels are elevated not only in the setting of acute deep vein thrombosis (DVT) and acute pulmonary edema (PE), but also in other conditions such as infection, pregnancy, and malignancy.[6] However during the COVID-19 pandemic, D-dimer is commonly elevated in patients with COVID-19.[7]

Several recent studies suggested that patients with COVID-19 showed a condition in a hypercoagulable state. Laboratory findings show high C-reactive protein (CRP), lymphocytopenia, leukopenia, mild thrombocytopenia, prolonged PT, high fibrinogen, and high D-dimers levels at the beginning of the disease course, which in severe cases might be complicated by low fibrinogen.[8] Therefore, we report a case of non-severe pneumonia COVID-19 with deep vein thrombosis as the main presentation.

CASE

A 48-year-old male was admitted to the Kiara in-patient isolation ward, presenting with complaints of cramping and swelling in his left leg. His symptoms were preceded by a bout of fever, cough, nausea, and vomiting, which prompted a visit to a general practitioner who initially suspected typhoid fever. Notably, the patient had no other underlying health issues.

Upon physical examination, aside from the visibly swollen left leg with pitting edema, the patient appeared fully conscious and oriented, with vital signs within normal limits-blood pressure measured at 122/70 mmHg, heart rate at 112 bpm, respiration rate at 22 bpm, and temperature at 37°C.

Figure 1. Swelling and pitting edema of the left leg of the patient

Laboratory investigations revealed several noteworthy findings, including elevated levels of CRP, Procalcitonin, and D-dimer, while other parameters such as hemoglobin, white blood count (WBC), platelet count, renal function, liver function, and blood glucose remained within normal ranges. A chest X-ray unveiled homogenous opacities and lung infiltrates primarily affecting the base of both lungs.

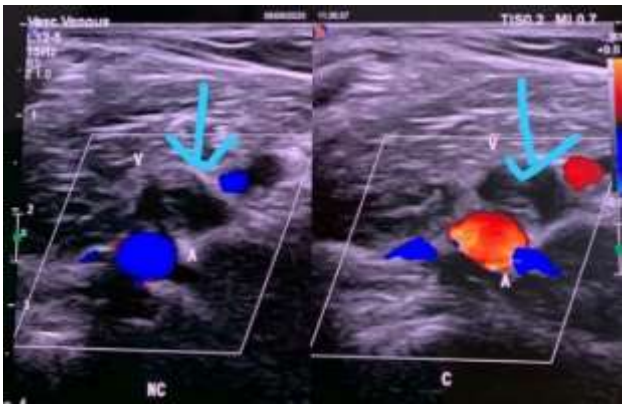

Figure 2. Doppler ultrasound image demonstrated an acute left popliteal vein DVT, hallmarked by dilation and non-compressibility (arrow) of the left popliteal vein (arrow).

Given the clinical presentation, laboratory results, and chest X-ray findings suggestive of COVID-19, a SARS-CoV-2 polymerase chain

reaction (PCR) Swab test was administered, confirming the viral infection. Furthermore, due to clinical suspicion and the patient's pretest probability based on Well's score, a Doppler ultrasound was performed to assess for deep vein thrombosis (DVT).

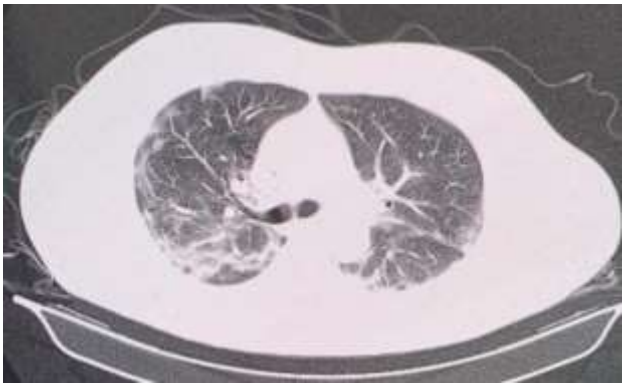

Figure 3. CT pulmonary angiography demonstrated no stenosis, aneurism, vascular malformation, or thrombus. Lung window showed ground glass opacities which supported COVID-19 pneumonia diagnosis.

The imaging revealed evidence of DVT in the left common femoral vein, popliteal vein, and anterior tibial vein. To rule out pulmonary embolism (PE) owing to markedly elevated D-dimer levels, a CT pulmonary angiography was conducted, which, while excluding PE, supported the diagnosis of COVID-19 pneumonia based on characteristic lung opacities.

Treatment encompassed empirical antibiotics, symptomatic management, multivitamins, and a full-dose regimen of unfractionated heparin to achieve a target-activated partial thromboplastin time (aPTT) of 1.5–2.5 times the control value.

Figure 4. The swelling and pitting edema of the left leg has already improved after parenteral anticoagulation followed by oral anticoagulant therapy.

Following a ten-day hospitalization period during which the left leg swelling showed improvement, the patient was discharged with a prescription of Rivaroxaban 15 mg b.i.d. for 21 days, followed by a maintenance dose of Rivaroxaban 20 mg once daily. These therapeutic measures were implemented alongside the continued management of COVID-19 pneumonia.

DISCUSSION

Venous thromboembolism is a complicated disease phenomenon, with huge interplaying factors. The disease itself used to be overlooked in Asian populations due to its lower incidence compared to Western countries. However, in medical patients, the risk of thrombosis in the Asian population seems to be higher and approximately equal to its Caucasian counterparts.[9]

The emerging COVID-19 global pandemic has opened a vast array of medical research, including the ones studying thrombosis and hemostasis. Current data from case reports in this new emerging infectious disease shows that although the virus mainly targets the respiratory systems, activation of coagulation leading to coagulopathy is one of the culprits leading to high mortality in COVID-19.[10] Another study by Helms et al showed that most COVID-19 deaths are associated with thrombosis.[11]

In this case report, our patient presented with unilateral leg swelling. The respiratory symptoms themselves were not significant and the patient had continued his treatment on an outpatient basis before admission. More frequently, patients with COVID-19 come to the hospital without established venous thromboembolism, although the risk of thrombosis has already elevated in the majority of the patients. Interim Guidelines by The International Society on Thrombosis and Hemostasis suggest that assessment of coagulation parameters should be done at patient admission.[12]

The guideline stratifies COVID-19 patients into high-risk and low-risk thromboembolism and provides guidance on prophylactic anticoagulation for each group.[12] Other reviews by Carfora et al stratifies the

anticoagulation strategy and dosing according to COVID-19 severity.[13] However, the aforementioned publications do not guide the treatment of established venous thromboembolism.

We established a confirmed COVID-19 case from the positive result of PCR obtained from nasopharyngeal and oropharyngeal swabs. Prompt lower extremity vascular ultrasonography played an important role in deciding which imaging modality should be requested as the next step. Had the ultrasound not demonstrated any filling defect or compression abnormalities, a non-contrast pulmonary CT scan would be ordered thus providing no additional diagnostic value in ruling out pulmonary embolism.

The sonographic findings of acute popliteal DVT warned us to proceed with contrast-enhanced CT pulmonary angiography, which not only confirmed ground glass opacities in the lung window but also provided a good image of the pulmonary arteries to rule out acute pulmonary embolism.

The diagnosis approach of DVT in this patient follows the clinical decision rule as described by Dronkers et al, a high probability of DVT on admission, followed by a positive compression ultrasound confirms the diagnosis of DVT.[14] Elevated D-dimer itself can occur in COVID-19 infection without established thromboembolism. Hence, the clinical probability scoring system and ultrasound play an important role in diagnosing DVT in our case.

In acute established thromboembolism, the anticoagulant treatment should be initiated promptly with a therapeutic dose. Either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) can be used. Some guidelines, such as the ISTH guideline recommend LMWH while other guidelines recommend either one of them.[12]

While LMWH provides simplicity and a lower risk of patient contact, UFH gives clinicians plenty of room for dosage adjustment even in severe renal failure. In our patient, we used UFH with dose titration to achieve the target aPTT level of 1.5–2.5 times control. We administered UFH as suggested by the review by Hajra et al.[4] Parenteral anticoagulation is chosen due to its minimal drug-to-drug interactions with antivirals used in treating COVID-19.[15]

After hospital admission, we continued the anticoagulation with a direct oral anticoagulant (DOAC). Therapy with DOAC should be continued and monitored according to the patient's symptoms and sonographic findings. Since this patient had both distal (anterior tibial) and proximal (common femoral and popliteal) DVT, the duration of oral anticoagulation should be longer, which is 3 months, as for proximal DVT.[5]

This study provides insights that patients with COVID-19 may exhibit a range of signs and symptoms, sometimes resembling other conditions such as unilateral leg swelling, even in the absence of significant respiratory symptoms. In the scenario of a young individual without comorbidities presenting with unilateral leg swelling during the pandemic, consideration of alternative causes, including the possibility of COVID-19 infection, is warranted.

While elevated D-dimer levels in COVID-19 patients serve as a warning sign for venous thromboembolism (VTE), it's important to note that increased D-dimer levels can also occur in COVID-19 infection without confirmed thromboembolism. This study sheds light on employing a clinical probability scoring system and promptly conducting lower extremity vascular ultrasonography to guide additional diagnostic imaging and represent practical approaches to diagnosing VTE in settings with limited resources.

LIMITATIONS

The limitation of this case report is the fact that COVID-19 variant analysis was not available at the time. It might show whether certain variant is associated with an increased risk of venous thromboembolism.

CONCLUSION

This study highlights the diverse manifestations of COVID-19, emphasizing the need for vigilance, particularly in young individuals presenting with unilateral leg swelling, and

underscores the utility of clinical probability scoring and prompt vascular ultrasonography in diagnosing venous thromboembolism amidst elevated D-dimer levels in COVID-19 patients. Prompt diagnosis of COVID-19 infection and acute DVT would improve patient care since the treating physician would be aware of this infectious disease and its dire thrombotic complications. Treatment with therapeutic dose parenteral anticoagulation followed by oral anticoagulant is the hallmark of the management of VTE in COVID-19 patients.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
2. World Health Organization. Clinical management of COVID-19: Living guideline, 18 August 2023 [Internet]. World Health Organization; 2023. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.2
3. Perhimpunan Dokter Paru Indonesia (PDPI), Perhimpunan Dokter Spesialis Kardiovaskular Indonesia, Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia, Perhimpunan Dokter Anestesiologi dan Terapi Intensif Indonesia, Ikatan Dokter Anak Indonesia. Pedoman tatalaksana COVID-19. Pedoman tatalaksana COVID-19 edisi 4. Indonesia; 2022.
4. Hajra A, Mathai SV, Ball S, Bandyopadhyay D, Veyseh M, Chakraborty S, et al. Management of thrombotic complications in COVID-19: An update. Drugs. 2020;80(15):1553–62.
5. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, diagnosis, and treatment of VTE in patients with Coronavirus disease 2019: CHEST guideline and expert panel report. Chest. 2020;158(3):1143–63.
6. Hirsh J, Lee AYY. How we diagnose and treat deep vein thrombosis. Blood. 2002;99(9):3102–10.
7. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J Intensive Care. 2020;8:49.
8. Tal S, Spectre G, Kornowski R, Perl L. Venous thromboembolism complicated with COVID-19: What do we know so far? Acta Haematol. 2020;143(5):417–24.
9. Angchaisuksiri P. Venous thromboembolism in Asia--an unrecognised and under-treated problem? Thromb Haemost. 2011;106(4):585–90.
10. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: Emerging evidence and call for action. Br J Haematol. 2020;189(5):846–7.
11. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089–98.
12. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023–6.
13. Carfora V, Spiniello G, Ricciolino R, Di Mauro M, Migliaccio MG, Mottola FF, et al. Anticoagulant treatment in COVID-19: A narrative review. J Thromb Thrombolysis. 2021;51(3):642–8.
14. Dronkers CEA, Tan M, Mol GC, Iglesias Del Sol A, Van De Ree MA, Huisman M V., et al.

Evaluation of the new simple and objective clinical decision rule “I-DVT” in patients with clinically suspected acute deep vein thrombosis. Thromb Res. 2016;141:112–8.

15. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, et al. Scientific and Standardization Committee Communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1859–65.