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Case Report

Arterial Thrombosis Induced By Coagulopathy Due To Coronavirus Infection Concomitant With Heparin Resistance: A Case Report

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ABSTRACT

Background : A newly emerging pandemic of Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory coronavirus 2 is responsible for significant morbidity and mortality worldwide. As one of the effects is hematological changes related to the COVID-19 infection causing patient tend to thrombosis than hemorrhagic. Current review of evidence and statements on management of coagulopathy and thrombotic complications related to this novel disease is needs to be explored

Case : Male 53 years old referred from Private Hospital, due to Severe pneumonia due to COVID-19 and Acute Limb Ischemia. This patient was assessed as Pneumonia COVID-19 severe with acute limb ischemia bilateral grade IIB and performed bilateral surgical thrombectomy with antegrade approach using fogarty catheter with the result was thrombus 10cm along the left femoral artery and thrombus 2cm in the right femoral artery.

Discussion : With consideration of atherosclerotic diseases in this patient, we decided to give rivaroxaban as an anticoagulant combined with aspilet and statin high dose. But due to lack of source in our hospital, and patient also denied for further management, treatment for the patient cannot be optimal, so the patient discharge with unresolved limb ischemia.

Conclusion : This case showed that the increase risk of heparin resistance in SARS-CoV-2 patient, it is recommended to monitor heparin activity of UFH treatment based on anti-Xa levels instead of aPTT alone.

1. Introduction

As pneumonia COVID-19 was announced as a pandemic disease by WHO at March 2020, the spreading of the cases was escalating worldwide. In the most cases of the diseases causing infection in the respiratory tracts, but in severe diseases, there is progression to the systemic organ failure and associated with an increase in mortality rate. COVID-19 pneumonia can result in cytokines storm and coagulopathy. COVID-19 induced coagulopathy (CIC) appears to be more prothrombic than hemorrhagic.[1]

The hypercoagulable state of COVID-19 infection also increases the possibility of thrombus formation in arterial known as acute limb ischemia, which is one of the most common emergencies in the vascular diseases. Nevertheless, revascularization was disappointingly low in patients with COVID-19 with the possibility of recurrence thrombosis.

Thus, we discuss the possibility and the best way to treat thromboembolism induced by COVID-19 infection, not solely in the vein but also in the artery system.

2. Case Illustration

Male 53 years old referred from Private Hospital, due to Severe pneumonia due to Coronavirus disease 2019 (COVID-19) and Acute Limb Ischemia. The patient suffered from pain and tingling in both of his feet since 11 days before admission with mild activity and did not relieve by rest. His complaint was getting worse accompanied by leg swelling, cold and pale. Then he seek for medical help due to his condition.

From physical examination, we found his blood pressure was 143/88mmHg, HR 112x/m regular, RR 20x/m with SaO2 98% on nasal canule. Moreover, for vascular status, we found pain, pale, paresthesia, pulseless, poikilothermia and motoric disturbance at both of his leg. From Chest X ray there is cardiomegaly with CTR was 65% and pulmonary infiltration. He then underwent a Doppler ultrasonography examination with the resulting thrombus >50% in the left superficial femoral artery and total occlusion in the left and right popliteal artery.

Laboratorium result showed increment in D-dimer from 2.15 mg/dL in to 3.42 mg/dL, ferritin 756.6 ng/mL, and fibrinogen 489 mg/dL. Swab antigen result for COVID 19 was positif.

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This patient was assessed as Pneumonia COVID-19 severe with acute limb ischemia bilateral grade IIB and performed bilateral surgical thrombectomy with antegrade approach using fogarty catheter with the result was thrombus 10cm along the left femoral artery and thrombus 2cm in the right femoral artery.

During hospitalization, aPTT target was difficult to reach target value even after dosing adjustment of heparin reach 66000 IU/day with aPTT 40sec. There is worsening of lower limb lesion and was planned to do re-thrombectomy but patient denied. He then discharge from hospital with unresolved lower limb ischemia.

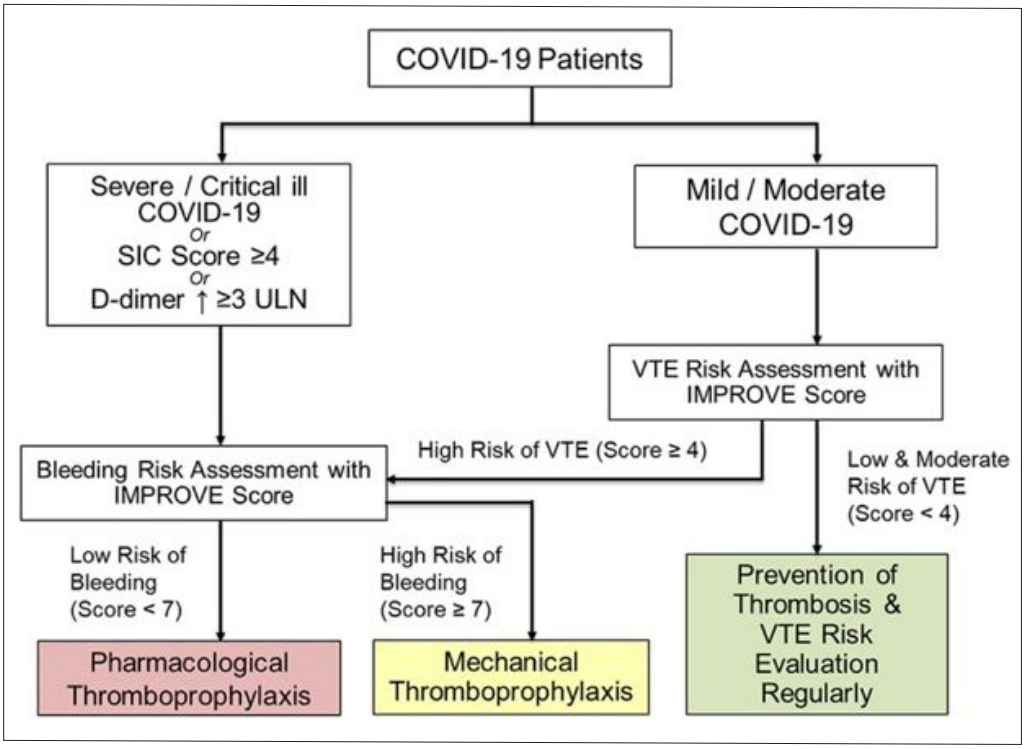

Figure 1. Proposed flowchart of anticoagulant prophylaxis in COVID-19 patients.[14]

3. Discussion

A remarkable inflammatory response can be observed in COVID-19 patients, attested by a significant increase in fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6) and ferritin levels, but D-dimer concentration was the most typical hematological changes in COVID-19 patient. Mean fibrinogen concentrations in patients with COVID-19 are at the upper limits of normal, presumably as an acute phase response, meanwhile increase in D-dimer can be a poor prognostic factor for patient infected with coronavirus and increase mortality rate.[2-6] For this patient, he had increase in D-dimer concentration accompanied by increase in ferritin level and fibrinogen.

COVID-19 infection is associated with increases pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukins (IL-1 and IL-6). IL-6 induced tissue factor expression on mononuclear cells that play a role in coagulation cascade, while TNF-α and IL-1 are mediators to suppress anticoagulation pathway.[3] Inflammation-induced endothelial cell injury could result in massive release of plasminogen activators, which could explain the high concentrations of D-dimer and fibrin degradation products in patients with severe COVID-19.[3] Other differences of hemostasis function in patient with corona viral infection was lower value of anti-thrombin.[6]

The coagulation changes associated with COVID-19 suggest the presence of a hypercoagulable state that might increase the risk of thromboembolic complications. Immobilization and vascular damage are other factors that can increase the risk of thrombosis.[3] As for this patient, he had risk factor of atherosclerotic diseases such as hypertension and smoker. This might increase the probability of thrombus formation especially in hypercoagulable condition induced by COVID-19 infection.

From the Klok et al show that the incidence of thromboembolic complications in patients with COVID-19 is 35–45% with pulmonary embolism as the most common thrombotic complication, and only 3.7% having arterial thrombotic events.[7] Even though arterial thrombotic lesion was only found in small proportional, but in fact, people with background of atherosclerotic diseases having bigger chance for thrombus formation.

Levy et al suggested monitoring coagulopathy in patient with severe COVID-19 by measuring pro-thrombin time, platelet count, and D-dimer concentrations every 2–3 days. And using thromboprophylaxis treatment for all COVID-19 patient that hospitalized in the absence of medical contraindication due to their hypercoagulable state. Low molecular weight heparin was recommended as thromboprophylaxis but if not available, unfractionated heparin can be used.[3]

Acute limb ischemia is one of the most common emergency in the vascular diseases. As the etiology can be multifactorial such as atherosclerotic diseases or patient with hypercoagulable states that can increase the risk of vascular thrombosis. Systemic pro-inflammatory cytokine response is a mediator of atherosclerosis by inducing the expression of pro-coagulant factors. And the receptor for SARS-CoV-2 (angiotensin-converting enzyme-2) is expressed on the membrane of vascular muscle and endothelial cells causing endotheliopathy as one of the systemic effect of infection. COVID-19 may predispose to both venous and arterial thromboembolism due to excessive inflammation,

hypoxia, immobilization and diffuse intravascular coagulation.[7–9]

As ALI was one of emergency in vascular surgery, thus the patient with ALI grade IIA-IIB need a prompt treatment, then we decided to perform thrombectomy as a definitive treatment meanwhile heparin drip intravenous was started since first patient was diagnosed as ALI. Unfortunately, after several days of follow up post thrombectomy, his condition of both lower extremities was getting worsen, with a difficulty to reach the target value of aPTT even with higher doses of UFH. He was treated with drip heparin 3000IU/day (more than 35000IU/ day) with aPTT 40sec (reference normal value of aPTT was 24.6 – 30.6). The patient then we diagnosed as heparin resistance because the target of aPTT was not achieved even with higher dose of heparin. Based on Durrani et al, heparin resistance is generally defined as either requiring >35,000 IU/day heparin to achieve therapeutic anticoagulation or being unable to achieve therapeutic anticoagulation.

Heparin is one of the anticoagulant produced mainly by basophilic mast cells in pericapillary connective tissue throughout the body. Heparin need to conjugate with antithrombin III for removing thrombus.[10] The rates of heparin resistance in COVID-19 patients with intravenous UFH are high (80%) and are likely due to the effects of increased fibrinogen and factor VIII on the APTT and acts to lower the APTT and as a risk factor for heparin resistance.[11] This is in accordance with the result of Beun et al, that SARS-CoV-2 patients had elevated levels of factor VIII, fibrinogen and D-dimer.[12] Management of heparin resistance was administration of antithrombin-III or transition to a direct-thrombin inhibitor such as argatroban.[13] But both of the drugs were not available at our hospital. Then we decided to optimizing anticoagulant therapy for this patient by increasing dose of heparin drip while monitoring of bleeding sign.

There are several protocol in administration of anticoagulant therapy in COVID-19 patient. One of the flowchart of anticoagulant prophylaxis in COVID-19 patients proposed by Eko et al was categorized patient as severe/ critical ill and mild to moderate COVID-19 infection.(14) For this patient with moderate criteria of COVID-19 infection with the IMPROVE score 5 and low bleeding risk (IMPROVE Bleeding RAM score 2) appropriate for pharmacological thromboprophylaxis management of thromboembolism.

With consideration of atherosclerotic diseases in this patient, we decided to give rivaroxaban as an anticoagulant combined with aspilet and statin high dose. But due to lack of source in our hospital, and patient also denied for further management, treatment for the patient cannot be optimal, so the patient discharge with unresolved limb ischemia.

4. Conclusion

Coagulopathy was one of the effect from systemic inflammation in COVID-19 patient and can induced both arterial and venous causing thromboembolic complication and giving bad prognosticator especially in people with atherosclerotic diseases. Despite some protocol was available, but most of them was more concern in venothromboembolism. There are high demand for more research related to the thrombosis and HR in arterial system in COVID-19 patient and develop a proper protocol for diagnostic and management. In addition, with the increase risk of heparin resistance in SARS-CoV-2 patient, it is recommended to monitor heparin activity of UFH treatment based on anti-Xa levels instead of aPTT alone.

5. Declarations

5.1. Ethics Approval and Consent to participate
Patient has provided informed consent prior to involve in the study.

5.2. Consent for publication
Not applicable.

5.3. Availability of data and materials
Data used in our study were presented in the main text.

5.4. Competing interests
Not applicable.

5.5. Funding source
Not applicable.

5.6. Authors contributions
Idea/concept: IK. Design: IK. Control/supervision: HM, NK, IP. Data collection/processing: IK. Extraction/Analysis/interpretation: IK. Literature review: IK. Writing the article: IK. Critical review: HM, NK, IP. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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