Pulmonary Embolism in Hospitalized Patient with Coronavirus Disease 2019 (COVID-19)

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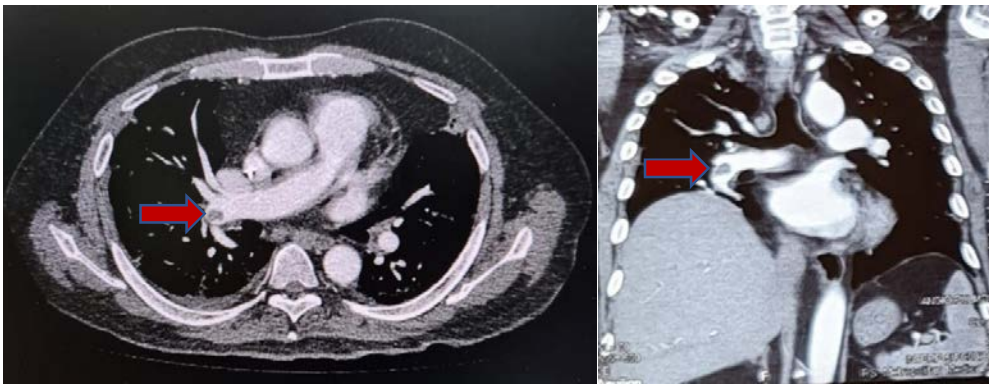

Figure 1. (A) and (B) CT-pulmonary angiography showed intra-luminary hypodense lesion in posterior and basal segment of right pulmonary artery suggesting pulmonary embolism.

Coronavirus disease 2019 (COVID-19) pandemic has affected healthcare policy globally more than ever. For the first time, a global pandemic was studied meticulously by scientists and clinicians worldwide. The virus was initially considered to be a respiratory disease. Meanwhile, several discoveries have been made, including the impact of this infectious disease on coagulation. Early studies showed that patients with COVID-19 had elevated D-dimer levels.[1] These findings were confirmed by autopsies which showed thrombosis in various sites in patients that died from COVID-19.[1]

Thrombosis occurs in up to one-third of hospitalized patients with COVID-19,[2] it happens at many sites by the diffuse activation of coagulation cascade. Furthermore, pulmonary embolism have been reported to be the most dangerous thrombotic event which greatly increases mortality in COVID-19.[2] However, the diagnosis of this condition is frequently overlooked. Pulmonary angiogram or Computed Tomography (CT) Pulmonary Angiogram is often difficult to obtain, meanwhile, echocardiogram and electrocardiogram might show pathognomonic abnormalities suggesting pulmonary embolism but lack sensitivity and specificity. Therefore, the demonstration of intraluminal filling defect by CT pulmonary angiogram or fluoroscopic pulmonary angiogram is considered the gold standard of diagnosis.

A 54-year-old male was presented to the emergency department and complained of worsening dyspnea associated with fever and cough 9 days before admission. The nasopharyngeal and oropharyngeal SARS-CoV-2 polymerase chain reaction (PCR) swab test was performed and the result was positive. The patient was hospitalized at COVID-19 isolation intensive care unit (ICU) with ventilatory support due to acute respiratory distress syndrome (ARDS) for 9 days. Fortunately, a good clinical response was achieved without endotracheal intubation and mechanical ventilation, i.e., good chest X-ray response without duplex pneumonia, and tested negative to the nasopharyngeal and oropharyngeal PCR swabs. Afterwards, the patient was transferred to non-COVID-19 ICU and later to the general ward after 3 days. However, in the inpatient ward, a sudden incidence of dyspnea, cough, and nervousness were observed. On physical examination, the patient was alert but moderately ill, blood pressure was 140/90 mmHg, heart rate 110x/ minute, respiratory rate 20x/ minute, and afebrile. Furthermore, peripheral O_2 saturation was 90% and improved to 98% with 15 L/ minute oxygen supplementation via non-rebreathing mask, while the laboratory values include Hb 14.5 g/dL, white blood cells (WBC) 9,810 cells/ μL, and platelets 276,000 cells/μL. Liver and renal function tests were within normal limits as well as random blood glucose and electrolytes. D-dimer was extremely elevated to 14,150 ng/ mL (reference value: <500 ng/mL), while chest X-ray imaging showed no infiltrates in both lungs. A doppler ultrasound was performed on both extremities and the result indicated chronic venous insufficiency, while CT-pulmonary angiography showed intra-luminary hypodense lesion in the posterior and basal segment of right pulmonary artery. The diagnosis of post-severe COVID-19 pneumonia-ARDS pulmonary embolism was established.

Low molecular weight heparin (LMWH): Enoxaparin 6,000 IU (0.6 mL) bid was administered subcutaneously to the patient. After 10 days, the clinical condition improved, the patient was discharged with direct oral anticoagulant Rivaroxaban 15 mg bid for 21 days and 20 mg qd for 3-6 months.

Hospitalized patients with COVID-19 are at high risk of thromboembolic complications such as deep vein thrombosis (DVT) and pulmonary embolism (PE).[3] A systematic review and meta-analysis by Suh, et al[4] reported that pooled incidence rates of PE and DVT in patients with COVID-19 were 16.5% (95%CI: 11.6-22.9) and 14.8% (95%CI: 8.5-24.5) respectively. Incidence of PE was higher in patients admitted to the ICU i.e. 24.7% (95% CI: 18.6-32.1) compared to 10.5% (95% CI: 5.1-20.2) in patients admitted to the general ward.[4]

About two centuries ago, German physician Rudolph Ludwig Karl Virchow described 3 factors that contribute to thrombosis namely endothelial vessel wall injury, venous stasis, and hypercoagulability widely known as the "Virchow's triad".[5] The primary function of the endothelium is maintenance of nonturbulent blood flow with homeostatic mechanisms to prevent thrombosis.[6] Meanwhile, viral particles of the SARS-CoV-2 virus penetrate the cells through the binding of spike-like protein (S-protein) with the angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor for SARS-CoV-2 is also present in endothelial cells. This endothelial invasion by SARS-CoV-2 leads to endothelial dysfunction and activates coagulation cascade, thereby contributing to thrombosis.[7] Furthermore, immobilization due to dyspnea and hypoxia induces thrombosis due to venous stasis and increasing blood viscosity.[8] Meanwhile, COVID-19-related hypercoagulable state and thrombotic complications are usually due to the increased thrombo-inflammation secondary to infection. This leads to severe hemostatic instability as typically seen in septic patients which promotes coagulation. Other complications include weakening of anticoagulation and fibrinolysis.[9]

Pulmonary embolism is a part of venous thromboembolism together with deep vein thrombosis (DVT).[10] As described above, COVID-19 hypercoagulable state leads to activation of the coagulation cascade. This process occurs throughout systemic circulation. In a classic case of pulmonary embolism, about 70% of patients have lower extremity

DVT.[10] However, in this study, lower extremity ultrasound did not find any evidence of DVT. The pathophysiology of hypercoagulation in COVID-19 differs from classic cascade activation caused by other infections. Given that pulmonary involvement is common in COVID-19, researchers have postulated a hypothesis on the pathogenesis of this coagulation process, which is termed pulmonary intravascular coagulation (PIC).[11] In the PIC process, the binding of SARS-CoV-2 to ACE 2 receptor on type II pneumocytes and endothelium increases procoagulant activity and activates the coagulation cascade.[11] This mechanism is assumed to be responsible for the formation of microthrombi in the lung capillaries. This process continues and promotes systemic coagulation. The thrombus produced travel through the systemic circulation and clog the pulmonary artery.

Several available modalities are used to diagnose pulmonary embolism. Point of care testing such as electrocardiography and bedside echocardiography aid pulmonary embolism diagnosis. However, these techniques lack sensitivity and specificity.[10] The classic McGinn White ($S_1Q_3T_3$) pattern occurs rarely. The electrocardiogram is useful in exploring the possibility of other differential diagnoses such as acute myocardial infarction and pericarditis.[10] Similarly, echocardiography is used to evaluate indirect signs of pulmonary embolism. The thrombus is rarely demonstrated in the echocardiogram.

Lung scintigraphy or ventilation-perfusion scan was used extensively in patients suspected of pulmonary embolism. However, perfusion defects might also be caused by other pathologies such as lung consolidation, fibrosis, and malignancy. In this COVID-19 pandemic era, CT pulmonary angiography is a versatile modality. Aside from being used to diagnose or exclude pulmonary angiography, the lung window also provides information on the extent of damage caused by COVID-19 to the lungs i.e., the amount of ground glass opacities. This modality also provides information on consolidation, tumors, and pleural diseases.

In acutely ill patients at general wards, initial treatment with LMWH have advantages in terms of minimal drug–drug interactions and risk of rapid clinical deterioration compared to oral treatment. Current guidelines by the International Society of Thrombosis and Hemostasis (ISTH) suggest LMWH for thromboembolism prophylaxis in hospitalized COVID-19 patients.[12] This is due to the simplicity in administration and low risk of drug-drug interaction. In cases of acute VTE, anticoagulants are given in therapeutic doses. In this study, the patient was treated with enoxaparin 6.000 IU (0.6 mL) bid subcutaneously.

Direct Oral Anti Coagulants (DOACs) provide advantages over vitamin K antagonists (VKAs), especially in the post-hospital setting, because it is safer, and does not require routine monitoring. Nevertheless, in hospitalized COVID-19 patients, DOAC is not recommended due to potential drug-drug interaction with antivirals.[13] Furthermore, VTE in COVID-19 patients is induced by a reversible risk factor, therefore, a treatment duration of 3 months is advised. An initial LMWH. Enoxaparin 0.6 mL was administered twice daily to the patient and then Rivaroxaban after discharge for 3 months.[14] Rivaroxaban and other DOACs are considered safe after discharge given that the patient had already finished the prescribed antibiotics and antivirals.

COVID-19 is often accompanied by thromboembolic complications. Meanwhile, pulmonary embolism occurs in COVID-19 patients without DVT. Based on the results, parenteral anticoagulant followed by DOAC is the mainstay of treatment in COVID-19 coagulopathy.

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