Covid-19 Cases Developing Dyspnea Under Anticoagulant Treatment

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Abstract:
Coronavirus disease 2019 (COVID-19) infection is thought to increase thrombotic events by activating coagulation system and making endothelial damage. The frequency of severe acute respiratory syndrome coronavirus 2 pneumonia and pulmonary embolism has drawn attention. There are recommendations for prophylactic low-molecular-weight heparin (LMWH) for COVID-19 at hospitalized patients. However, there is no consensus regarding the duration and doses of LMWH given with COVID-19 treatment. We presented three cases of pulmonary embolism at different times of COVID-19 infection who were diagnosed with pulmonary embolism under anticoagulant treatment. Subsegmental thrombus was detected in computed thoracic pulmonary angiography in all cases and treated with LMWH in the hospital, two cases were discharged with warfarin and one case with LMWH. Care should be taken in dyspnea that develops in the of COVID-19 infection, especially in terms of subsegmental pulmonary embolism. This paper shows that COVID-19 is an important risk factor for venous thromboembolism and the duration and dose of anticoagulant treatment should be re-evaluated.

Keywords:
Anticoagulant agents, low-molecular-weight heparin, pulmonary thromboembolism, severe acute respiratory syndrome coronavirus 2, thrombosis

Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which started in China and spread all over the world, is a newly developed infectious disease in humans. Acute respiratory distress syndrome (ARDS) and multi-organ dysfunction have been observed in severe SARS-CoV-2 patients. Novel CoV disease 2019 (COVID-19) infection is a disease associated with systemic inflammation, activation of the coagulation system, and endothelial dysfunction. Venous thromboembolism (VTE) is at higher risk of developing COVID-19 in the acute phase of the disease. In studies, the coexistence of COVID-19 and VTE was found to be high. VTE has been found to be responsible for some of the morbidity and mortality in COVID-19 disease. Although prophylactic doses of anticoagulants are recommended in hospitalized patients with SARS-CoV-2 pneumonia, the diagnosis of VTE is high. There are recommendations for higher doses of heparin for thromboprophylaxis in hospitalized high-risk COVID-19 patients. The Italian Drug Agency has recommended 80–100 mg of enoxaparin instead of 40 mg of enoxaparin per day for hospitalized high-risk COVID-19 patients.

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We presented three cases had COVID-19 infection and developed pulmonary embolism despite taking anticoagulants at different times of the infection.

Case Reports

Case presentation-1
A 67-year-old male patient with no comorbidities; he was admitted to the emergency department with the complaint of dyspnea. In physical examination; the pulse: 84 beats/min, blood pressure (BP): 117/85 mmHg, respiratory rate (RR): 28/min, SpO2 was 80% in room air. The left lower leg was more edematous than the right. D-dimer level was 3.5 mg/L at his emergency admission. The patient who was positive for COVID-19 18 days ago, was hospitalized for 9 days since the diagnosis of COVID-19. The patient received enoxaparin 1 × 60 mg during hospitalization and was discharged with the same dose. Two days after discharge, acute deep-vein thrombosis (DVT) was detected in lower extremity venous Doppler ultrasound, and warfarin treatment was initiated, and enoxaparin was increased to 2 mg × 60 mg. He was admitted to the emergency department on the seventh day of DVT treatment. A subsegmental thrombus was detected in computed thorax pulmonary angiography (CTPA) performed with the suspicion of pulmonary thromboembolism (PTE) [Figure 1]. He was hospitalized and given nasal oxygen support and low-molecular-weight heparin (LMWH). Warfarin dose was regulated to keep the INR value between 2.5 and 3, and discharged.

Case presentation-2
A 40-year-old woman presented to the emergency service with dyspnea and 1 teaspoon of hemoptysis per day for 3 days. Her vital signs were in normal values. Pulmonary and cardiac system examinations were normal. The patient, who had a history of recurrent miscarriage and stillbirth, was diagnosed with PTE 4 years ago. Heterozygous mutation was detected in the TTC37 NM-014639.3 gene in previous genetic analysis. She has been under anticoagulant treatment for 4 years and has been using rivaroxaban 20 mg/day regularly for the last 2 years. The COVID-19 polymerase chain reaction (PCR) test was positive, who was found to have a subsegmental filling defect in the CTPA taken at the emergency admission [Figure 2]. DVT was not detected in the lower extremity venous Doppler ultrasound. Desaturation did not develop in the follow-up of the inpatient and her treatment was changed to enoxaparin 2 mg × 60 mg.

Case presentation-3
A 65-year-old male patient with a history of smoking 16-packs/year, asthma, and diabetes presented to the emergency room with dyspnea and chest pain. At the emergency admission, the pulse was 120 beats/min, BP: 100/60 mmHg, RR: 36/min, 10 L/min nasal O2 support, and SpO2 was 58%. COVID-19 PCR was positive 44 days ago and received 1 mg × 40 mg enoxaparin. He applied to the outpatient clinic with right leg pain 11 days ago, was found to have acute DVT in lower extremity venous Doppler ultrasound, and enoxaparin was started at 2 mg × 60 mg. On the 11th day of the enoxaparin, CTPA taken to the patient who was admitted to the emergency department revealed a filling defect in the subsegmental branches and an appearance of ~1 cm wide and 2 cm long intracortical thrombosis in the distal part of the aorta [Figure 3]. He was taken to the intensive care unit, 2 mg × 80 mg enoxaparin was started. Warfarin was added by adjusting the INR value between 2.5 and 3 and he was discharged with nasal oxygen support.

Discussion
COVID-19 infection can often progress with mild
symptoms. Less frequently while rapidly progressing causes severe pneumonia and ARDS in patients; it can also be mortal by causing complications such as thromboembolic events such as PTE.\(^2\) In a study conducted on patients diagnosed with COVID-19, they found that D-dimer and fibrin degradation product levels, which are known to be risky in terms of the prothrombotic process, were higher in the mortal group.\(^6\) In COVID-19 patients with high D-dimer levels, the association of reduced mortality with anticoagulant drugs added to the treatment has been shown, but it is not clear how long the treatment should continue.\(^3\) It is thought that COVID-19 infection increases the risk of VTE by direct or indirect endothelial damage, micro-thrombotic disease with inflammation, stasis due to immobility.\(^7\) COVID-19 was not among the previously identified VTE risk factors for nonsurgical hospitalized patients, but it is predicted that it will be added to the guidelines with an increased risk.\(^2\) D-dimer was within the normal range in one of our cases who developed VTE under anticoagulant treatment. For patients at high clinical risk of pulmonary embolism, D-dimer does not rule out. As in our cases, the thrombus was predominantly located in the small branches of the pulmonary artery. It is likely that some of the diagnoses of subsegmental pulmonary embolism will be missed in COVID-19 patients who are young or/and without comorbidity. In the cases we presented, PTE developed under anticoagulant. In new guidelines, it has been recommended to switch to LMWH in COVID-19 patients with recurrent VTE while receiving treatment with apixaban, dabigatran, rivaroxaban, or Vitamin K antagonists.\(^10\) COVID-19 poses a high risk in terms of thrombosis, although there are no previously identified risk factors. In terms of VTE as in our cases, PTE was observed to develop even under anticoagulant treatment after COVID-19 infection, so the criteria for discharge need to be determined. We recommend that COVID-19 patients with VTE should keep their INR values higher and increase their follow-up.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**References**