Six cases of acute pulmonary embolism in patients with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) can cause severe respiratory distress syndrome requiring intensive care. Recent studies suggest that SARS-CoV-2 infection predisposes to thromboembolic events such as pulmonary embolism. The overlap between signs and symptoms of pulmonary embolism and COVID-19 presents a diagnostic challenge and could potentially be fatal. This case series describes six cases of pulmonary embolism associated with COVID-19. Based on our findings, we suggest administering prophylactic anticoagulation to all patients hospitalised with COVID-19.

Keywords: Coronavirus; COVID-19; Deep vein thrombosis; Pulmonary embolism; SARS-CoV-2

1. Introduction

Since December 2019, people worldwide have been affected by coronavirus disease 2019 (COVID-19) caused by the new coronavirus, SARS-CoV-2 [1].

The most common symptoms of COVID-19 are fever, cough, dyspnoea, myalgia, and fatigue. Patients may also have diarrhoea, headaches, sputum and haemoptysis. Most cases (81%) are moderate and may be accompanied by pneumonia, which seems to be the most serious manifestation of disease. Meanwhile, 14% of patients develop severe illness with dyspnoea and hypoxia, and 5% develop myocarditis, experience respiratory failure, shock, or multiple organ dysfunction syndrome [2].

Although COVID-19 is known to trigger a proinflammatory and hypercoagulable state, it remains difficult to estimate the risk of thromboembolism given the different diagnostic strategies and preventive measures of local health systems [3]. According to the literature, the incidence of thromboembolic events (pulmonary embolism and deep vein thrombosis) is between 1.6% and 2.4% in patients in acute care, and between 3.3% and 31% in critically ill patients [3-6].

In this paper, we present 6 cases of pulmonary embolism in COVID-19 patients in our hospital between 15 March and 30 April 2020. Patient characteristics are presented in Table 1.

2. Case presentations

2.1. Case 1

A 58-year-old woman was sent to emergency with a sudden onset of dyspnoea associated with right-sided lower chest pain. Her relevant medical history included hypothyroidism treated with hormone replacement therapy and high blood pressure treated with angiotensin-converting enzyme (ACE) inhibitors.

The patient had a prior hospitalisation for mild respiratory failure in the context of COVID-19, diagnosed by a PCR (Polymerase Chain Reaction) test for SARS-CoV-2 and a chest CT scan indicative of viral pneumonia. During her hospital course, the patient had responded well to oxygen therapy and hydroxychloroquine. Her condition had improved and she had been discharged after 4 days in the hospital.

Seven days after discharge, the patient presented to the emergency department. On admission, she was pale, afebrile, and was complaining of acute right-sided lower chest pain radiating to the right hypochondrium and right flank. On exam, her temperature was 37.3°C, her heart rate was 96 beats per minute (BPM), and her oxygen saturation was 97% on room air. Auscultation of the heart and lungs was normal.

Laboratory results showed signs of inflammation (Table 2) and an increase in D-dimers (1.91 mg/l). Arterial blood gases (ABG) (Table 3) and electrocardiogram (ECG) were non-specific. Blood culture and urinalysis were also unremarkable. Given the elevated D-dimers, a chest CT angiogram was ordered and revealed a bilateral pulmonary embolism primarily affecting the right side. Thrombi were found in various segmental arteries in the three right lobes and at the subsegmental level in the left lower lobe posterior segment. Chest CT scan also showed a peripheral pulmonary infarction in the right lower lobe lateral segment, multifocal peripheral ground glass opacities consistent with COVID-19, as well as mild bilateral pleural effusion and a small pericardial effusion.

Transthoracic echocardiogram (TTE) did not show signs of acute right-sided heart failure. A Doppler ultrasound of the legs was not done in the emergency department. The patient was admitted and started on low-molecular-weight heparin (LMWH) anticoagulant therapy. She progressed well during admission.

2.2. Case 2

A 78-year-old woman presented to emergency with a fever associated with cough, asthenia, myalgia, headache, and a loss of appetite ongoing for 10 days. In terms of medical history, she was being treated for high blood pressure and high blood cholesterol.

On admission, she had a 38.9°C fever, her heart rate was 73 BPM, her blood pressure was 140/80 mmHg, and her oxygen saturation was 93% on room air. Bilateral basal crackles were heard on auscultation. The rest of the physical exam was unremarkable. Laboratory results (Table 2) indicated lymphopenia, D-dimers at 1.19 mg/l, and CRP at 73 mg/l. An ABG test measured the partial pressure of oxygen at 59.9 mmHg, indicating hypoxaemia (Table 3). ECG

showed a known left bundle branch block and a QT interval over 500. Urinalysis was unremarkable. A PCR test returned positive for SARS-CoV-2.

Chest CT scan with contrast (Fig. 1) showed two non-occlusive pulmonary emboli in the branches of bilateral lower lobes. The lung window showed multiple bilateral and subpleural ground glass opacities, consistent with COVID-19.

TTE did not show signs of acute right-sided heart failure. The patient was admitted and started on LMWH anticoagulant therapy. She progressed well during admission.

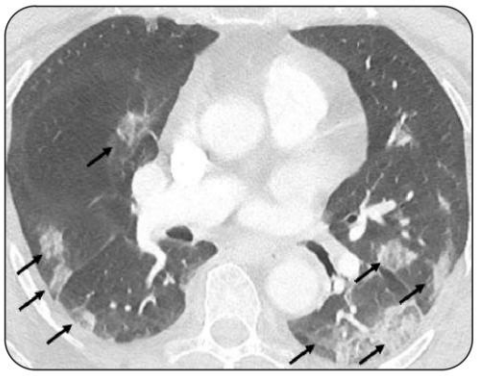

Fig. 1

Lung window of chest CT scan showing multiple bilateral ground glass opacities.

2.3. Case 3

A 37-year-old man with no significant medical history was brought to emergency for syncope without prodrome leading to loss of consciousness.

Upon arrival at emergency, the patient complained of nausea and holocranial headache. He had a fever of 37.9°C. The rest of his vital signs, physical and neurological exams were unremarkable. Laboratory results (Table 2) indicated lymphopenia, D-dimers at 5.30 mg/l, and CRP at 19 mg/l. ABG revealed respiratory alkalosis. Both a COVID-19 antigen test and a SARS-CoV-2 PCR test via nasopharyngeal swab returned negative. Urinalysis was normal.

Brain CT scan without contrast done in the emergency department was unremarkable. Chest CT scan, performed straight away with contrast, revealed a pulmonary embolism affecting several segmental and subsegmental branches of the left lower lobe. Other emboli were found in two subsegmental branches of the right lower lobe. In the lung window, many ground glass opacities and areas of pulmonary consolidation in the periphery and subpleural region of the right lower lobe were observed. These findings are consistent with early COVID-19.

The patient was admitted and started on LMWH anticoagulant therapy. He progressed well during admission.

2.4. Case 4

A 40-year-old woman with no significant medical history presented to emergency with dyspnoea associated with right-sided lateral chest pain ongoing for 5 days.

On admission, the patient was eupnoeic and afebrile. She had a tachycardia of 130 BPM and was hypoventilating. Basal crackles were noted in the right lung as well as tenderness of the lower right chest on palpitation. The rest of the physical exam was unremarkable.

Laboratory results (Table 2) indicated D-dimers at 6.63 mg/l, and CRP at 145 mg/l. ABG indicated mild hypoxaemia with a PaO2 of 70.1 mmHg (Table 3). ECG measured a tachycardia of 112 BPM. Both a COVID-19 antigen test and a SARS-CoV-2 PCR test returned negative. Urinalysis was normal.

Chest CT scan with contrast revealed a rather large bilateral pulmonary embolism affecting most of the branches of the right pulmonary artery, including many segmental and subsegmental branches. On the left side, many main branches of the pulmonary artery were affected along with segmental and subsegmental branches. We also noticed a right pleural effusion and subpleural ground glass opacities in the periphery of bilateral upper lobes and the middle lobe, consistent with COVID-19.

The patient was admitted and started on anticoagulant therapy. She progressed well during admission.

2.5. Case 5

A 78-year-old man with a history of exercise-induced asthma was admitted to emergency after suffering a cardiac arrest at home, preceded by syncope with chest pain. After 20 minutes of out-of-hospital CPR and an endotracheal intubation, return of spontaneous circulation was achieved and the patient was transferred to the hospital.

Upon arrival to emergency, the patient was sedated and intubated. Laboratory results (Table 2) showed signs of inflammation, elevated D-dimers (25 mg/l), renal failure, liver enzyme alteration, and elevated bilirubin and ferritin. An ABG test performed under mechanical ventilation showed respiratory acidosis. ECG revealed an atrial fibrillation with rapid ventricular response (130/minute). A PCR test returned positive for SARS-CoV-2.

Chest CT scan with contrast (Fig. 2) showed a massive bilateral pulmonary embolism, lung congestion in bibasilar alveoli, especially on the left side, and ground glass opacities consistent with COVID-19. TTE showed pulmonary hypertension with a right ventricular-right atrial gradient of 45 mmHg. The pericardium was normal and the inferior vena cava was dilated with inspiratory collapse.

The patient was transferred to intensive care for further treatment. He progressed well during admission.

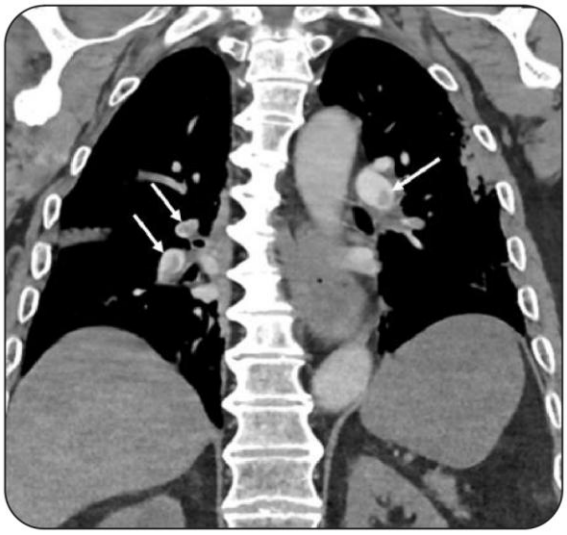

Fig. 2

Chest CT angiogram showing bilateral pulmonary embolism.

2.6. Case 6

A 64-year-old man with no significant medical history presented to emergency with dyspnoea associated with a sudden onset of right-sided lower chest pain at home.

The patient had been hospitalised 10 days earlier for hypoxaemic COVID-19 pneumonia. He had improved after treatment with hydroxychloroquine and oxygen and had been discharged.

On exam in the emergency department, he had a tachycardia of 110 BPM and crackles, most notably at the base of the right lung. Laboratory results showed elevated D-dimers (2.29 mg/l), inflammation (CRP 97 mg/l), and hyperbilirubinaemia (Table 2). ABG demonstrated hypoxaemia (59.3 mmHg) (Table 3).

Chest CT angiogram showed a bilateral pulmonary embolism with the most proximal end reaching the lobar arteries on the right and the segmental arteries on the left.

We also noticed the persistence of subpleural ground glass opacities in the periphery, most notably at the base of the lungs, consistent with the context of COVID-19. The extent of the ground glass opacities was comparable to previous findings. TTE showed no cardiac involvement.

The patient was admitted for oxygen and anticoagulant therapy. He progressed well during admission.

3. Discussion

The reported incidence of pulmonary embolism associated with COVID-19 differs in the literature. Recent studies suggest that the incidence rate of severe pulmonary embolism in

COVID-19 patients in intensive care will exceed 10% [7]. Although the causes of pulmonary embolism in this context are still not completely clear, many aetiologies have been proposed.

Smeeth et al. [8] have demonstrated an increased risk of thromboembolic events, especially deep vein thrombosis and pulmonary embolism, in acute infections. The link between pulmonary embolism and viral pneumonia was also suggested in the previous SARS epidemics in 2002-2003 [9]. Visseren et al. [10] reported prothrombotic activity in endothelial cells infected by respiratory viruses in their *in vitro* study.

Furthermore, Gralinski et al.'s study [11] demonstrated that the SARS virus interacts with urokinase to induce a hypercoagulable state in an animal model. Therefore, SARS-CoV-2 infection may increase the risk of thrombosis through the inflammatory response linked to infection. The severity of infection may correlate with an increase in D-dimers, and thus may partly be linked to the development of coagulopathy. A Chinese case series [12] reported that 36% of patients infected with SARS-CoV-2 had elevated D-dimers.

In our study, we also note an elevated neutrophil-to-lymphocyte ratio (NLR) in 4 of 6 patients (Table 2). An elevated NLR indicates a systemic inflammatory response. While NLR is used to predict the prognosis of cardiovascular disease and neoplasia, an elevated NLR can also be seen in cases of COVID-19 [13] and pulmonary embolism [14]. In fact, the increased production of neutrophils associated with inflammation could also contribute to a prothrombotic state, most notably through the extrusion of DNA in a process called NETosis [15].

We report two cases of pulmonary embolism that occurred at home after discharge. Decreased physical activity from quarantine and bed rest during admission along with COVID-19 infection are factors that may increase the risk of lower extremity deep vein thrombosis and pulmonary embolism.

In our case series, all patients had bilateral emboli affecting not only the main branches of the pulmonary arteries, but also the segmental and subsegmental branches. This topography may suggest that the thrombus originated at another site, for example from a deep vein thrombosis (DVT). Therefore, investigation of DVT via Doppler ultrasound of the legs may be indicated in COVID-19 patients with elevated D-dimers. Unfortunately, this test was not performed on any of the patients in our case series.

However, in two other case series by Lodigiani et al. [3] and Helms et al. [4], most of the COVID-19 patients that suffered from pulmonary embolism did not have an associated DVT. Rodríguez et al. [16] remarked that the incidence of DVT in patients admitted for COVID-19 was no higher than those without COVID-19. It seems then that pulmonary embolism is more so caused by lung inflammation rather than DVT.

Pulmonary embolism in COVID-19 patients can be fatal and is difficult to diagnose given the overlap in symptoms. In this case series, the laboratory results were typical of SARS-CoV-2 infection: lymphopenia, high levels of ferritin, lactate dehydrogenase and CRP [2]. ABG results

were non-contributory. This would suggest that hypoxaemia may not be directly linked to pulmonary embolism but to the degree of lung inflammation.

Chest CT scans of every patient in this study showed signs of COVID-19, but in each case affecting less than 25% of the lung parenchyma. Two of the six patients tested negative for SARS-CoV-2 via PCR.

One patient had a cardiac arrest with massive pulmonary embolism. The other patients had no cardiac complications as a result of pulmonary embolism.

Presently, some authors [7] propose the following classification of patients based on thrombotic risk:

- Low risk: non-hospitalised patients with a body mass index (BMI) <30 kg/m², and no associated risk factors.

- Moderate risk: patients with a BMI <30 kg/m², with or without associated risk factors, and not requiring high-flow nasal cannula (HFNC) oxygen therapy or mechanical ventilation.

- High risk: BMI <30 kg/m², with or without risk factors, and on HFNC or mechanical ventilation; BMI >30 kg/m² without associated risk factors; BMI >30 kg/m² with associated risk factors, and on HFNC or mechanical ventilation.

- Very high risk: BMI >30 kg/m² with risk factors, and on HFNC or mechanical ventilation.

Overall, we recommend strictly inpatient prophylactic anticoagulation for every patient hospitalised with COVID-19.

The same authors proposed administering a 4000 lU/24h subcutaneous (SC) dose of enoxaparin for moderate risk patients, a 4000 IU/12h SC dose of enoxaparin for high risk, and a curative dose of enoxaparin (100 IU/kg/12h SC) for very high risk. In cases of renal failure (creatinine clearance <30 ml/min), administration of unfractionated heparin (UFH) is recommended at a dose of 200 IU/kg/24h for high risk and 500 IU/kg/24h for very high risk. It is also recommended to adjust the dosage of enoxaparin for patients over 120 kg, as well as based on regular anti-Xa monitoring [7].

Based on recent recommendations from a panel of experts [17], direct oral anticoagulants (DOAC) are a good alternative for patients with no contraindications. For critically ill patients with pulmonary embolism or DVT, LMWH or fondaparinux are preferred over DOAC. The course of anticoagulation must be three months. In case of a recurrent thromboembolic event on DOAC, the patient should be switched to LMWH [17].

4. Conclusion

COVID-19 is a possible risk factor for thromboembolic events. Patients with COVID-19 often have elevated D-dimers, and pulmonary embolism should be suspected especially if the patient

presents with dyspnoea, chest pain, or desaturation. Diagnosis should be done by chest CT angiography or V/Q scan when angiography is contraindicated. Anticoagulation must be initiated if pulmonary embolism is detected. Prophylactic anticoagulation should be considered in patients presenting with COVID-19.

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