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SHORT COMMUNICATION

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The novel coronavirus disease (COVID-19) complicated by pulmonary embolism and acute respiratory distress syndrome

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Abstract

Acute respiratory distress syndrome and coagulopathy played an important role in morbidity and mortality of severe COVID-19 patients. A higher frequency of pulmonary embolism (PE) than expected in COVID-19 patients was recently reported. The presenting symptoms for PE were untypical including dyspnea, which is one of the major symptoms in severe COVID-19, especially in those patients with acute respiratory distress syndrome (ARDS). We reported two COVID-19 cases with coexisting complications of PE and ARDS, aiming to consolidate the emerging knowledge of this global health emergency and raise the awareness that the hypoxemia or severe dyspnea in COVID-19 may be related to PE and not necessarily always due to the parenchymal disease.

KEYWORDS

ARDS, COVID-19, hypoxemia, PE

1 | INTRODUCTION

The novel coronavirus disease (COVID-19) pandemic had killed more than 400 000 people. About 5% of COVID-19 patients experience complications including septic shock, acute respiratory distress syndrome (ARDS), acute cardiac or kidney injury, and disseminated intravascular coagulation (DIC).[1] These complications are thought to be manifestations of the cytokine storm triggered by the host immune response of the virus.[2] In critically ill patients, ARDS was the most common complication in 67% of the patients with a 28-day mortality of 61.5%. DIC has been widely reported in COVID-19.[1,3-8] Pulmonary embolism (PE) in COVID-19 patients has been reported in a few studies.[9,10] A recent study pointed to a higher incidence of PE with 23% in severe COVID-19 patients.[11] The relationship between virally triggered inflammation, venous thromboembolism, and ARDS in COVID-19 is still under investigation. Given that patients with severe COVID-19 often present with shortness of breath and pulmonary infiltrates, the diagnosis of PE may be overlooked in the context of an ARDS diagnosis. In this report, we describe the clinical presentation, laboratory results, and imaging findings in two COVID-19 patients who developed PE concurrently with ARDS.

2 | CASE 1

A 57-year-old male patient living in Wuhan, China with unknown medical history presented with fatigue and chills for 10 days and worsening shortness of breath for 2 days. He was a nonsmoker. Vital signs on presentation were $T = 36.7°C$, HR = 78 bpm, BP = 129/89 mm Hg, RR = 35 breaths/minute. Mild cyanosis of the lips was noticed as well as bilateral coarse breath sounds were heard at auscultation. The laboratory tests showed slight leukocytosis (white blood cell count: 11.75×10^9/L) with reduced lymphocytes (14.6%, normal range 20%-50%), elevated C-reactive protein

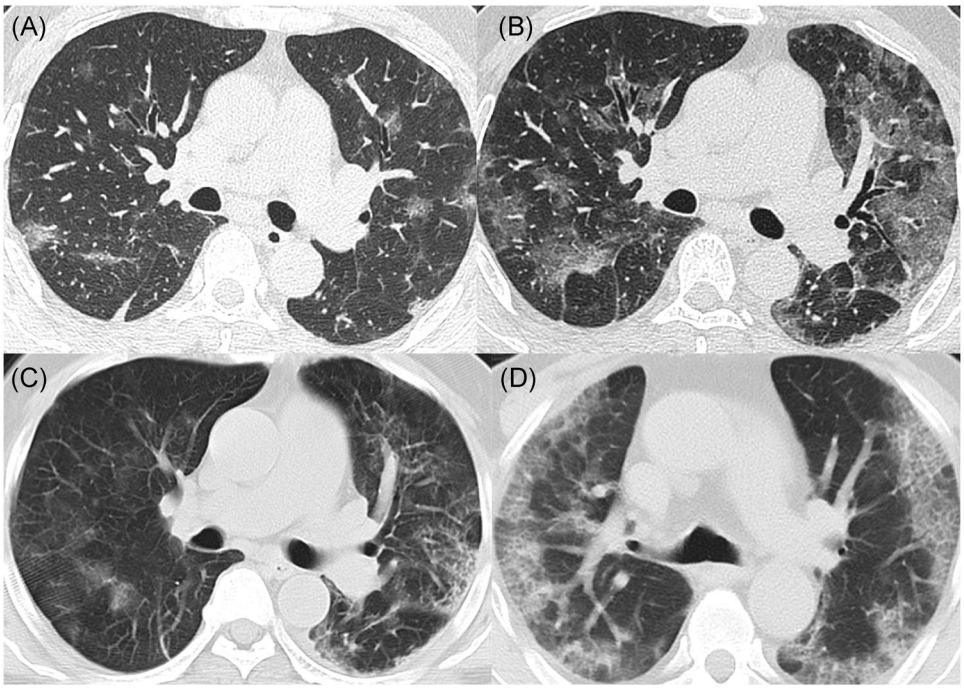

FIGURE 1 Case 1 (A-C). A, Ten days before admission. Scattered patchy of peribronchovascular and subpleural ground glass opacities was seen in bilateral lungs. B, Five days before admission. Diffuse and confluent ground-glass opacities with reticulation, interlobular septal thickening in bilateral lungs showed progression of the disease. C, Day 3 after admission. Ground-glass opacities were partially resolved with more linear densities when compared to prior CTs. D, Case 2. Chest CT on admission revealed Bilateral peripherally distributed confluent ground-glass opacities with superimposed inter- and intralobular septal thickening (crazy paving pattern). CT, computed tomography

(0.78 mg/dL; normal range, 0-0.5 mg/dL), increased level of brain natriuretic peptide (3032.00 pg/mL; normal range, <125 pg/mL) and significantly elevated levels of D-dimer (29.00 μg/mL fibrinogen-equivalent-units (FEU); normal range, 0-1 μg/mL FEU). The PaO_2/FiO_2 was 160.6 mm Hg and the patient was diagnosed with moderate acute respiratory distress syndrome (ARDS). The follow-up of the lab tests 3 days later after admission showed further increases in the level of D-dimer (38.73 μg/mL). Real-time fluorescence polymerase chain reaction (PCR) of the patient's sputum was positive for the SARS-CoV-2 nucleic acid.

An unenhanced chest computed tomography (CT) acquired at an outside clinic 10 days before admission showed multiple patches of peribronchovascular and subpleural ground-glass opacities bilaterally (Figure 1A). Five days later, a second unenhanced chest CT performed at an outside clinic before hospital admission showed diffuse and confluent ground-glass opacities superimposed with inter- and intralobular septal thickening (Figure 1B). After admission, the patient was treated with Ribavirin (antiviral medication), Cefoperazone-sulbactam (antibiotics), Methylprednisolone (anti-inflammatory medication), as well as supportive care with nasal cannula oxygen supplementation (3 L/minute). The CT imaging on hospital day 3 showed partial resolution and improvement of the ground-glass opacities (Figure 1C), however, the patient complained of progressive dyspnea. Due to the continuing elevation of D-dimer, venous thromboembolism (VTE) was suspected in this patient. A pulmonary CT angiography on hospital day 5 showed multiple emboli in the lobe and segmental pulmonary arteries (Figure 2A). The venous ultrasound showed the absence of lower extremity deep vein thrombosis. On the basis of epidemiologic history, clinical characteristics, laboratory findings and chest CT abnormalities, the diagnosis of COVID-19 pneumonia complicated by PE and ARDS was made. After adding the anticoagulant medications (Heparin calcium and Rivaroxaban), the patient's symptoms resolved at day 9 after admission and the PaO_2/FiO_2 improved from 160.6 to 236.4 mm Hg with nasal cannula oxygen supplementation (3 L/minute). A repeat Pulmonary CT angiography on hospital day 16 showed resolution of the pulmonary emboli (Figure 2B). The patient was discharged on hospital day 29.

3 | CASE 2

A 70-year-old male Wuhan resident with a history of hypertension presented to the hospital with 10 days of dyspnea, chills, and fever. He reported a history of active cigarette smoking of 50 pack-years. Vital signs on presentation were T = 39°C, HR = 75 bpm, BP = 130/86 mm Hg, RR = 20 breaths/minute. The laboratory tests on admission showed lymphopenia with a lower lymphocyte percentage (8%), the elevated C-reactive protein lever (5.68 mg/dL) and increased D-Dimer (9.36 μg/mL). Chest CT on admission revealed bilateral peripherally distributed confluent ground-glass opacities with crazy paving pattern (Figure 1D). The nasal swab PCR test was negative for the SARS-CoV-2. Due to the strong epidemiological link to Wuhan, unexplained acute respiratory symptoms, typical

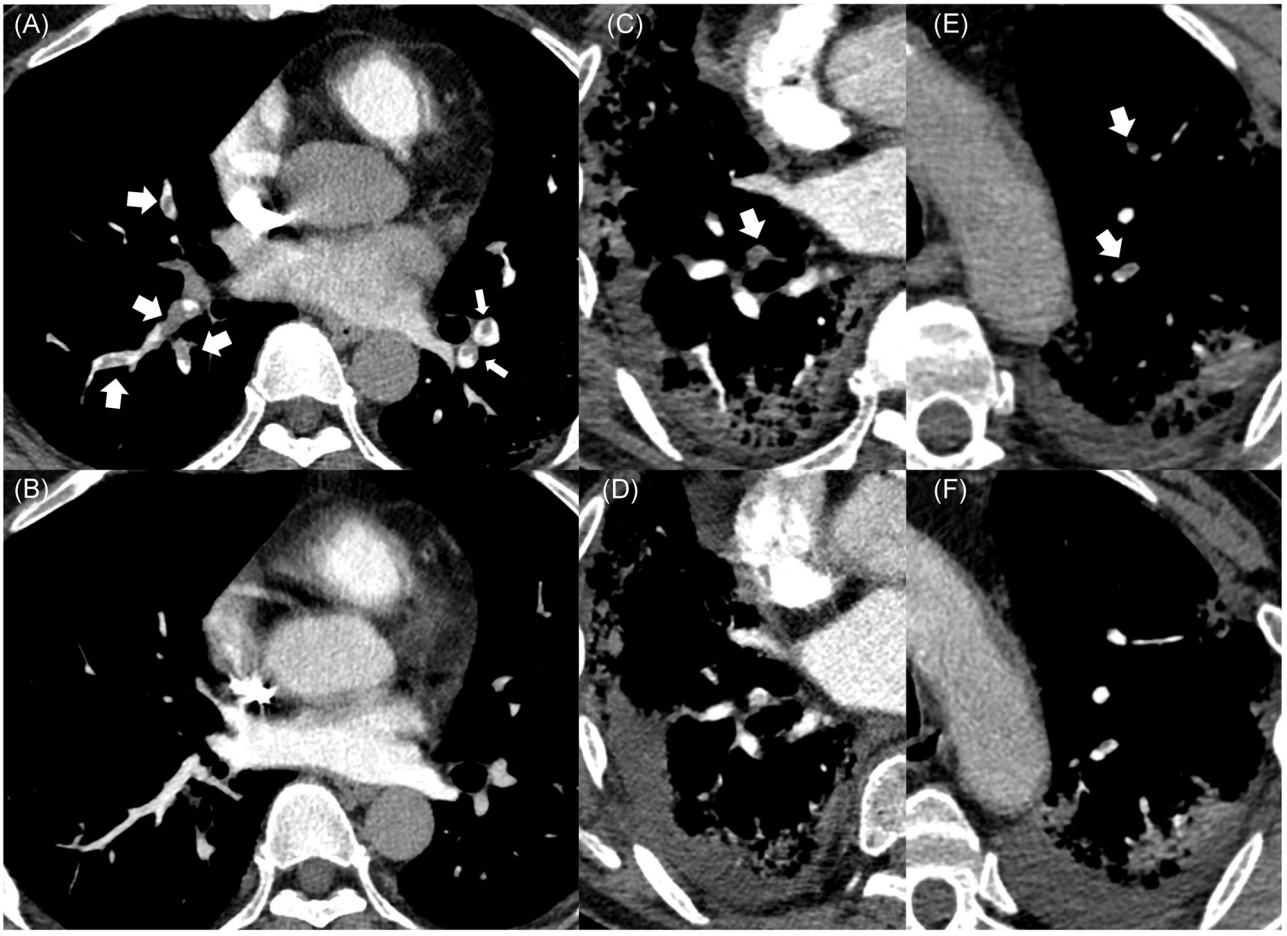

FIGURE 2 Case 1 (A,B). A, Multiple filling defects were seen in the right lobar, segmental and left segmental pulmonary arteries (arrows). B, The emboli resolved after anticoagulant treatment. Case 2 (C-F). C, Complete blockage of the right lower lobe medial basal segmental pulmonary arteries was seen (arrow). D, The emboli partially resolved after anticoagulant treatment. E, Filling defects were observed in the LUL segmental and subsegmental pulmonary arteries (arrows). F, The emboli partially resolved after anticoagulant treatment. LUL, left upper lobe

imaging, and absence of evidence of other respiratory pathogens, the patient was diagnosed with COVID-19. He was treated with ribavirin, ceftazidime, methylprednisolone, as well as oxygen supplementation with 3 L/minute. The follow-up of the lab tests on hospitalization day 3 and 6 showed further increase in D-dimer (17.22 μg/mL FEU and 19.35 μg/ml FEU, respectively). On hospital day 6, the PaO_2/FiO_2 remained 149 mm Hg with increased nasal cannula oxygen supplementation (4 L/minute). Pulmonary CT angiography was performed on hospital day 9 which revealed scattered bilateral segmental and subsegmental pulmonary emboli (Figure 2C,E). Lower extremity duplexes were negative for deep vein thrombosis. Heparin sodium was then started. The patient's symptoms improved 5 days later and the PaO_2/FiO_2 significantly improved to 297 mm Hg with nasal cannula oxygen supplementation (4 L/minute). The repeat pulmonary CT angiography performed on hospital day 16 showed partial resolution of the pulmonary emboli (Figure 2D,F). The repeat swab test on hospital day 28 was positive for the SARS-CoV-2 nucleic acid. The patient was discharged at hospital day 29 and transferred to another local hospital for further supporting treatment.

4 | DISCUSSION

Acute PE can occur in a variety of clinical contexts, and is known increase in-hospital morbidity and mortality.[12] Acute infection has been reported to trigger VTE independent of concomitant immobilization.[13] Notably, infection confers greater risk for PE than deep vein thrombosis. In addition, respiratory tract infection had a greater impact on VTE or PE than nonrespiratory infections.[14] An inflammatory coagulopathy due to the viral infection has been widely observed in COVID-19.[3-8] In this case series, the highly increased level of D-dimer raised the suspicion of VTE and diffuse pulmonary emboli without lower extremity deep vein thrombosis was found. Neither patient had typical VTE risk factors including major surgery, oncologic disease, trauma, or prior VTE. In the first case, the CT imaging showed partial resolution of the pulmonary abnormalities but with new pulmonary emboli. After anticoagulant treatment, there was prominent improvement of dyspnea as well as the PaO_2/FiO_2. In the second case, PaO2/FiO2 did not improve until the implementation of anticoagulant treatment. Both cases suggest that PE contributed to severe dyspnea and hypoxemia in these COVID-19. In murine models of ARDS, infection with influenza virus increases

platelet aggregation, pulmonary microvascular thrombosis, endothelial damage and hyperinflammatory cytokine responses.[15-17] A recent case series reported that fibrin deposition in the pulmonary microvasculature could be contribute to ARDS. Tissue plasminogen activator was used to prevent recurrence of the suspected pulmonary microvascular thrombosis underlying COVID-19 ARDS. Consequently, all three patients had initial improvement in the PaO_2/FiO_2.[8] While the causal inference among virally triggered inflammation, venous thromboembolism and ARDS in COVID-19 remain under investigation, it is important to be aware that persistent dyspnea or hypoxemia in COVID-19 can be related to PE, especially in the context of discordant clinical symptoms and parenchymal imaging findings later in the course of disease.

5 | CONCLUSION

Acute severe COVID-19 infection can trigger pulmonary embolism. The exact incidence of pulmonary embolism in COVID-19 patients is still unknown and is likely to be underestimated by the nonspecific presenting symptoms. For COVID-19 patients, the hypoxemia or severe dyspnea symptoms may be related to PE and not necessarily always due to the parenchymal disease.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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