



Cardiopulmonary Imaging Case Series

Thromboembolic Disease in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was initially recognized in late December 2019 and has quickly spread globally with over 114 million reported cases worldwide at the time of this publication. For the majority of patients infected with COVID-19, the clinical manifestations are absent or mild. In more advanced cases, severe respiratory dysfunction is the leading cause of morbidity and mortality. However, increasingly, there have been reports of increased thrombotic complications including pulmonary embolism and deep vein thrombosis seen in these patients. We present herein a series of cases of concomitant COVID-19 pneumonia and venous thromboembolism. These cases highlight the importance of clinical and radiologic vigilance to ensure this often clinically silent complication is not missed.

Keywords: COVID-19, Thrombus, SARS-CoV-2, Pulmonary embolism, Deep vein thrombosis

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially began in late December 2019, when a cluster of cases of pneumonia was reported in Wuhan Municipal Health Commission, China.^[1] It quickly spread globally and to date with over 114 million reported cases with over 2.5 million deaths worldwide at the time of the submission of this manuscript.^[2]

For the majority of patients infected with SARS-CoV-2, the clinical manifestations are absent or mild, mimicking common upper respiratory tract viral infections. In more advanced cases, severe respiratory dysfunction, requiring hospitalization and advanced respiratory support, is the leading cause of morbidity and mortality. The main findings in severe cases are bilateral pneumonia, acute respiratory distress syndrome (ARDS), systemic inflammation, coagulation activation, myocardial injury, and multi-organ failure.^[3] Increasingly, there have been reports of thrombotic complications including pulmonary embolism (PE), deep vein thrombosis (DVT), myocardial infarction, and ischemic stroke.

We present herein a series of cases of concomitant COVID-19 pneumonia and venous thromboembolism (VTE). These cases highlight the importance of clinical and radiologic vigilance to ensure this often clinically silent complication is not missed.

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CASES

Case 1

A 74-year-old male with a medical history significant for hypertension, presented to the emergency department (ED) with a 1 week history of cough and lethargy. In the ED, he was afebrile and slightly hypoxic requiring 2L of O₂ to maintain oxygen saturations above 90%. Physical examination demonstrated diffuse crackles on chest auscultation. His laboratory work-up showed a normal leukocyte count and an elevated D-dimer of 795 ng/mL (normal reference range ≤ 500 ng/mL). Testing of nasopharyngeal swab specimen by polymerase chain reaction (PCR) for COVID-19 was positive. Due to clinical concern for a possible PE, computed tomography (CT) angiogram of the chest and pulmonary arteries with intravenous (IV) contrast was performed. This was negative for an acute PE but showed diffuse patchy ground-glass opacities (GGOs) throughout both lungs [Figure 1a]. On day 3 of hospitalization, the patient developed progressive hypoxic respiratory failure with evidence of ARDS, requiring intubation and admission to the intensive care unit (ICU). On day 10 of admission, the patient was noted to have bilateral upper extremity edema. Upper extremity ultrasounds performed with color and spectral Doppler analysis demonstrated acute non-occlusive thrombus in the right internal jugular, left subclavian, and left axillary veins [Figure 1b]. The patient was commenced on IV therapeutic heparin and transitioned to Coumadin. Ultimately, the patient recovered with supportive cares and was extubated on day 25. He was dismissed after a prolonged 33 day hospital stay to continue on Coumadin for an unspecified duration.

Case 2

A 71-year-old female with a medical history of Type 2 diabetes mellitus and hyperlipidemia, presented to the ED with a 2

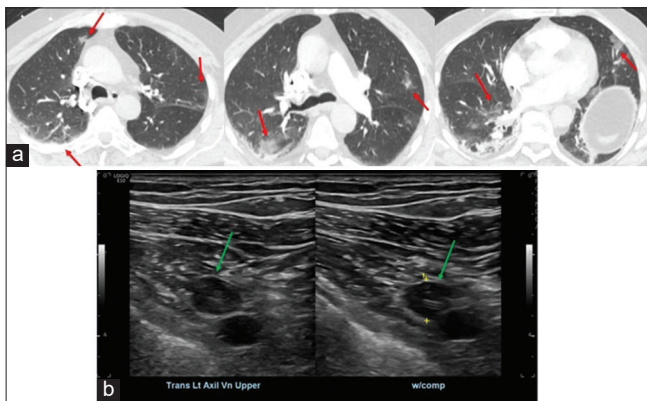


Figure 1: (a) A 74-year-old male presenting with cough and lethargy diagnosed with COVID-19. Contrast-enhanced axial chest computed tomography demonstrates bilateral patchy ground glass opacities (red arrows). (b) A left upper extremity gray-scale ultrasound demonstrated acute non-occlusive thrombus (green arrows) in the left axillary veins.

week history of intermittent fevers up to 38.2°C, dry cough, dyspnea, fatigue, reduced appetite with reduced taste, 2 kg unintentional weight loss, and diarrhea. In the ED, she was afebrile and hemodynamically stable, maintaining normal oxygen saturation on ambient air. Initial laboratory work-up was unremarkable with a normal leukocyte count and a D-dimer of 406 ng/mL. Nasopharyngeal swab PCR testing for COVID-19 was positive. A chest radiograph showed bilateral patchy airspace opacities in the lower lungs, greater on the left side [Figure 2a]. A lower extremity ultrasound was significant for an acute distal DVT with occlusive thrombus in the left soleal vein [Figure 2b]. The patient was commenced on oral anticoagulation (OAC) therapy with rivaroxaban and did not require hospital admission. After 3 months of OAC, follow-up ultrasound showed resolution of thrombus, and OAC was discontinued.

Case 3

A 49-year-old male with no significant medical comorbidities, presented to the ED with a 10 day history of progressive dyspnea, cough, and fevers. Laboratory tests were significant for an elevated D-dimer of 823 ng/mL. Nasopharyngeal swab PCR testing for COVID-19 was positive. CT angiogram of the chest with IV contrast was performed and was negative for acute PE, but revealed diffuse GGOs, bibasilar consolidation, left upper lobe collapse secondary to mucus plugging, and small pleural effusions bilaterally [Figure 3a]. He developed acute hypoxic respiratory failure secondary to severe ARDS, requiring emergency cricothyroidotomy. The patient was found to have an acute non-occlusive DVT of the right internal jugular vein [Figure 3b]. The patient was treated with IV therapeutic heparin with transition to Apixaban for 3 months. He was discharged after a 32-day hospital course.

Case 4

A 56-year-old male with a medical history significant for Type 2 diabetes mellitus, presented to the ED with a 10 day history of dry cough and worsening dyspnea. In the ED, he was hypoxic, with O₂ saturations of 73% on ambient room air. Initial laboratory tests were notable for an elevated D-dimer (30,934 ng/mL) and a normal leukocyte count. Nasopharyngeal swab specimen by PCR was positive for COVID-19. He was quickly intubated and transferred to the ICU. CT chest showed diffuse bilateral GGOs [Figure 4a] and bilateral upper lobe segmental pulmonary emboli [Figure 4b]. A lower limb Doppler ultrasound was positive for acute DVT in the left peroneal vein [Figure 4c]. Patient was initiated on Heparin drip and transitioned to Enoxaparin (Lovenox), which was briefly stopped briefly for anemia and then re-started. Patient passed away 1 month after initial admission secondary to multisystem failure.

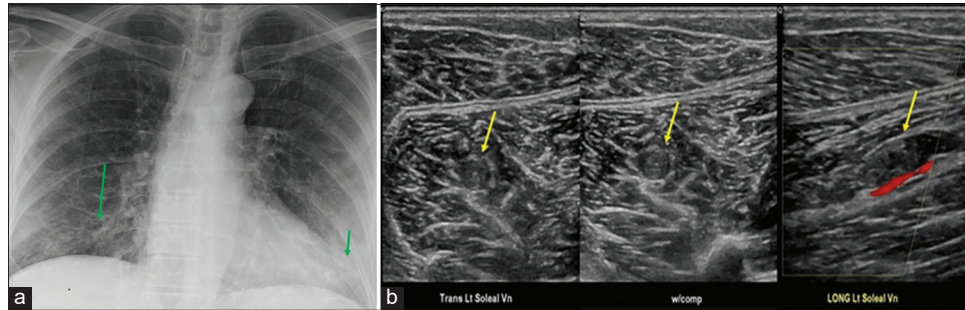


Figure 2: (a) A 71-year-old female presented to the emergency department with a 2 week history of intermittent fevers, dry cough, shortness of breath, reduced appetite with reduced taste, and diarrhea. A frontal chest radiograph showed bilateral patchy airspace opacities in the lower lungs, greater on the left side (green arrows). (b) Left lower extremity gray-scale ultrasound demonstrates a non-compressible left soleal vein (yellow arrows) with no flow consistent with occlusive deep vein thrombosis.

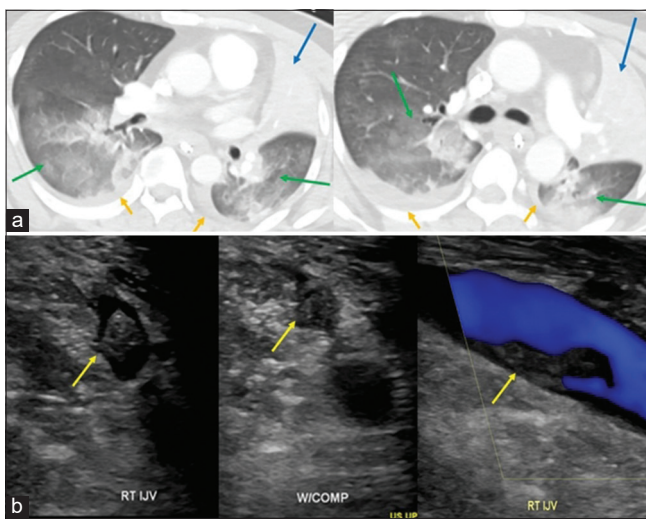


Figure 3: (a) A 49-year-old male with a 10 day history of progressive shortness of breath, cough, and fevers. Computed tomography of the chest with intravenous contrast demonstrated diffuse bibasilar ground-glass opacities (green arrows), left upper lobe collapse secondary to mucus plugging (blue arrows), and small pleural effusions (yellow arrows) (b) Color flow Doppler ultrasound of the neck demonstrates non-occlusive thrombus in the right internal jugular vein (yellow arrows).

Case 5

A 63-year-old male with a medical history of hypertension, presented to the ED with a 10 day history of dry cough, dyspnea, myalgia, and lethargy. The patient worked as an airline pilot and feared he may have been exposed to COVID-19 on recent flights. He had been self-isolating at home as directed by his primary care provider, however due to worsening dyspnea he presented to the ED. He was afebrile but hypoxic on admission, required intubation and ICU transfer. Nasopharyngeal swab specimen by PCR for COVID-19 was positive. Laboratory work was unremarkable apart from an elevated C-reactive protein of 8.3 mg/dL. CT chest demonstrated diffuse peripheral GGOs [Figure 5a] and a right lower lobar PE [Figure 5b].

Lower limb ultrasound was significant for bilateral posterior tibial DVTs [Figure 5c]. Patient was initiated on Heparin drip and transitioned to Apixaban. He was discharged to a nursing home and was lost to follow-up as he was from out of state.

DISCUSSION

COVID-19 induced lung injury with resultant acute respiratory distress is the most common cause for hospitalization in infected patients. Chest radiograph findings are non-specific and are those of atypical pneumonia or organizing pneumonia. Chest radiographs can be normal in early or mild disease. The majority of hospitalized patients will have abnormal radiographs either at presentation or during hospitalization. The radiographic findings when present include airspace opacities either consolidation or GGOs. CT is more sensitive and specific and plays a variable role in both diagnosis and prognostication. CT findings include GGOs, consolidation, crazy paving and less commonly pulmonary nodules, pleural effusions, and cavitation. Findings are most commonly bilateral and peripheral with lower zone predominance.

COVID-19 infection is associated with coagulation abnormalities. Multiple studies have reported a high prevalence of VTE in COVID-19 patients, with rates higher than usually reported in the ICU (0.4–2.0%) or the ED setting.^[4] It is postulated that this is due to an underlying pro-inflammatory state with coagulation activation.^[5] In particular, there is a marked elevation of the D-dimer value. While the majority of patients develop mild-to-moderate symptoms, others progress to acute lung injury and respiratory failure due to an exaggerated inflammatory response, which has been likened to disseminated intravascular coagulation (DIC). Connors and Levy described this as “thromboinflammation”^[6] and although comparable to DIC, there are important distinctions in the COVID-19 cohorts. DIC is characterized by systemic activation of blood coagulation with resultant widespread deposition of fibrin leading to microvascular thrombi in

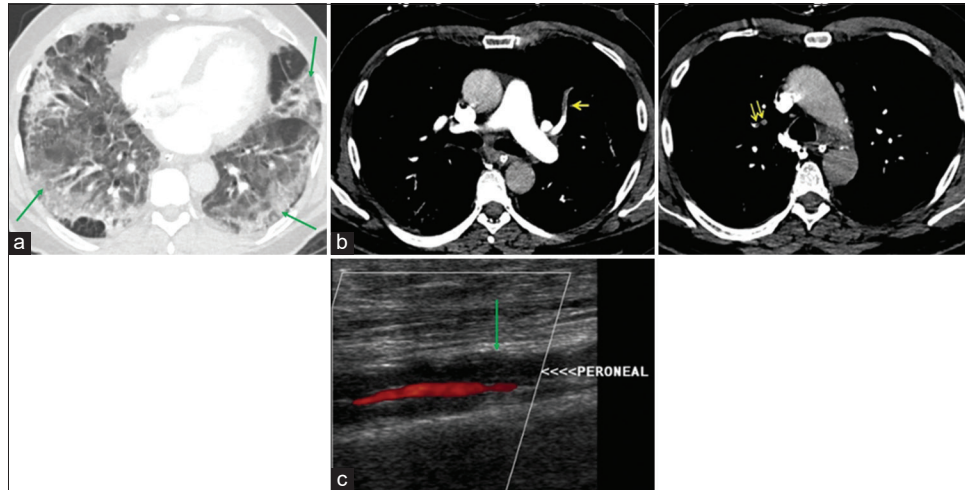


Figure 4: (a) A 56-year-old male presented to the emergency department with a 10 day history of dry cough and worsening shortness of breath. Initial laboratory tests were notable for an elevated D-dimer. Axial computed tomography of the chest showed diffuse bilateral ground-glass opacities (green arrows). (b) Bilateral upper lobe segmental pulmonary emboli were also present (yellow arrows). (c) A lower limb Doppler color flow ultrasound demonstrated lack of flow in the left peroneal vein (green arrow) in keeping with deep vein thrombosis.

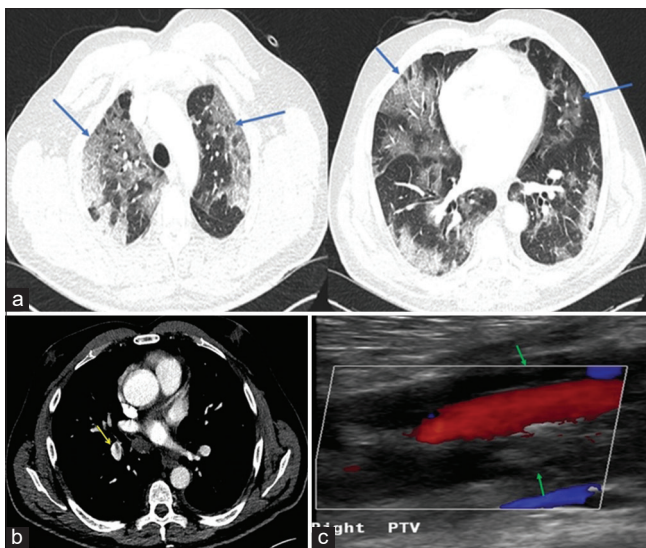


Figure 5: (a) A 63-year-old male who presented to the emergency department with a 10 day history of dry cough, dyspnea, myalgia, and lethargy. Computed tomography of the chest demonstrated diffuse peripheral ground-glass opacities (blue arrows). (b) Axial computed tomography angiography of the chest at the level of pulmonary arteries demonstrated a pulmonary embolus (yellow arrow) in the right lower lobar pulmonary artery. (c) Sagittal color flow Doppler ultrasound demonstrated non-compressible occluded right posterior tibial veins (green arrows).

various organs, similar to what is seen with COVID-19 infection. However, with DIC there is an associated consumption of clotting factors and platelets which, in turn, can result in potentially fatal hemorrhage. Consumptive coagulopathy and bleeding disorders have not been reported in COVID-19 infection.^[7]

Lodigiani *et al.* reported an approximately 8% rate of venous and arterial thromboembolic complications in hospitalized COVID-19 patients, despite the use of prophylactic anticoagulation.^[3] The authors acknowledge that this study was retrospective and that the true event rate may be an underestimation as only symptomatic patients were investigated for PE/VTE. Leonard-Lorant *et al.* demonstrated that 30% of CT pulmonary angiograms performed for COVID-19 patients were positive for acute PE, with higher D-dimer thresholds.^[8] Grillet *et al.* reported a high prevalence (23%) of acute PE in COVID-19 patients and noted that these patients were more likely to require care in the critical care setting and to require mechanical ventilation.^[9] Klok *et al.* reported a 31% incidence of thrombotic complications in ICU patients with COVID-19 despite the use of systemic thromboprophylaxis.^[10]

In addition to PE and DVT, multiple studies have emerged describing cerebral venous thrombosis (CVT) associated with COVID-19.^[11,12] The hypercoagulable state induced by COVID-19, with higher than normal D-dimer, fibrin, fibrinogen, and degradation products, is felt to be the etiology behind this usually uncommon cause of stroke. Zhang *et al.* reported a positive correlation between coagulopathy and antiphospholipid antibodies in patients with COVID-19 and cerebral infarcts^[13]. Cavalcanti *et al.*^[14] described a series of young patients, previously healthy patients, with COVID-19 and CVT, all of whom had a fatal outcome. Case reports studies also demonstrate a higher rate of CVT in more severe forms of COVID-19 infection. While the majority of these studies share the limitations of being predominantly retrospective single-center studies, they all address important emerging clinical questions and do so in a clearly defined way

with appropriate patient sampling and data analysis, providing important clinical insights which are widely applicable.

The overlap of symptoms between COVID-19 and PE creates a diagnostic dilemma for physicians. In the majority of our cases, D-dimer levels are elevated in both COVID-19 and PE and are therefore non-specific and unhelpful as a screening tool in this patient cohort. Hemoptysis is an infrequent symptom of COVID-19 but is reported in up to 13% of cases of PE and therefore may be useful in establishing pre-test probability.^[15]

Current guidelines recommend thoracic imaging with non-contrast CT for patients with moderate-to-severe symptoms of COVID-19 or patients with COVID-19 and worsening respiratory status.^[16,17] Imaging is not routinely recommended as a screening tool or in patients with COVID-19 and mild symptoms.

Given the high incidence of VTE in these patients, in addition to the standard risk factors of thromboembolism such as ICU setting, and mechanical ventilation, this is an important consideration in the both the acute clinical setting and in the intermediate and long-term follow-up of COVID-19 patients. The use of contrast-enhanced CT should be considered in patients with severe or worsening symptoms. This would allow evaluation of both the lung parenchyma as well as assessment of the pulmonary vasculature.

CONCLUSION

The full spectrum of clinical manifestations of COVID-19 is still emerging, but thrombotic complications are an ever more recognized cause of increased morbidity and mortality. This is an important consideration for the radiologist, and when imaging these patients, the use of contrast enhanced CT studies should be considered.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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