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Case report

SARS-CoV2 induced pulmonary embolism and complications from anticoagulation

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ABSTRACT

Coronavirus disease (COVID-19) pandemic has rapidly spread around the world. As new complications associated with the virus become more apparent, concerns in the medical community continue to grow. One of the more commonly encountered and more troubling complications in critically ill patients has been hypercoagulable state and subsequent thrombotic events. Within the spectrum of observed thrombotic events, pulmonary embolism seems to prevail. These trends are concerning and reinforce current recommendations on anticoagulation in critically ill with the virus. To illustrate the variety of possible presentations of pulmonary emboli in COVID-19 population, two cases of patients in their sixties are described, one without any predisposing risk factors and one with history of asthma and obesity. These patients developed pulmonary emboli at different points during their hospital course, were treated differently, and had different outcomes. Important observations are made that may shed some light on possible etiology of pulmonary emboli. One of the patients presented still developed pulmonary embolism despite being on full dose anticoagulation. Literature review suggests that pulmonary clot burden in COVID-19 patients could be due to pulmonary thrombus rather than pulmonary embolism and is triggered by profuse vascular damage and severe inflammatory response. Literature review also proposes changes to the diagnostic work up in COVID-19 patients, such as earlier screening for pulmonary embolism in critically ill. In addition, rare and severe complications of current anticoagulation therapy is illustrated and discussed through one of the cases presented.

1. Introduction

First cases of coronavirus (SARS-CoV-2) emerged in December of 2019 in Wuhan, China, and have since spread rapidly around the world [1]. As the pandemic continues to evolve, a number of complications are noted to have an association with the virus. One of the more commonly encountered complications of coronavirus disease (COVID-19) is hypercoagulable state and subsequent thrombotic events [2]. The incidence of thrombotic events in COVID-19 patients in the intensive care unit (ICU) has been noted to be 31% [2]. In the spectrum of thrombotic events associated with COVID-19, pulmonary embolism seems to be the most frequent [2]. These trends are concerning and reinforce current recommendations of anticoagulation in critically ill patients. To illustrate the variety of possible presentation of pulmonary emboli in COVID-19 population, two cases of critically ill patients of similar age but different risk factors, different treatment and hospital course as well as different outcomes are presented.

2. Case series

2.1. Case 1

A 65-year-old gentleman with no history of smoking or alcohol use, obesity, lung or heart disease, and diabetes presented to the emergency department on March 28th, 2020 after testing positive for COVID-19 and experiencing worsening dyspnea. His symptoms gradually deteriorated over the course of the week manifesting in myalgias, malaise, poor intake, nausea, mild chest pain, and dyspnea. Upon presentation to the emergency department, patient was afebrile, mildly hypertensive, and saturating well on room air. He became hypoxic acutely, requiring non-rebreather at 15 L per minute and was transferred to the ICU. Due to worsening hypoxia, patient was intubated and started on hydroxychloroquine and azithromycin. On admission, patient had no leukocytosis but had significant elevation in the following inflammatory markers: D-dimer 957, fibrinogen 868, ferritin 1,122, and C-reactive protein (CRP) 112.4. Patient was only able to complete four days of hydroxychloroquine and azithromycin due to QTc prolongation. His ICU
course was complicated by acute hypotension with maximal vasopressor support secondary to massive pulmonary embolism on April 4th, 2020 requiring administration of full dose systemic tissue plasminogen activator (tPA). CT angiography (CTA) of his lungs was concerning for extensive pulmonary emboli within all five lobes with medium clot burden including a large thrombus within the distal right main pulmonary artery (Fig. 1). Bedside echocardiogram revealed positive McConnell sign, but no evidence of deep vein thrombosis (DVT) on bilateral Doppler ultrasound of lower extremities. Following tPA, patient was started on heparin infusion. Of note, on April 4th, 2020 patient’s D-dimer rose to over 20,000 units, ferritin and CRP tripled from admission to 3020 and 347 respectively. Repeat echocardiogram showed improvement in right-sided heart strain. Once stabilized, patient continued on the ventilator. Patient was noted to have significant buildup of mucous that was difficult to control with suction, which required nebulizer treatment. His hospital course was further complicated by acute pneumothorax while on spontaneous breathing trial on April 9th, 2020. Needle decompression was only partially successful, which necessitated chest tube placement. Patient was able to come off the ventilator on April 10th, 2020 and was transferred to intermediate care unit (IU). Before transfer to IU, heparin infusion was discontinued and therapeutic dose of lovenox was started. Chest tube was removed on April 20th, 2020 and he was discharged soon afterwards on apixaban for treatment of pulmonary embolism.

2.2. Case 2

A 69-year-old lady with history of asthma, anxiety, breast cancer, and morbid obesity presented to the emergency department on April 6th, 2020 for worsening dyspnea. She was having productive cough and dyspnea on ambulation at home. In the emergency department patient was febrile to 102.5 F, tachypneic, but able to maintain her saturations. She was intubated for impending respiratory compromise and transferred to the ICU. On admission, patient had no leukocytosis and had the following inflammatory markers elevated: D-dimer 573, fibrinogen 570, ferritin 461, and CRP 127. COVID-19 test came back positive on April 8th, 2020, and she was started on hydroxychloroquine and azithromycin. She also qualified for one dose of tocilizumab for elevated interleukin-6 levels. She was also started on solumedrol for concern of possible asthma exacerbation. Her ICU course was complicated by pneumothorax developed on April 16th, 2020. She was successfully extubated on April 18th, 2020 and transferred to IU for further management. Her hospital course was complicated by neurologic symptoms concerning for a cerebrovascular accident, but a non-contrast CT of the head was negative for acute pathology or bleeding. Due to concern of rising inflammatory markers and hypercoagulable state, patient was started on a full-dose anticoagulation with heparin. While she appeared to be stable on non-invasive ventilation and anxiolytics, on April 21st, 2020 patient was re-intubated for respiratory failure. Chest x-ray was concerning for an effusion, which when drained by chest tube proved to be hemothorax. Due to concern for heparin-induced thrombocytopenia (HIT), heparin was discontinued and replaced with intermediate dose lovenox. Patient subsequently required two units of blood transfused and intermittent vasopressor support. Upon successful resolution of hemothorax, patient was successfully extubated on April 23rd, 2020 to nasal cannula and transferred to IU. Thrombocytopenia continued to worsen on April 30th, 2020 with platelets of 22,000 and D-dimer greater than 20,000. CTA showed bilateral segmental pulmonary emboli (Fig. 2) and lovenox was held due to concern for second episode of HIT. Heparin PF4 antibody returned positive and patient was started on argatroban infusion. Later on, following an extensive discussion between hematology/oncology and nephrology teams, it was decided to proceed with plasmapheresis. Patient continues to be critically ill.

3. Discussion

The two cases highlight the association of COVID-19 with thrombotic events, particularly pulmonary emboli. Thrombotic events put a colossal burden on patients’ physiology complicating their already critical condition. This is why it is important to further study pathophysiology of pulmonary emboli in COVID-19 patients and their response to current therapy.

A study performed by Klok et al. analyzed 184 COVID-19 patients in the intensive care setting, all of whom received at least standard doses of thrombophylaxis [2]. They concluded that there was a 31% incidence of thrombotic complications among critically ill COVID-19 patients and that pulmonary embolism was the most frequent complication of COVID-19 prothrombotic state [2]. These findings further reinforce the recommendations of thrombophylaxis in all critically ill COVID-19 patients.

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*Fig. 1.* Chest CTA demonstrating medium clot burden including a large thrombus within the distal right main pulmonary artery (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

*Fig. 2.* Chest CTA showed bilateral segmental pulmonary emboli, distal right main pulmonary artery visualized in this picture (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
patients. Because of such high incidence of thrombotic complications in COVID-19 patients, Rotzinger et al. suggested considering CT-A rather than CT for diagnostic work up [3]. Leonard-Lorant et al. in their study further supported the point made by Klok at al. suggesting that 32 of 106 (30% [95% CI 22–40%]) patients with COVID-19 were positive for acute pulmonary embolus on pulmonary CTA[4]. As a result, using CTA rather than CT for diagnostic work up can help identify pulmonary emboli earlier and prevent hemodynamic instability as well as further complications.

While anticoagulation remains a treatment choice for COVID-19 induced coagulopathy, it is unclear why patients like the one described in case two fail even therapeutic doses of anticoagulation. The explanation lies in better understanding of the pathophysiology of the clot formation in COVID-19 patients. Cattaneo et al. distinguished an important difference between pulmonary thrombi and pulmonary emboli [5]. They described that the difference in etiologies of these conditions explains the different approaches to their treatment [5]. They pointed out the rarity of DVT in COVID-19 patients suggesting that thrombophylaxis is effective in preventing venous thromboembolism [5]. Patient one developed pulmonary emboli while no DVT was identified on Doppler. Cattaneo at al. suggested that etiology of pulmonary thrombotic events may share pathophysiology with COVID-19 microangiopathy rather than coagulopathy [5]. Pulmonary thrombi may develop as a result of vascular damage by the virus and severe inflammatory response [5]. They suggested that high dose heparin in this setting is not only ineffective but may potentially contribute to hemorrhagic complications of angiopathy [5]. Patient in case two developed pulmonary emboli despite being on full dose anticoagulation, which may support theory proposed by Cattaneo et al. that pulmonary emboli are in fact pulmonary thrombi making them more resistant to anti-coagulation therapy. While it supports Cattaneo et al. theory, it is difficult to definitively conclude that case two had pulmonary thrombi rather than emboli without a negative lower extremity Doppler. The other explanation for what happened in case two is HIT-induced prothrombotic state. More studies have to be done to evaluate if microangiopathy induced by COVID-19 puts patients at risk for pulmonary thrombotic events and bleeding complications when combined with therapeutic doses of heparin.

Remarkably, there was a case report published of a COVID-19 patient with respiratory failure and septic shock who avoided mechanical ventilation and improved clinically and radiologically after plasma exchange and intravenous immunoglobulin [6]. While patient in case two had a different indication for a plasma exchange, having another case report of clinical and radiological improvement following plasma exchange raises an interesting option for therapy. Plasma exchange and intravenous immunoglobulins may prevent disease progression and reduce requirements for mechanical ventilation, but more research needs to be done before this conclusion can be made.

Lastly, it was interesting to note that while patient in second case had pre-existing conditions that were putting her at risk for COVID-19 complications, the first case had no underlying lung or heart disease, diabetes or excess weight. More research needs to be done to better understand risk factors that predispose patients to severe complications and prolonged hospital stay.

4. Conclusion

Two presented cases illustrated an association of COVID-19 with thrombotic events, particularly pulmonary emboli in critically ill patients. The two patients were diagnosed with pulmonary emboli after becoming hemodynamically unstable. Critically ill COVID-19 patients may benefit from using CTA rather than non-contrast CT for diagnostic work up, as it can help identify pulmonary emboli earlier and help prevent hemodynamic instability. This, of course, would not be appropriate in patients with renal dysfunction. While this may not be the best use of hospital resources, this approach is worth researching to further assess its clinical value.

While anticoagulation remains the treatment of choice for COVID-19 prothrombotic state, failure of this therapy in some cases, like in the one presented in case two, raises concerns about our understanding of the pathophysiology of pulmonary emboli in COVID-19 patient population. Pulmonary clot burden in these patients could be pulmonary thrombi rather than pulmonary emboli, caused by vascular damage and severe inflammatory response. This is a clinical theory that needs to be researched further and if true may change our management of this complication.

While we continue to treat critically ill COVID-19 patients with anticoagulation to prevent thrombotic events, anticoagulation complications such as HIT need to be considered. A vigilant laboratory monitoring of platelets needs to be done for critically ill patients on heparin or lovenox to help avoid severe bleeding complications by intervening early. Plasma exchange and intravenous immunoglobulins have also been described in one other case report thus far and may be worth researching further as one of the possible treatments for COVID-19 associated complications. Lastly, one out of two patients presented had no underlying lung or heart disease, diabetes or excess weight. More research needs to be done to better understand risk factors that predispose patients to severe complications and prolonged hospital stay.

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