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Letter to the Editors-in-Chief

Pulmonary embolism: A complication of COVID 19 infection

1. Introduction

In late December 2019, a novel Coronavirus Disease (COVID 19) outbreak has emerged in Wuhan, Hubei province of China [1]. The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is continuously posing a worldwide public health threat. Although the immunological susceptibility and response for the disease have not been determined yet, more insight is being gained regarding its prothrombotic state. Abnormal coagulation parameters have been observed, especially elevated D-dimer levels, and has correlated with poorer prognosis among COVID 19 infected individuals [2].

Pulmonary embolism is not a well-established complication of acute respiratory distress syndrome (ARDS), yet the critical illness and accompanied prolonged hospital stay represents a hypercoagulable state in general. Nevertheless, ARDS secondary to COVID 19 infection appears to represent a more complex scenario. Recently, there has been evidence for a possible role of empiric anticoagulation among infected individuals with marked elevation in the D-dimer level [3]. This observation has been related to hypercoagulability and possible pulmonary vasculature micro-thrombosis [3]. Klok et al. reported an increased incidence of thrombotic complications in COVID 19 infected patients admitted to the intensive care unit (ICU) [4]. It has also been recently documented that a high number of venous thromboembolic events (VTE) have been diagnosed within 24 h of admissions [5]. This suggests that such events occur early on in the disease course and are not a complication of acute illness or prolonged hospitalization solely. Herein, we present six patients who were not in critical illness yet presented with pulmonary embolism in admission in association with COVID 19 infection. (Table 1, Fig. 1) This emphasizes a potential thrombotic state in those patients regardless of their pneumonia severity.

2. Case 1

An otherwise healthy 28-year-old female patient presented to the hospital with progressively worsening dyspnea, cough, myalgias, and subjective fevers for 3 days in duration. She denied any use of oral contraceptive pills. On initial presentation, she was in sinus tachycardia at 120 beats per minute (bpm); she had a normal blood pressure but remained hypoxemic on room air, a decision was made to proceed with Computed Tomography Angiography (CTA) scan of the chest which was remarkable for multiple, extensive and occlusive pulmonary emboli bilaterally along with right heart strain. In addition, there were multi-lobar consolidations confirmed to be secondary to SARS-CoV-2 infection later on the day of presentation. A 2D echocardiogram revealed a dilated right ventricle with interventricular septal flattening. She was treated with systemic thrombolysis using tissue plasminogen activator (t-PA) followed by therapeutic enoxaparin (1 mg/kg subcutaneously twice daily). In addition, she received hydroxychloroquine and azithromycin and was subsequently discharged on Apixaban after a marked improvement in her symptoms.

3. Case 2

A 52-year-old diabetic male patient presents to the hospital with...
progressively worsening dyspnea, cough, and subjective fevers for few days in duration. On initial evaluation, he was tachycardic and saturating at 85% on room air. A 12-lead EKG was remarkable for sinus tachycardia at 135 bpm. Chest X-ray performed showed extensive bilateral pulmonary infiltrates suggestive of COVID 19 infection, pneumomediastinum, and subcutaneous neck emphysema. CBC was remarkable for leukocytosis, neutrophilia, and lymphopenia. D-dimer level was >20 μg/mL (reference: ≤0.5 μg/mL), troponin I level was unremarkable at <0.01 ng/mL, along with a normal BNP level of 13 pg/mL. A CTA scan of the chest was performed which revealed extensive embolus in the right pulmonary artery and an embolus in the left upper lobe branch of the left pulmonary artery along with the previously seen pneumomediastinum. In addition, there were widespread peripheral ground-glass opacity and areas of consolidation in the posterior lower lobes suggestive of COVID 19 infection which was confirmed later on the day of presentation. He was anticoagulated with enoxaparin during his hospital stay and required mechanical ventilation for 3 days. Consequently, he was discharged on Rivaroxiban with marked improvement in his symptoms.

4. Case 3

A 62-year-old male patient with past medical history of diabetes mellitus type 2 and hypertension presents with progressively worsening shortness of breath. He was hospitalized 10 days prior to presentation after being diagnosed with COVID 19 pneumonia. During that admission, he had a normal BNP and troponin I level; however, D-dimer level was not performed. He remained in the hospital for 3 days requiring intermittent oxygen therapy via nasal cannula and discharged subsequently. He didn’t receive any thromboprophylaxis during that admission as he was ambulatory and wasn’t deemed high risk for VTE. Three days after discharge, he started having shortness of breath again which he attributed to his infection. Nevertheless, as his condition continued worsening, he presented back to the hospital 10 days post-discharge. On initial evaluation, he was hemodynamically stable, tachypneic but adequately saturating at room air. A 12-lead EKG was remarkable for new T wave inversions in the right precordial leads. Laboratory analyses revealed a slightly elevated BNP at 132 pg/mL (reference: ≤100 pg/mL), and an unremarkable troponin I level. A bedside 2D echocardiogram performed revealed the presence of McConnell’s sign along with enlarged right ventricle and interventricular septal

| Case 1 | Female | 28 | None | 17 | 160 | – | 0.5 | 378 | Yes | Yes | Apixaban |
| Case 2 | Male | 52 | DM | >20 | 260 | 862 | <0.01 | 13 | No | No | Rivaroxaban |
| Case 3 | Male | 62 | DM, HTN | 5 | 19.4 | 387 | <0.01 | 132 | Yes | Yes | Apixaban |
| Case 4 | Male | 49 | None | >20 | 306 | 4109 | 0.3 | 604 | Yes | No | Rivaroxaban |
| Case 5 | Female | 59 | Afsb | 2.85 | 41 | 220 | <0.01 | 23 | No | No | Apixaban |
| Case 6 | Male | 69 | None | >20 | 58.7 | 1494 | <0.01 | 53 | No | No | Apixaban |

Abbreviations: Afsb: atrial fibrillation; BNP: brain natriuretic peptide; CRP: C-reactive protein; DM: diabetes mellitus; HTN: hypertension; PE: pulmonary embolism; PMHx: past medical history; t-PA: tissue plasminogen activator.

Laboratory references: BNP (≤100 pg/mL), CRP (<10 mg/L), D-dimer (≤0.5 μg/mL), Ferritin (14–233 ng/mL), Troponin I (<0.030 ng/mL).

* Represents pulmonary embolism severity and the risk of early (in-hospital or 30 day) death according to the 2019 European Society of Cardiology (ESC) guidelines [13].

** The oral dose used for Apixaban was 10 mg twice daily for 7 days followed by Apixaban 5 mg twice daily. The oral dose used for Rivaroxaban was 15 mg twice daily for 21 days followed by Rivaroxaban 20 mg daily.
flattening at diastole and end-systole. A CTA scan of the chest was performed and revealed bilateral pulmonary emboli involving the distal right and left main branches and extending to the segmental branches. The decision was made to proceed with systemic t-PA and was followed by therapeutic heparin infusion. He improved markedly without any complications and was discharged on Apixaban.

5. Case 4

An otherwise healthy 49-year-old male patient presents to the hospital with shortness of breath. He had associated fevers, chills, and a dry cough. On presentation, he was hypoxicemic and de-saturating but responded well to oxygen supplementation via nasal cannula. A 12-lead EKG performed was remarkable for marked QT prolongation of > 550 ms along with deep T wave inversions in the anterior precordial leads. A CBC was remarkable for leukocytosis and lymphopenia. Other laboratory analyses revealed elevated ferritin level at 4109 ng/mL (reference: 14–233 ng/mL), a troponin I of 0.3 ng/mL (reference: <0.030 ng/mL), a CRP of 306 ng/mL (reference: < 10 ng/mL), and a D-dimer level above 20 μg/mL. He was confirmed to have SARS-2-CoV infection. A 2D echocardiogram was performed and revealed right ventricular dilatation along with systolic and diastolic flattening of the septum. A CTA scan of the chest was performed which revealed a right segmental pulmonary artery embolus. He was subsequently started on therapeutic enoxaparin during his hospital stay and discharged on Rivaroxaban.

6. Case 5

A 59-year-old female patient with a past medical history of atrial fibrillation maintained on aspirin presents to the hospital for worsening dyspnea, fever, and a dry cough. On initial evaluation, she was tachypneic but saturating at 98% on room air. She was hemodynamically stable and afebrile. A 12-lead EKG was unremarkable. Laboratory analyses revealed lymphopenia, elevated CRP at 41 mg/L (reference: ≤0 mg/L),Troponin I and BNP levels were within normal limits. Her initial chest X-ray showed patchy bilateral infiltrates. A CTA scan of the chest was remarkable for multiple bilateral segmental and subsegmental pulmonary emboli. In addition, peripheral pulmonary opacities were noted which were confirmed to be secondary to SARS-2-CoV pneumonia. She was subsequently started on enoxaparin during her hospital stay and discharged on Apixaban.

7. Case 6

A 69-year-old male patient without any significant past medical history presents to the hospital with progressively worsening shortness of breath of 1-week duration. He was hemodynamically stable and saturating at 99% on room air. Laboratory analyses were remarkable for a ferritin level of 1494 ng/mL (reference: 14–233 ng/mL), a CRP of 58.7 mg/mL (reference: < 10 mg/mL), and a D-dimer level of > 20 μg/mL (reference: ≤0.5 μg/mL). His troponin I and BNP levels were within normal limits. A 12-lead EKG was unremarkable. CTA scan of the chest revealed multiple bilateral pulmonary emboli with a large right main pulmonary artery thrombus but no right heart strain. Also, there were bilateral peripheral ground-glass opacities that were confirmed later on to be secondary to SARS-2-CoV infection. He was subsequently started on therapeutic heparin, hydroxychloroquine, and azithromycin. He had an uneventful hospital stay and was discharged on Apixaban.

8. Discussion

VTEs and hypercoagulability have been reported previously in severe respiratory tract infections such as influenza [6,7]. It is believed that respiratory viruses might play a major role in the coagulation cascade. Vissers et al. showed that in vitro infection of cultured human endothelial cells with respiratory viruses induce a procoagulant state [8]. This was characterized by decreased assay clotting time along with a 4 to 5-fold increase in tissue factor expression [8]. As the COVID 19 pandemic continues to progress, we are learning more and more about the dysregulated hemostatic pathways and coagulation defects observed in the disease. Inflammation of lung parenchymal cells and pulmonary vascular endothelial cells may cause an increased release of procoagulant factors. Thereby, inducing the coagulation cascade and causing de novo thrombosis and fibrin deposition within the pulmonary vasculature. Tang et al. showed in a recent study an association with decreased mortality among patients with severe COVID 19 infection who were treated initially with anticoagulation. This augments the possibility of thrombi or microthrombi formation within the pulmonary vasculature [3]. In addition, it is possible that this excessive cytokine release in the plasma of infected individuals has a crosstalk role with the coagulation cascade and its activation [9,10].

In all of our presented cases there were no identifiable major risk factors for VTE, and the patients were not in severe pneumonia or severe ARDS and were not admitted to the ICU. Although the incidence of VTEs appears to be elevated in the ICU setting, it is less clear for non-critically ill patients. It is possible that clinicians are underdiagnosing venous thromboembolic disease in this population. Potential reasons might be overlapping symptoms, limiting diagnostic studies as a result of increased demand, concern for infectious droplet exposure during the study and during transport, and longer turnover times due to disinfection measures.

Whenever VTEs are diagnosed, the decision regarding the duration of anticoagulation should take into account the existence of provocative events. It is generally agreed upon that the minimum duration is 3 months for provoked VTEs. It is reasonable to consider VTEs in COVID 19 infected patients admitted to the ICU as provoked. Nevertheless, it is less clear for ambulatory and non-critically ill patients, especially as in our present cases who had the VTEs prior to hospitalization. Moreover, it might be reasonable to consider extended thromboprophylaxis in COVID 19 infected patients without VTEs following hospital discharge. Criteria from the APEX and the MARINER trials, in addition to clinical judgment and patients’ comorbidities might be helpful in identifying patients who might derive benefit [11,12].

In conclusion, we presented six cases of pulmonary emboli that we believe were precipitated by COVID 19 infection. We should be aware of the possibility of overlapping symptoms between the two diseases. Clinicians should maintain a low threshold for CT angiography scans and anticoagulation in COVID 19 infected patients, taking into consideration the severity of the illness and D-dimer levels.

Declaration of competing interest

The authors report no conflict of interests.

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