Pulmonary thromboembolism associated with coronavirus infection: A possible correlation-case series

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Abstract

We present a case series of patients with pulmonary embolism of unknown etiology who did not have any risk factors. According to the findings, the most likely cause of the pulmonary embolism was undiagnosed, asymptomatic, or mild Corona Virus disease-2019 (COVID-19) infections in the recent past. In the current post-pandemic era, where there has been a surge of sudden unexplained deaths and pulmonary embolism cases, this case series emphasizes the importance of pulmonary embolism evaluation in patients seeking medical care for dyspnea. Physicians should be aware of the possibility of pulmonary embolism as a late complication in patients with mild, asymptomatic, or undiagnosed COVID-19 infection.

Introduction

Acute COVID 19 infection is a risk factor for thromboembolism on its own.[1] Pulmonary Embolism (PE) after COVID-19 infections is a well-known and feared complication with a high mortality rate. COVID-19 thrombotic and vascular complications have been linked to moderate to severe COVID-19 pneumonia.[2] However, the duration of pro-coagulable state persistence in patients with COVID 19 infection is unknown.[3] Surprisingly, pulmonary embolism has been observed in a few case reports even months after mild COVID-19 infections.[4]

Increased susceptibility to developing PH and right ventricular dysfunction has also been documented in deceased COVID-19 patients, as well as in patients who recovered from mild to moderate cases.[5,6] The development of chronic pulmonary hypertension due to organized thrombus after asymptomatic, undiagnosed, or mild COVID-19 disease has not been thoroughly studied. We present a case series of pulmonary hypertension and pulmonary embolism with unknown etiologies in the current COVID-19 pandemic era. This series demonstrates the plausible link between increased incidences of pulmonary vascular complications in the current post-pandemic scenario and an undiagnosed COVID-19 infection.

Case Reports

Case #1

A 67-year-old hypertensive male, non-smoker, patient who received two doses of whole virus inactivated COVID-19 vaccine (Covaxin), last dose taken two months prior without any risk factors for venous thromboembolism, presented to the hospital with progressive dyspnea on exertion for the last one month. The patient was tachycardiac, and blood pressure was 120/78 mmHg with peripheral oxygen saturation of 92% breathing ambient air. General Physical Examination (GPE) and respiratory system examination were normal. Pan systolic murmur over the tricuspid area was heard on cardiovascular assessment with no other signs of cardiac decompensation. Routine lab investigations (complete blood counts), troponin T and D-Dimer (0.95) were also within reference limits. Real-time Reverse Transcription–polymerase chain reaction (real-time RT–PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was negative. An electrocardiogram (ECG) showed sinus tachycardia. An Echocardiogram (ECHO) demonstrated dilated right chambers, severe tricuspid valve insufficiency, and severe Pulmonary Hypertension (PH). Computerized Tomography of Pulmonary Angiography (CTPA) was done as Pulmonary Embolism (PE) was suspected. The CTPA revealed filling defects in the right pulmonary artery extending into the segmental and sub-segmental segments with bilateral dilated pulmonary artery (right pulmonary artery of 36 millimeters (mm) and left pulmonary artery of 26 mm), features were suggestive of chronic pulmonary thromboembolism (Figure 1). Other etiologies were ruled out. The patient was managed with oxygen supplementation and anticoagulation. Later discharged with oral anticoagulants, with a treatment recommendation for six months.

Case #2

A 41-year-old hypertensive male smoker patient, vaccinated against COVID-19 infection with recombinant adenovirus vaccine (Covishield), last doses of two doses received three months prior, reported dyspnea (Modified Medical Research Council Grade -MMRC-grade 3) for two months. The patient gave an account of incidentally detected COVID-19 infection on RT-PCR testing one and a half months before. He underwent home quarantine then and had no symptoms during the two weeks of the

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disease. He observed exercise-induced dyspnea (MMRC-grade 2) a fortnight after recovering from a COVID-19 infection. The vitals, GPE, and systemic examinations revealed no discrepancies. Routine blood investigations, cardiac biomarkers, and D-Dimer values were within reference ranges. Real-time RT–PCR for SARS-CoV-2 infection was reported negative on admission. ECG showed sinus tachycardia. ECHO showed moderate insufficiency of the tricuspid valve with moderate PH and Right Ventricular Systolic Pressure (RVSP) of 45 mmHg. CTPA was done to rule out PE and showed no evidence of PE. However, because the study was conducted a few days after the patient's initial presentation due to the patient's unwillingness, acute resolution of PEs could not be ruled out. Screening for other etiologies for pulmonary hypertension, including autoimmune, congenital cardiac, toxins, and vascular causes, were negative. The patient was started on anticoagulation and planned to continue for a total duration of 3-6 months.

Case #3

A 52-year-old non-smoker female, who received two doses of whole virus inactivated COVID-19 vaccine (Covaxin), last dose was taken six months prior, with a past medical history of hypertension, came to the OPD with complaints of progressive exercise-induced dyspnea grade 2 MMRC over two weeks. She had a history of preceding fever and cough lasting for three days before the onset of dyspnea, for which she underwent self-quarantine without any evaluation, including COVID-19. The patient was hemodynamically stable with GPE and systemic examinations within normal limits. Routine lab parameters (complete blood counts), cardiac biomarkers, and D-Dimer values were within normal reference ranges. Real-time RT–PCR for COVID-19 infection was negative on presentation. ECG showed sinus tachycardia. ECHO showed moderate insufficiency of the tricuspid valve with moderate PH. CTPA was performed as PE was suspected, which showed bilateral, patchy peripheral consolidation suggestive of COVID-19 infection, CO-RADS- 5 with left lower lobe subsegmental arterial partial thrombosis. Autoimmune disorder screening was negative. The patient was started on anticoagulation and planned to continue for a total duration of 3-6 months.

Case #4

A 66-year-old non-smoker, unvaccinated against COVID-19 infection female with a past medical history of hypertension and without a history of past SARS-CoV-2 infection or risk factors for venous thromboembolism came to the emergency department with complaints of exercise-induced dyspnea (MMRC-grade 2) for the last three months with worsening of dyspnea (progressed to Grade 4 MMRC) for past two days. She had tachycardia with a rate of 128 regular beats per minute and a blood pressure of 136/54 mmHg. She was tachypneic with peripheral oxygen saturation was 83% on ambient air. The GPE and systemic examinations revealed no discrepancies. Routine blood investigations and cardiac biomarkers were within reference ranges. D-Dimer value was elevated with a titer of 2.4 µ/mL (reference normal <0.4 µ/mL). Real-time RT–PCR for SARS-CoV-2 infection was negative. ECHO showed severe insufficiency of the tricuspid valve with severe pulmonary hypertension. CTPA was done to rule out PE and showed bilateral dilated pulmonary arteries with segmental and sub-segmental arteries filling defects, suggestive of bilateral pulmonary embolism (Figure 2). Autoimmune disorder screening was reported negative. Her IgG antibodies against COVID-19 were positive with significant titers. The patient was started on oxygen supplementation and anticoagulation and planned to continue anticoagulation for a total duration of 3-6 months.

Discussion

In the current COVID-19 pandemic era, we describe four cases of pulmonary hypertension with pulmonary embolism of unknown etiology in patients with no known risk factors. When compared to asymptomatic or mild cases of COVID-19

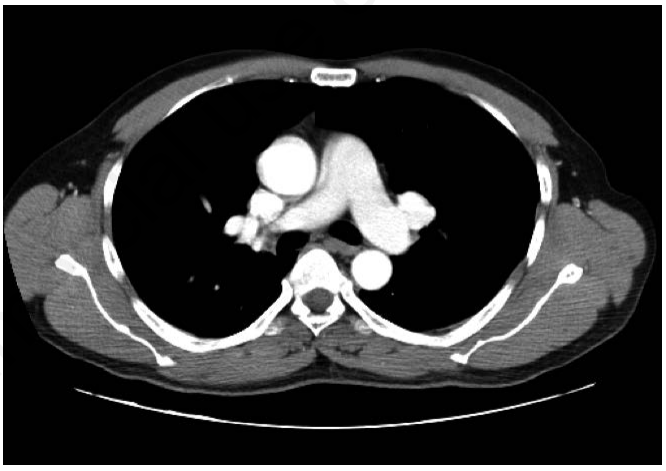

Figure 1. CTPA image of case 1 showing filling defects in the right main pulmonary artery.

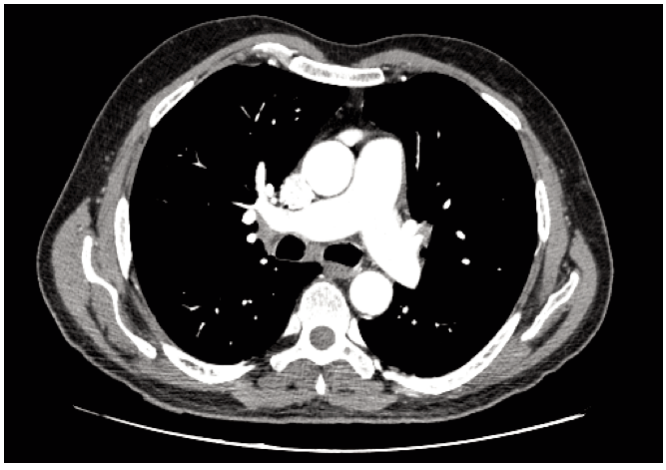

Figure 2. CTPA image of case 4 showing bilateral dilated pulmonary artery with segmental and submental filling defects.

infection, the incidence of pulmonary Thromboembolism (VTE) is higher in hospitalized severely ill patients.[7,8]

Anticoagulation has significantly improved the clinical outcome in severely ill COVID-19 infected patients.[9] The hypercoagulable state caused by COVID-19 infection is attributed to a number of mechanisms, including oxidative stress, mitochondrial dysfunction, DNA damage, inflammation, hypoxia, endothelial dysfunction, and pulmonary micro-embolism.[10] VTE usually occurs during the acute phase of COVID-19 infection. PE has been reported even six months after a mild COVID-19 infection.[11]

None of the patients in our case series had a history of COVID-19 infection or risk factors for venous thromboembolism. Three of the four patients described in this case series had received full COVID-19 vaccinations, while one was unvaccinated. A CTPA study revealed signs of pulmonary embolism in three patients. In one case, CTPA did not show embolism but did show severe pulmonary arterial hypertension features. This could be attributed to the fact that a delayed radiological study may not show pulmonary embolism because PE in the main pulmonary arteries resolves completely or peripheral micro-emboli organize.[12] Only one case had a history of microbiologically confirmed RT-PCR positivity for SARS-CoV-2 infection, with a temporal onset of symptoms strongly suggesting COVID-19 as the likely cause of pulmonary thromboembolism. Another case had an HRCT CO-RADS 5 score and CTPA thromboembolism, implying COVID as the etiology. We found anti-COVID antibodies in an otherwise asymptomatic patient, making COVID-19 the most likely cause after ruling out other possibilities. In one case, thromboembolism was linked to COVID-19 as a diagnosis by exclusion, meaning that all other known causes were ruled out.

Our case series highlights the concerning possibility of late hypercoagulable complications following previously undiagnosed COVID-19 infection. Due to mild or absent symptoms or a lack of testing, such infections may go unnoticed, and the proportion of undiagnosed cases in the general population during the pandemic is not small.[13]

Elevated D-dimer (2.0 mg/mL on admission) is associated with significantly higher mortality in cases of PE, even if thromboembolic complications directly cause it.[14] In line with this finding, none of the five patients in our case series had higher D-Dimer levels and a better prognosis.

Out-of-hospital sudden cardiac deaths have increased significantly in the last two years, coinciding with the COVID-19 pandemic.[15,16] Although a direct causal relationship has not been established, the most likely causes are COVID 19-induced vascular and thromboembolic events. The clinical significance and prevalence of thromboembolic disease among asymptomatic COVID-19 positives, asymptomatic carriers, and those with mild disease remain unknown and warrant further investigation, as sudden unexplained deaths have been increasingly reported in this population.[17]

In the post-pandemic era, clinicians are seeing an increase in cases of disproportionate dyspnea with unexplained pulmonary hypertension. Some of these cases have a history of moderate to severe COVID in the distant past, while others do not have a clear link to COVID 19 illness. In such a clinical setting, clinicians face a monumental challenge in determining the cause of pulmonary hypertension and thromboembolism. In the post-pandemic era, this case series serves to highlight the fact. In patients with chronic pulmonary hypertension, a post-COVID-19 complication must be considered first, and the presence of pulmonary thromboembolism caused by COVID-19 must be assessed.

In the current scenario, more research with a larger body of evidence is required to determine the risk factors, prevention, progression, prognosis, and morbidity associated with PE following an asymptomatic or undiagnosed COVID-19 infection.

Clinical highlights

In the post-pandemic period, physicians are increasingly encountering chronic pulmonary thromboembolism, as well as chronic pulmonary hypertension of unknown cause. It is necessary to rule out any post-COVID complications.

In COVID-19 cases with mild disease and asymptomatic patients, thrombovascular complications are frequently underreported and undiagnosed.

Following the pandemic, the COVID-19 complication should be included in the management algorithm for pulmonary hypertension and chronic thromboembolism.

Close monitoring, risk stratification, or interventional protocols involving prophylactic anticoagulants in the high-risk category must be researched and advocated for in close contact with confirmed asymptomatic and mild COVID-19 cases.

Conclusions

In the post-pandemic era, this case series emphasizes the importance of screening for pulmonary hypertension and pulmonary embolism in patients seeking medical care for dyspnea. Physicians should be aware of the possibility of pulmonary embolism as a late complication in COVID-19 subjects, even in those who are not severely affected by the infection or who have an asymptomatic or undiagnosed COVID-19 infection.

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