PH GRAND ROUNDS

COVID-19 Infection Causing Delayed Pulmonary Arterial Hypertension

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INTRODUCTION

A42-year-old woman was readmitted to the hospital 6 weeks after being treated for COVID-19 infection. She presented in the emergency department with shortness of breath (SOB). Her SOB was progressively getting worse after being almost normal to baseline from the original infection.

Her clinical course during the previous 20 days of hospital admission during initial infection in April of 2020 was complicated by respiratory failure requiring noninvasive ventilatory support and treatment with azithromycin, hydroxychloroquine, dexamethasone, tocilizumab, and convalescent plasma therapy for COVID-19 infection. She had an echocardiogram which showed normal ejection fraction (EF) with no sign of pulmonary hypertension (PH) with normal right ventricular size (Figure 1). Her chest x-ray showed bilateral patchy infiltrates. Her chest computed tomography (CT), as shown in Figure 2, showed no pulmonary embolism with diffuse bilateral infiltrates. Pertinent laboratory values on admission included elevated d-dimer of 388 ng/mL (≤230 ng/mL) and elevated C-reactive protein of 32.25 mg/dL (0.0–0.9 mg/dL). Her beta natriuretic peptide (BNP) on initial admission was 324 pg/mL. Her CT chest angiogram was neg-

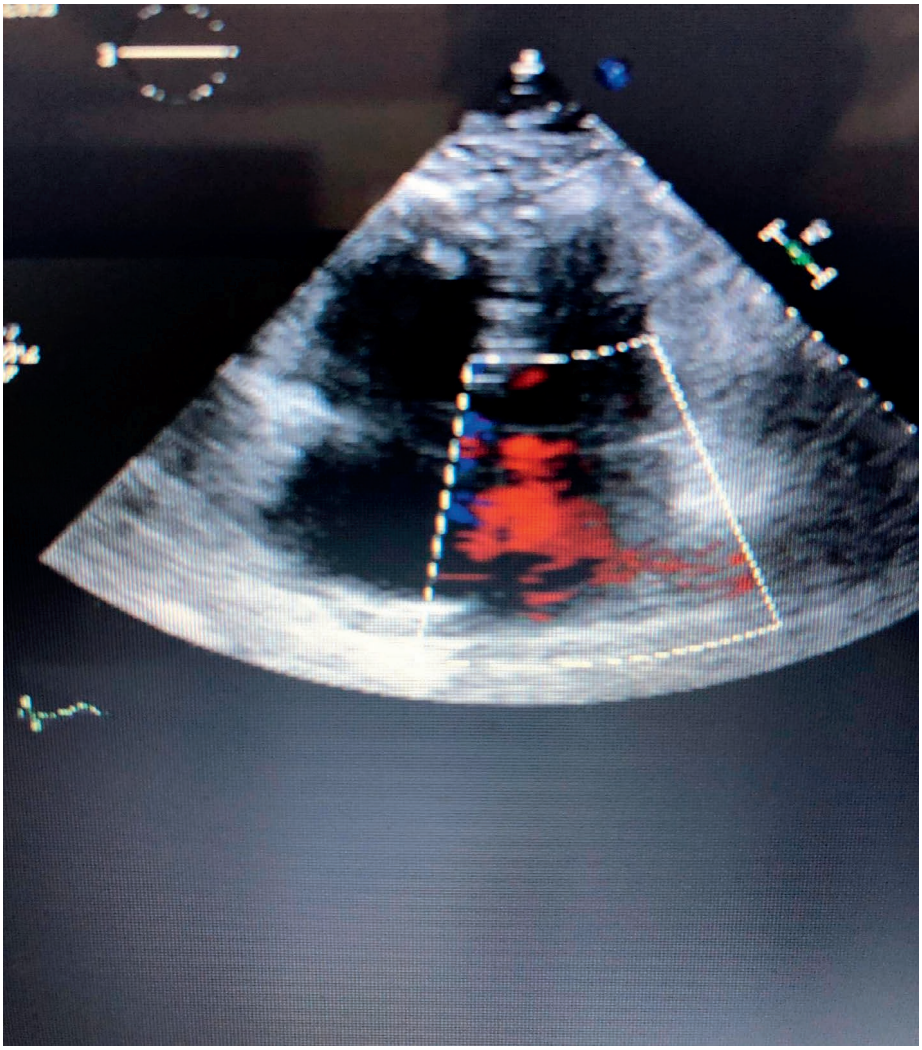

Figure 1: Echocardiogram.

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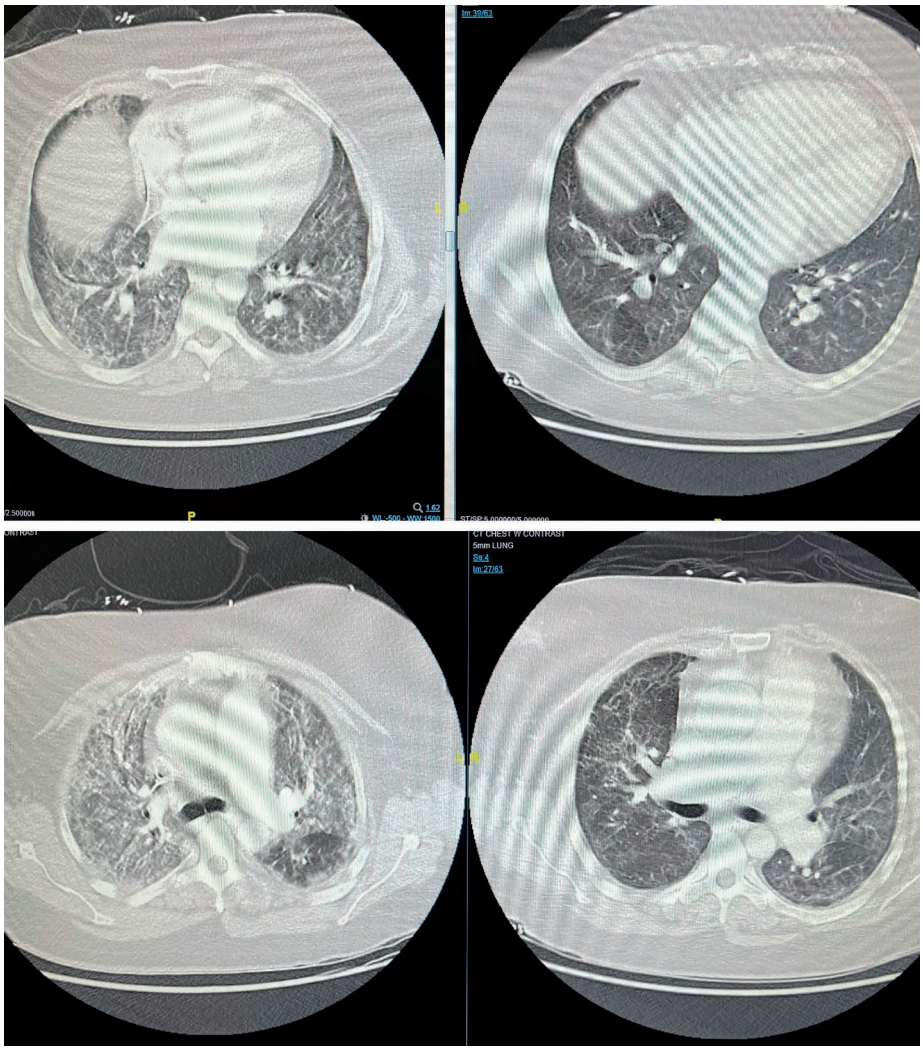

Figure 2: Computed tomography chest comparison, April 2020 to June 2020 (lower lobes).

Table 1. Patient Workup During 6 Week Span of COVID-19 Related Hospitalization

Test	Results
Computed tomography (CT) chest scan (June 2020)	Negative for pulmonary embolism and negative pulmonary venogram. Second CT scan showed improving infiltrates (Figure 2)
Echocardiogram (echo), 2 separate echos	First baseline echo April 3, 2020: Normal ejection fraction (EF), mild left ventricular hypertrophy, and normal right ventricular systolic function (RVSP).
	Second echo on June 17, 2020, in second admission: Normal EF, worsening right ventricular (RV) function with RVSP of 65. Noted mild RV enlargement and tricuspid annular plane systolic excursion of 1.9.
Pro-BNP (June 17, 2020)	1824 pg/mL (0–125 pg/mL)
Ventilation–perfusion scan (June 19, 2020)	Low probability scan with no sign of subsegmental emboli.
Venous duplex (June 18, 2020)	Negative for venous thromboembolism.
Cultures	All blood cultures, urine culture, and urine streptococcal antigen were negative.
Trend in pro-BNP (April 30, 2021)	324 pg/mL

ative for pulmonary embolism, showed bilateral diffuse infiltrates.

She was discharged home without any requirement for home oxygen therapy with a 10-day course of Decadron, and she had a negative COVID-19 reverse transcription polymerase chain reaction test 10 days after discharge and was able to resume her work.

Due to worsening SOB almost 6 weeks after her discharge from the original infection, given her recent diagnosis of COVID-19, cardiopulmonary and thromboembolic events were high on differential, causing rebound SOB. Bacterial pneumonia, recurrent COVID-19, and other pulmonary pathologies including PH were also considered in differential diagnosis. Further workup during the current hospitalization is described in Table 1.

Due to new onset of PH with significant change in her echocardiogram without any obvious etiology like thromboembolic disease and improving lung parenchymal changes, primary COVID-19-associated PH was considered as a primary differential diagnosis. She underwent right heart catheterization (RHC) which revealed moderate PH with high pulmonary vascular resistance (PVR) of 5 Wood units, right atrial pressure of 8 mmHg, pulmonary capillary wedge pressure (PCWP) of 9 mmHg, mean pulmonary arterial pressure of 34 mmHg, and cardiac output of 5 L/min (Figure 3). The patient was diagnosed with COVID-19-associated pulmonary artery hypertension (PAH), with high PVR and normal PCWP. She was started on single-agent phosphodiesterase-5 therapy, tadalafil. Follow-up chest x-ray showed improvement in infiltrates, and the pro-BNP levels also decreased significantly to 160 ng/mL with judicious diuresis. Oxygen support was completely weaned off, and the patient was discharged home after 6 days of hospitalization with a plan to have a follow-up echocardiogram in 3 months, which showed normal EF, no major tricuspid regurgitation, right ventricular systolic function of 42, and tricuspid annular plane systolic excursion of 21. Currently, the patient is off diuretic therapy and continuing with tadalafil

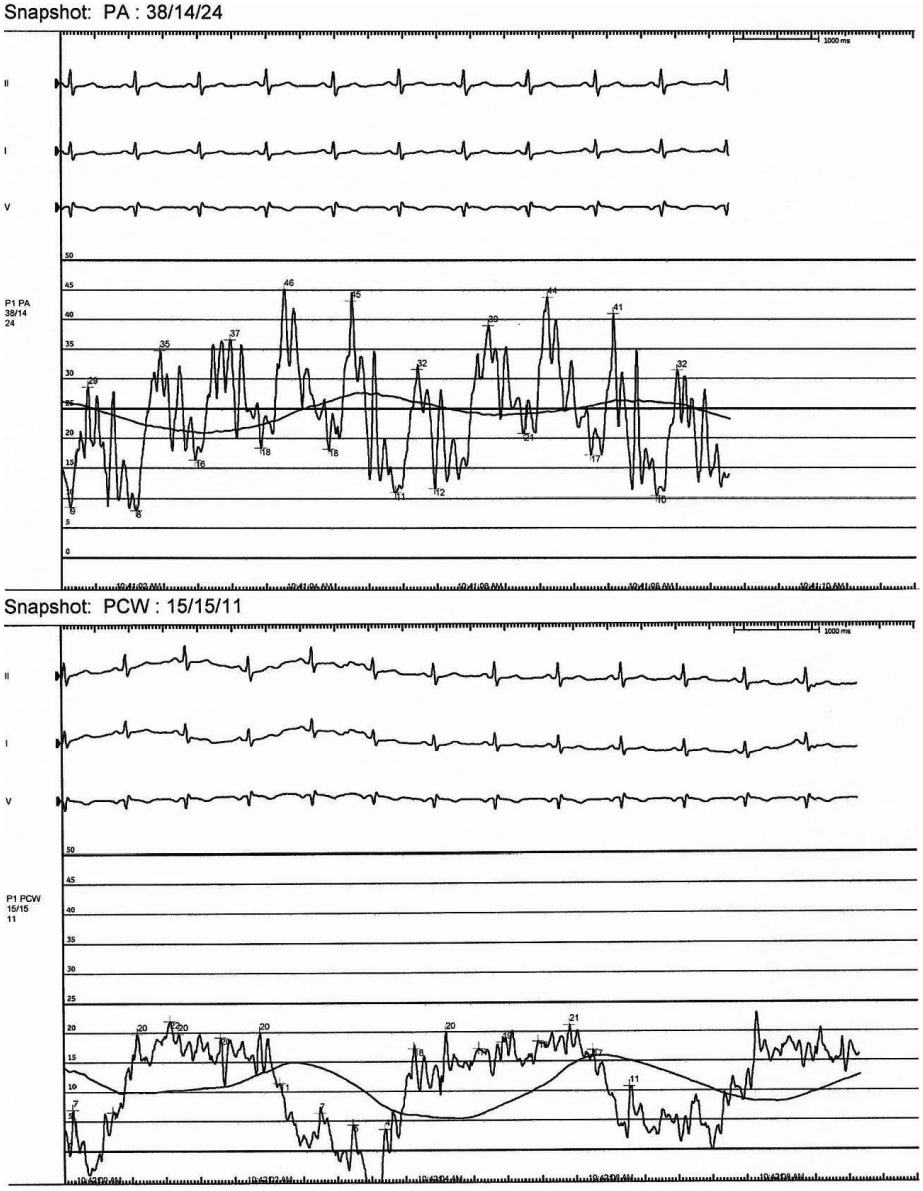

Figure 3: Right heart catheterization wave form.

with improvement in symptoms, and recent 6-minute walk test was 520 m.

DISCUSSION

Symptomatology of COVID-19 has been variable, with most patients predominantly presenting with pulmonary symptoms,[1] which include cough, SOB, and fatigue. Gastrointestinal symptoms have also been reported in COVID-19 patients.[2,3] COVID-19 is known to cause several cardiovascular sequelae, as outlined in Table 2. There have also been several reports about SARS-CoV-2 causing hypercoagulable conditions and contributing to several thrombotic complications.[4,5] The new onset of PH, diagnosed on RHC, associated with a history of COVID-19 infection in the absence of thromboembolic disease is unique as reported in our case. One of the mechanisms which explains the pathophysiology of SARS-CoV-2 is binding of the virus to the enzymatic domain of angiotensin converting enzyme 2 receptors located on various cell surfaces which include type 2 pneumocytes, perivascular pericytes, and cardiomyocytes, leading to entry of the virus into these cells and causing subsequent pulmonary and cardiovascular manifestations of the disease.[6] Another mechanism is the suppression of endothelial nitric oxide (NO) synthase with concomitant NO deficiency which hastens endothelial dysfunction, resulting in thrombotic and vascular disease.[7] In one case report, inhaled NO resulted in improved functional status and symptomatic relief in a patient with PAH and COVID-19.[8]

Table 2. Cardiovascular Complications of COVID-19 Infection

Complications
• Arrythmias (atrial fibrillation, ventricular tachycardia, ventricular fibrillation)
• Cardiac injury
• Fulminant myocarditis
• Heart failure
• Pulmonary embolism
• Disseminated intravascular coagulation
• Acute coronary syndrome or myocardial infarction
• Transient diastolic dysfunction
• Transient cardiomegaly
• Subendocardial infarction
• Valvular vegetations

The World Health Organization (WHO) classifies PAH as Group I PH, and known disease states that are associated with PAH include connective tissue disease, human immunodeficiency virus, portal hypertension, congenital heart disease, schistosomiasis, and the use of methaphetamines.[9] Our case sheds light into the possibility that COVID-19 viral illness represents a disease state that can cause new onset PH with a precapillary component. There is always a possibility of developing PH in COVID-19-infected patients due to development of pulmonary parenchymal injury and significant hypoxia, which causes secondary pulmonary vasoconstriction, leading to PH. This classifies as WHO Group 3 PH associated mainly with hypoxic drive from primary lung pathology. Generally, in this situation, primary treatment of the underlying pulmonary condition and oxygen supplementation is the main course of action until recently, when inhaled prostacyclin has become available as a treatment alternative.

In a COVID-19 patient, it would be reasonable to link hypoxia-induced lung injury or hypercoagulability-induced embolic phenomenon to the development of PH. Interestingly, in our patient, neither hypoxia nor thromboembolic disease were identified during the workup, indicating COVID-19 infection

as a primary trigger for pulmonary vascular disease. Post-COVID-19 delayed vascular complications are becoming increasingly recognized.[10] Similarly, postacute COVID-19 syndrome or long-hauler syndrome, which comprises various symptoms that persist for many weeks to months after the initial infection, is also being increasingly recognized with SOB as the most common persistent symptom.[11] PH should be considered in the differential diagnosis in a post-COVID-19 patient presenting with a new onset of SOB.

TEACHING POINTS

1. Post-COVID-19 infection-related complications are an emerging problem.
2. PH should be considered in the differential diagnosis of SOB occurring in a patient with a history of COVID-19 infection.
3. PH should also be considered among a specific group of patients known as long haulers who have persistent post-COVID-19 symptoms which impact their quality of life.
4. Considering some mechanisms of development of PH, the role of NO modification-dependent pathways should be entertained as a treatment choice in COVID-19-induced PH.

References

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720. doi:10.1056/NEJMoa2002032
2. Kant R, Chandra L, Antony MA, Verma V. Case of COVID-19 presenting with gastrointestinal symptoms. *World J Virol*. 2020;9(1):1–4. doi:10.5501/wjv.v9.i1.1
3. da Silva FAF, de Brito BB, Santos MLC, et al. COVID-19 gastrointestinal anifestations: a systematic review. *Rev Soc Bras Med Trop*. 2020;53:e20200714. doi:10.1590/0037-8682-0714-2020
4. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26:1017–1032. doi:10.1038/s41591-020-0968-3
5. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. *N Engl J Med*. 2020;382(20):e60. doi:10.1056/NEJMc2009787
6. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res*. 2020;116(10):1666–1687. doi:10.1093/cvr/cvaa106
7. Green SJ. COVID-19 accelerates endothelial dysfunction and nitric oxide deficiency. *Microbes Infect*. 2020;22(4):149–150. doi:10.1016/j.micinf.2020.05.006
8. Zamanian RT, Pollack CV Jr, Gentile MA, et al. Outpatient inhaled nitric oxide in a patient with vasoreactive idiopathic pulmonary arterial hypertension and COVID-19 infection. *Am J Respir Crit Care Med*. 2020;202(1):130–132. doi:10.1164/rccm.202004-0937LE
9. Kovacs G, Dumitrescu D, Barner A, et al. Definition, clinical classification and initial diagnosis of pulmonary hypertension: updated recommendations from the Cologne Consensus Conference 2018. *Int J Cardiol*. 2018;272S:11–19. doi:10.1016/j.ijcard.2018.08.083
10. SeyedAlinaghi SA, Afsahi AM, MohsseniPour M, et al. Late complications of COVID-19; a systematic review of current evidence. *Arch Acad Emerg Med*. 2021;9(1):e14. doi:10.22037/aaem.v9i1.1058
11. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27:601–615. doi:10.1038/s41591-021-01283-z