



A Case of Complex Pulmonary Hypertension: the Importance of Diagnostic Investigation

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ABSTRACT

Pulmonary hypertension (PH) encompasses several heterogeneous groups of multiple diseases characterized by abnormal pulmonary arterial blood pressure elevation. Unrepaired atrial septal defect (ASD) may be associated with pulmonary arterial hypertension (PAH), indicating pulmonary vascular remodeling. Furthermore, unrepaired ASD could also be associated with other conditions, such as left heart disease or thromboembolism, contributing to the disease progression. We present a case of a 61-years-old woman with complex PH comprising several etiologies, which are PAH due to unrepaired Secundum ASD, mitral regurgitation caused by mitral valve prolapse as a group 2 PH, pulmonary embolism (PE) which progress to chronic thromboembolism PH (CTEPH) and post-acute sequelae of SARS Cov-2. We highlighted the importance of diagnostic investigation in PH, which is crucial to avoid misdiagnosis and inappropriate treatment that could be detrimental for the patient.

KEYWORDS: Atrial septal defect, mitral valve prolapse, pulmonary arterial hypertension (PAH), pulmonary embolism, post-acute sequelae of SARS Cov-2 (PASC)

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Background

Atrial septal defect (ASD) is one of the most common forms of congenital heart disease (CHD), and pulmonary arterial hypertension (PAH) is noted in 9 to 35% of patients.^{1,2} Pathological processes in PAH associated with CHD (PAH-CHD) are consequences of molecular and pathologic alterations in the pulmonary vasculature, resulting in increased pulmonary vascular resistance (PVR).³ Although PAH is the most common type of PH associated with CHD; another disease could also contribute to PH development in CHD; hence, a meticulous evaluation is essential.⁵

We described a case of complex PH in a patient with unrepaired secundum ASD. She has PAH as a consequence of her unrepaired CHD and pulmonary venous hypertension (PH group 2) due to severe mitral regurgitation (MR). She also developed pulmonary embolism (PE), which progressed into chronic thromboembolic PH (CTEPH). Later, she got COVID-19 which progressed as post-acute sequelae after SARS-COV2 (PASC). We emphasized the importance of diagnostic investigation and evaluation of PH and its associated conditions, which is vital for the patient's diagnosis and management.

Case Illustration

A 61-year-old female came to the outpatient department due to shortness of breath for one year before admission. The vital

signs were within normal limit, with peripheral oxygen saturation (SpO₂) was 94% on room air. Remarkable physical examinations were jugular vein distension and wide-fixed-splitting heart sound with systolic murmurs at Erb's point. The electrocardiography (ECG) showed sinus rhythm and an incomplete right bundle branch block. Chest X-ray showed cardiomegaly with the vascularity pruning of the PA (Figure 1a). Echocardiogram (Figure 2) showed dilated right atrium (RA) as well as right ventricle (RV) with good RV function (TAPSE 19 mm), dilated left atrium (47 mm), large Secundum ASD (19–24 mm) left to right shunt, moderate MR due to MVP, moderate tricuspid regurgitation, and dilated PA with a high PH probability (TR Vmax 4.8 m/s).

Right heart catheterization (RHC) revealed mean pulmonary arterial pressure (mPAP) 85/29(47) mmHg, aortic pressure 105/66 (79) mmHg, and pulmonary arterial wedge pressure (PAWP) 25 mmHg. Hemodynamic assessment calculates the Q_p/Q_s is 1.67, PVR 5 WU, and diastolic pulmonary gradient (DPG) of 9 mmHg.(Figure 3) Hence, we diagnosed Secundum ASD, high flow - high resistance. We treated the patient with sildenafil, furosemide, and ramipril. The patient was also recommended for surgical repair, but she refused.

Three months later, the patient was admitted to the emergency ward due to worsening shortness of breath for two days



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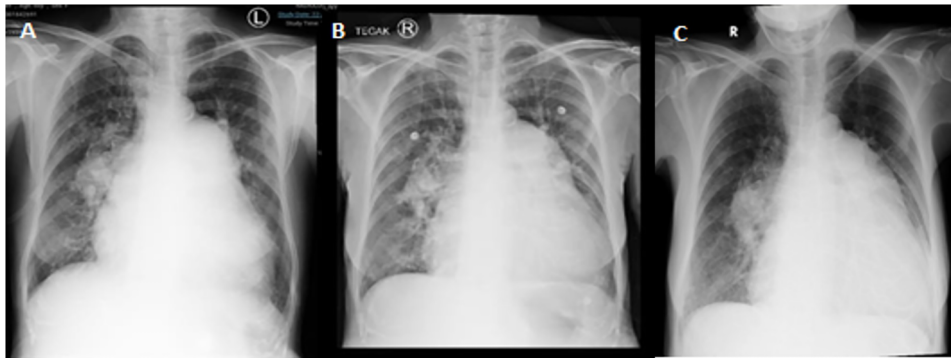


Figure 1. Chest X-ray the patient. Cardiomegaly (RV enlargement) with pulmonary arteries' pruning at initial admission (A) three months when diagnosed with acute PE (B), and eight months later when diagnosed with COVID-19.

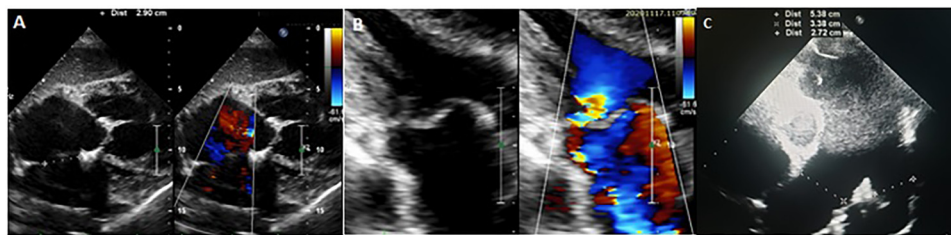


Figure 2. Echocardiography of the patient showing (A) large secundum ASD; (B) moderate MR and mitral valve prolapse due to tethered PML and prolapsed AML; and (C) dilated pulmonary artery.

before admission. Her vital signs were stable, but the SpO₂ was dropped to 80%. ECG reveals new atrial fibrillation. On laboratory examination, the results were hemoglobin 13.1 g/dL, leucocyte 6430/mm³, thrombocyte 194000/mm³, urea 32 mg/dl, creatinine 1.07 mg/dL, random blood glucose 127 mg/dl. Hypoxic respiratory failure was detected from blood gas analyses. Chest X-ray showed a new infiltrate on the bilateral lower lung field (see Figure 1B). Bedside echocardiography showed an increase of estimated PA pressure (TRVmax 5.04 m/s), but no thrombus nor sign of massive acute pulmonary embolism (McConnell and 60/60' sign) were found. We made a provisional diagnosis of pneumonia due to Covid-19, differential diagnosed with acute PE.

The patient's PCR Covid-19 exam was negative. CT PA showed thrombus and filling defect at the inferior segment of the superior lobe on the right and left PA and lung infarction at the peripheral segment (Figure 4). Therefore, we diagnosed acute PE with stable hemodynamically and treated with rivaroxaban 15 mg twice daily for three weeks and continued with 20 mg daily. The patient was consulted with a Rheumatologist and Hematologist for evaluation, but no abnormalities were found. The patient's condition was stabilized in the following days. She was discharged from the hospital and prescribed rivaroxaban, sildenafil, ramipril, and furosemide.

A lung perfusion scan (Figure 5) was performed three months later. It revealed a segmental perfusion defect at the inferior segment of the upper lobe bilaterally and anterobasal segment of the right lower lobe that suggests pulmonary

embolism at that area. There was also a pattern of inhomogeneous radioactivity in other parts of the lung bilaterally. These concluded as CTEPH.

One month later, the patient was readmitted to the emergency room due to worsening shortness of breath. Her vital signs were stable, but the SpO₂ was dropped to 70%. ECG was atrial fibrillation. On laboratory examination, the results were hemoglobin 12.2 g/dL, leucocyte 6120 /mm³, thrombocyte 197000/mm³, urea 44.8 mg/dl, creatinine 1.51 mg/dL, random blood glucose 123 mg/dl, fibrinogen 167.4, d-dimer 1.54 mg/L, and blood gas analyses, which showed hypoxic respiratory failure. Chest X-ray showed a new infiltrate on the bilateral lung field (Figure 1C). Swab PCR revealed positive for SARS-CoV2. Then, she was treated with remdesivir, n-acetylcysteine, bisoprolol, sildenafil, and furosemide. The anticoagulant was switched to fondaparinux 1×5 mg sc during hospitalization. She was also given supportive treatment such as vitamin C, vitamin D, omega 3. After ten days of treatment in the COVID ward and seroconversion of COVID-19, the patients still complained of worsening shortness of breath.

A pulmonary function test was performed two months later, revealing FVC 28%, FEV₁ 28%, FEV₁/FVC 79.7%, and PFM 30% conclude as a severe restriction pattern. The patient was then sent for Lung High-Resolution CT scan (HRCT) evaluation (Figure 6) with ground glass and multiple patchy consolidations. We also detected tree-in-bud patterns and nodules but with minimal fibrosis process. These results were suggestive of an inflammatory process. The patient was then diagnosed

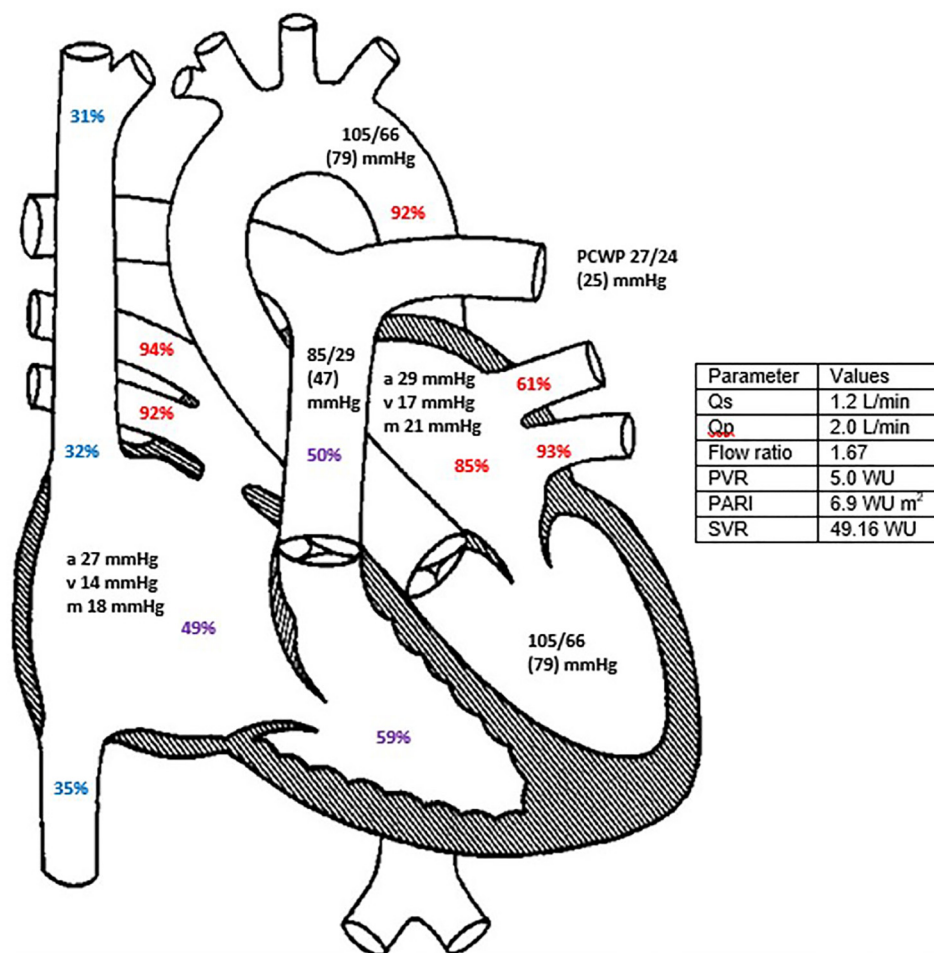


Figure 3. Result of Right Heart Catheterization Secundum Atrial Septal Defect, Left to Right Shunt Pulmonary Hypertension. High flow, Low resistance.

with post-acute sequelae of SARS Cov-2 (PASC). The patient was then referred to chest physiotherapy and discharged from the hospital with home oxygen therapy.

The timeline of the patient’s medical history, present illness, treatment, and outcome is in figure 7.

Discussion

PH is a group of diseases with a hemodynamic definition of mPAp >20 mmHg.⁶ PAH, as a group 1 PH, have additional hemodynamic profiles of PAWP ≤15 mmHg and PVR of ≥3 WU; hence, classified as pre-capillary PH.⁶ The global incidence of PAH-CHD estimates that up to 10% of adults with CHD develop PAH.⁷ Post capillary PH is caused by the backward transmission of high left-sided filling pressures to the post-capillary pulmonary vessels and the rest of the pulmonary circulation, marked by increased PAWP.⁶

Hemodynamic consequences in ASD are related to the anatomic location, size, and associated anomalies. The pathophysiology of PAH in ASD results from pulmonary over circulation caused by the left-to-right cardiac shunt, resulting in endothelial dysfunction, inflammation, smooth muscle hypertrophy, and proliferation. These processes lead to

remodeling of the pulmonary vasculature characterized by excessive vasoconstriction, medial hypertrophy, intimal fibrosis, and plexiform lesions.^{9,10}

ASD often has slow clinical progression and is a high probability of survival into adulthood. Patients usually present have high toleration of the symptoms; hence the diagnosis of ASD could be delayed and detected in older age. The patient’s late manifestation varies, from right heart failure, arrhythmias, paradoxical embolism, or PH.⁸ These findings are consistent with our patient.

PH-associated RV overload could alter the left ventricle’s (LV) geometry and mitral valve apparatus; beget MVP and MR. These led to increased LV filling pressure and pulmonary venous hypertension, subsequently worsened pulmonary vascular remodeling.¹¹ PH associated with left heart disease is subclassified into three broad etiologies: left ventricular systolic dysfunction or left heart valvular dysfunction.¹³ Our patient had MVP that contributed to pulmonary venous hypertension and PAH due to shunt from ASD.

The patient was treated with sildenafil, ramipril, and furosemide. Sildenafil, a PDE-5 inhibitor, is recommended as targeted PAH therapy with class I recommendation by the

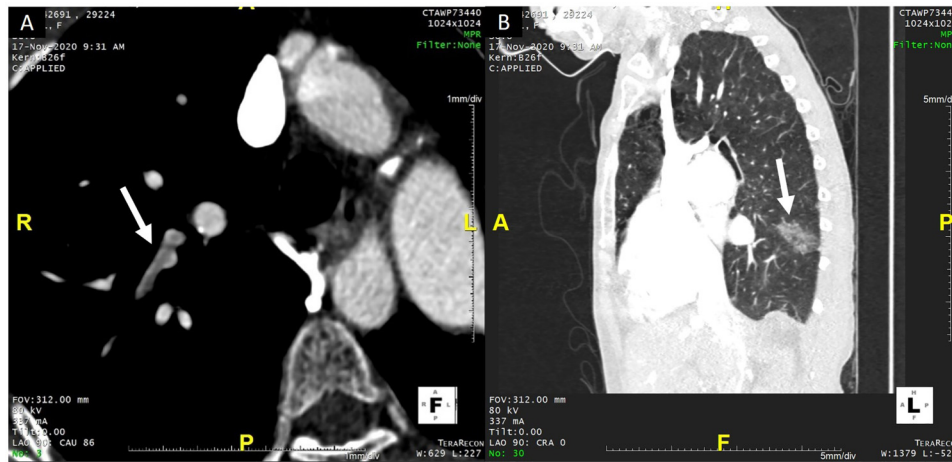


Figure 4. CT pulmonary angiography of the patient showing (A) a filling defect that suggests a pulmonary embolism (white arrow) in the superior pulmonary arteries of the inferior lobes of the lungs bilaterally and (B) a lung infarction (white arrow) in the periphery of the superior segments of the inferior lobes of the lungs bilaterally.

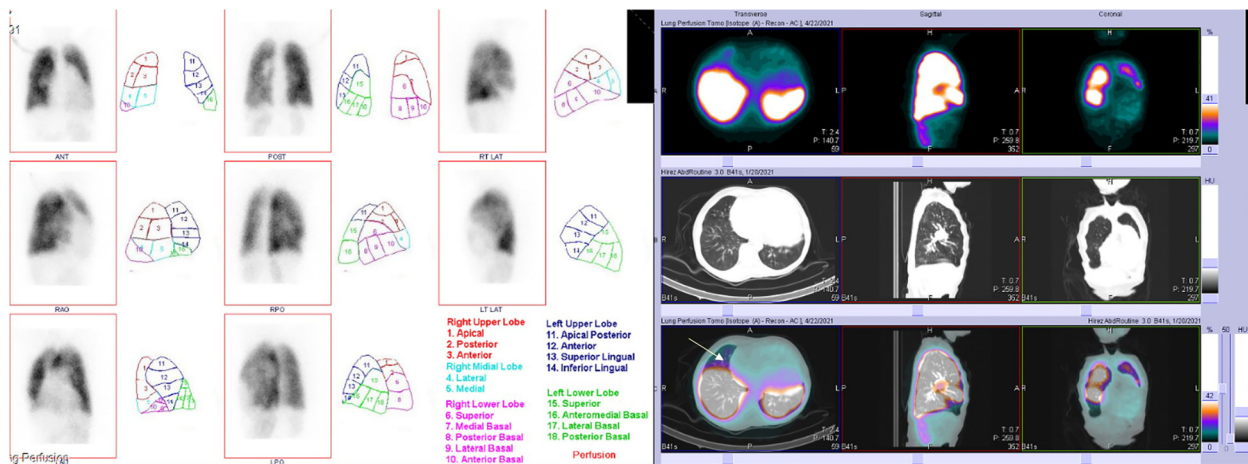


Figure 5. Lung Perfusion Scan of the Patient. The appearance of a segmental perfusion defect in the inferior segment of the bilateral upper lobe (segment number 14) and the anterobasal segment of the right lower lobe (White Arrow) supports the presence of pulmonary embolism in these areas.

CHEST guideline for adult PAH in 2019.¹⁴ A Study from Zeng et al. demonstrates the role of sildenafil in PAH related to ASD; which improve PVR, arterial oxygen saturation, and six-minute walk distance.¹⁵ Hidayati et al. also described sildenafil's improved quality of life in PAH patients due to unrepaired secundum ASD.¹⁶ We also treated the patient with ramipril for heart failure management recommended by recent ACC/AHA guidelines for ACHD.¹⁷ Previous studies have described the benefit of ramipril on chronic MR secondary to MVP, reducing regurgitation and reducing LV end-diastolic pressure and afterload.¹⁸

Hemodynamic assessment for ASD closure should be evaluated carefully in patients with PH. Concomitant left heart disease also made the evaluation more complex, as in our patient, MR, secondary to MVP. Interventional testing such as balloon occlusion test should be considered in the hemodynamics assessment in such conditions.⁶ Recent ACC/AHA

guidelines for ACHD proposed class IIb recommendation for patients with $PVR > 1/3$ SVR or $PASP > 50\%$ systemic pressure.¹⁷ In our case, RHC results also showed differences in pulmonary vein saturation, we assume there are pulmonary abnormalities in these patients. Saturation in LA 85% are because there is a bidirectional shunt which shows an increase in saturation in RA and a decrease in saturation in LA, accompanied by a difference in pulmonary vein saturation. There is no significant stepdown from RV PA. The flow ratio in this patients is 1.67, considered high flow.

In our patients, surgical ASD closure with repair of the mitral valve is the preferred option. Our patients also had Atrial Fibrillation; thus, cryo- or radiofrequency ablation (modified maze procedure) should be considered at the time of surgery.⁶ However, our patient refused surgical repair.

PA thrombosis should be considered in PH patients who deteriorated. Humbert et al. have described patients with PH

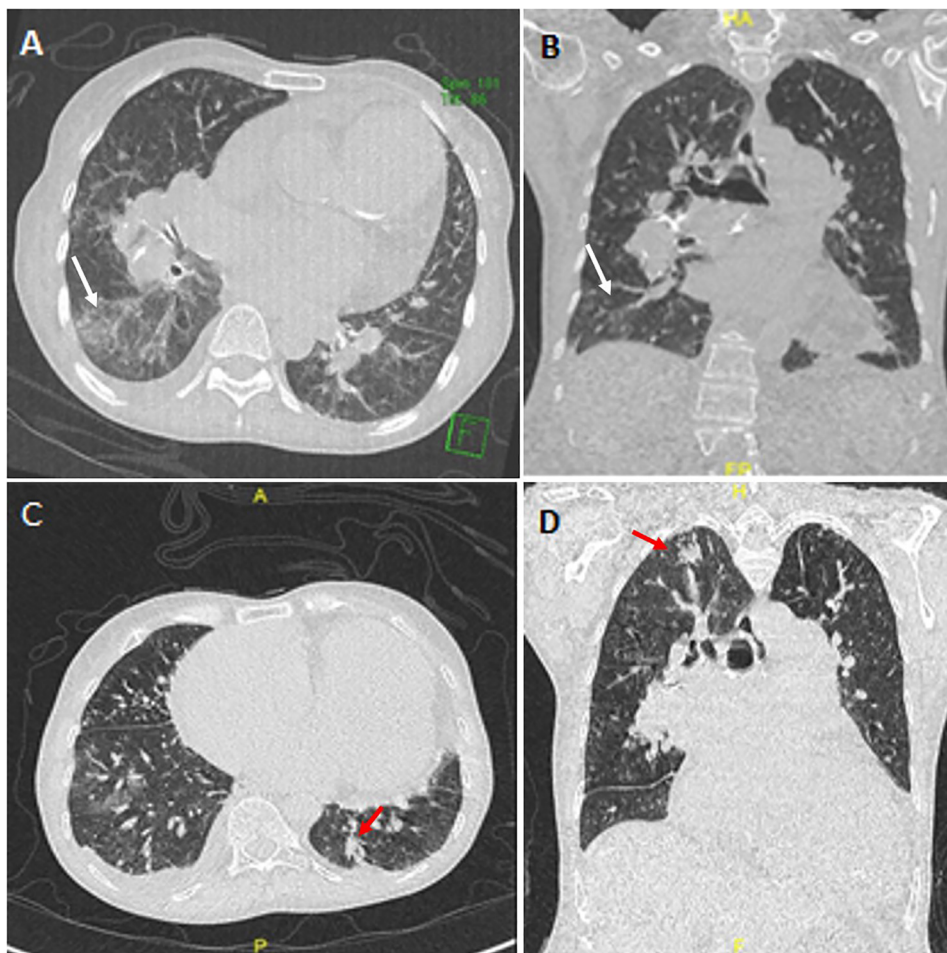


Figure 6. High-Resolution Computed Tomography of the Patient. High Resolution Computed Tomography (A and C) Axial View. (B and D) Coronal View. Showed groundglass opacity in superior segment of inferior lobe of right lung (white arrow Figure A) and anterior basal segment of inferior lobe of right lung (white arrow Figure B); Patchy consolidation of part of the left inferior lobe (red arrow Figure C) and the right superior lobe (red arrow Figure D).

have elevated plasma levels of fibrinopeptide A-, D-dimers, fibrinogen, and decreased fibrinolytic response, which increased the risk of thrombosis.¹⁹ Our patient developed PE with stable hemodynamic. We treated her with intravenous heparin followed by rivaroxaban, as recommended by the American Society of Hematology guideline for VTE management.²⁰ The patient was discharged and planned for life-long anticoagulation.

Three months later, we performed a follow-up lung perfusion scan. The results were typical for CTEPH. CTEPH can develop several months or years after an acute PE, despite continuing anticoagulation in the absence of new symptoms or any new acute event. Failure of thrombi resolution may be related to abnormal fibrinolysis or due to underlying hematological or autoimmune disorders. Other factors that contributed to the development of CTEPH are inflammation, infection, and abnormal right heart function.²¹ Our patient was referred to the hematologic and rheumatologic departments. However, no abnormalities were found. We presumed that our patient's risk factors for CTEPH development were abnormal right

heart function and endothelial dysfunction with concomitant inflammation on the PA due to PH.

Management for CTEPH consists of surgical and medical treatment. Non-surgical approach including anticoagulants, diuretics, and O₂ in hypoxemia cases. Pulmonary endarterectomy (PEA) is the surgical approach for CTEPH, in which operability is determined by the patient's suitability and the expertise of the surgical team and available resources. General criteria include preoperative WHO-FC II-IV and surgical accessibility of thrombi in the main, lobar, or segmental pulmonary arteries.¹⁰ To date, there is no uniformity agreement for optimal treatment for a patient with complex PH, which consists of PAH, group 2 PH, and CTEPH, or could be considered WHO group 5 PH (multifactorial). Hence, we continue anticoagulants, sildenafil, and furosemide.

Our patient was finally diagnosed with PASC due to a severe restrictive pattern from pulmonary functional tests but an inflammatory pattern with minimal fibrosis from the HRCT scan. Effects of COVID 19 are pneumonia and diffuse alveolar damage. Superimposition of consolidation on the existing

Hospital Admission	3 months Follow Up: Readmission	6 months Follow Up	7 Months Follow Up: Readmission	9 Months Follow Up
<ul style="list-style-type: none"> Chief complaint shortness of breath SpO₂ 98% with O₂ 4lpm Chest X-ray showed cardiomegaly with the vascularity pruning of the PA RHC: ASD Secundum L to R shunt; Moderate MR ec MVP; High Flow, low resistance (FR 1.67, PARI 6.98 WU m²), Dx: ASD secundum L to R shunt Plan to surgical closure but the patient refused 	<ul style="list-style-type: none"> Readmission due to recurrent dyspnea Laboratorium : <ul style="list-style-type: none"> hemoglobin 13.1 g/dL leucocyte 6430/mm³ thrombocyte 194000/mm³ urea 32 mg/dl creatinine 1.07 mg/dL Blood gas analyses : Hypoxic respiratory failure Chest X-ray: new infiltrate on the bilateral lower lung field Echocardiography: increase of estimated PA pressure (TRVmax 5.04m/s), sign of massive acute pulmonary embolism (-) CTPA : Acute PE Diagnosed with Acute PE Treated with rivaroxaban 15 mg twice daily 3 weeks, followed by 20mg daily 	<ul style="list-style-type: none"> No worsening of dyspnea V/Q scan: CTEPH Diagnosed with CTEPH Treatment : rivaroxaban 20mg daily 	<ul style="list-style-type: none"> Readmission due to recurrent dyspnea Laboratorium: <ul style="list-style-type: none"> hemoglobin 12.2 g/dL leucocyte 6120 /mm³ thrombocyte 197000/mm³, urea 44.8 mg/dl creatinine 1.51 mg/dL fibrinogen 167.4 d- dimer 1.54 mg/L, Blood gas analyses: hypoxic respiratory failure Chest X-ray showed a new infiltrate on the bilateral lung field Swab PCR : (+) → Confirmed COVID-19 Diagnosed with Confirmed COVID-19 Treatment : <ul style="list-style-type: none"> Remdesivir 200mg IV, followed by 100mg IV n-acetylcysteine 400mg tid bisoprolol 1.25mg daily sildenafil 25mg tid furosemide 40mg IV fondaparinux 5mg SC vitamin C 5000mg daily vitamin D 5000 IU daily omega 3 once daily 	<ul style="list-style-type: none"> worsening of shortness of breath HRCT: ground glass opacity with multiple patchy consolidations. TFP: Severe restrictive Diagnosed with Post Acute Sequele of SARS-CoV 2 Treatment: Chest physiotherapy and oxygen therapy

Figure 7. Timeline of the patients.

ground-glass opacities occurs at the progression/complication stage that evolution to the organizing phase of diffuse alveolar damage. The lesions' pattern can progress to pure consolidation in the later stages of the disease and complicate the recovery phase.²²

The data regarding risks associated with COVID-19 in PH patients are limited. In a US survey of 77 PAH Comprehensive Care Centers, the incidence of COVID-19 infection was 2.1 cases per 1,000 patients with PAH, which is similar to the incidence of COVID-19 infection in the general population. Nonetheless, the mortality rate is higher, which is at 12% in the PAH population. Besides, 33% of patients with PAH who were infected with COVID-19 ended up being hospitalized.²³

PASC is defined as persistent symptoms and delayed or long-term complications of COVID-19 with symptoms of restrictive pulmonary physiology. Several potential mechanisms are contributing to the pathophysiology, including virus-specific damaged and inflammatory processes.²⁴ The prevalence estimates from 13% to 87%. Cardiovascular disease had a higher prevalence of PASC at 30 days. CT finding includes ground-glass opacities, fibrotic changes consisting primarily of reticulations or traction bronchiectasis, as in our patient. However, no specific therapy is recommended for PASC, and

current consensus recommended oxygen therapy and chest physiotherapy.²⁴

Conclusion

PAH is a frequent complication that can occur in a patient with untreated ASD. Various conditions, such as left heart disease, pulmonary embolism, and infections, could also worsen PH. Physicians should not simplify the diagnosis of PH despite clear evidence of structural heart disease. A thorough investigation is crucial to avoid misdiagnosis and inappropriate treatment, which could be fatal.

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Authors' Contributions

AS made conception, determined purpose of the case report, what point will be discussed, analysed and interpreted the case results, drafted the manuscript and revised it. VM contributed in collection of the data and analysis. CJC, HS, HSK, PS, MRA contributed to the analysis of the case and interpretation data. They also gave final approval of the version to be published.

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Ethical Approval/Patient Consent

The informed consent was obtained from participants before taking part in the research


Ethics approval


Our institution does not require ethical approval for reporting individual cases or case series

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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