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Diagnosis and management of combined post- and precapillary pulmonary hypertension in a patient with multiple comorbidities

Abstract

Diagnosis of pulmonary hypertension requires a laborious investigation that must be performed in accordance with international guidelines. Right-heart catheterization is the gold standard examination to assess the degree of hemodynamic impairment of post- or precapillary origin, guiding management. The presence of comorbidities is becoming rather frequent in real-life pulmonary hypertension cases, thus creating diagnostic and therapeutic complexity. We present a case of combined post- and precapillary pulmonary hypertension in a patient with ischemic heart disease and combined pulmonary fibrosis and emphysema, in order to describe the diagnostic algorithm for pulmonary hypertension and elucidate the problematic aspects of managing this debilitating disease in a patient with several comorbidities. Current guidelines do not support the use of specific vasodilator treatment in group II -due to heart disease and group III -due to lung disease pulmonary hypertension, unless the patient presents with severe pulmonary hypertension (mean pulmonary artery pressure >35 mm Hg or cardiac index < 2.0 L/min) with right ventricular dysfunction and is treated in an expert center and preferably in the context of a randomized control trial. In the case presented, therapeutic management focused, firstly, on treatment of the underlying heart and lung disease and, subsequently, on specific vasoactive therapy, due to severe hemodynamic deterioration.

Key words: diagnostic algorithm, combined post- and precapillary pulmonary hypertension, combined pulmonary fibrosis and emphysema

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Introduction

Pulmonary hypertension (PH) arises as a complication of chronic lung or heart disease, increasing morbidity and mortality of the primary disease. Diagnosis requires early clinical suspicion and a laborious investigation. Currently, there is no approved treatment for PH associated with chronic lung disease and heart failure. The objective of this presentation is to describe the diagnostic algorithm for pulmonary hypertension and elucidate the problematic aspects of managing this debilitating disease in a patient with several comorbidities.

Material and methods

A 70-year-old white male (BMI 30.6 kg/m²) presented with worsening dyspnea and fatigue during the last 6 months. He also reported retrosternal chest pain during activity lasting less than 10 minutes. He suffered from emphysema and bronchiectasis and had a history of pneumothorax that was surgically managed by lung decortication 15 years ago. He was a former smoker with a smoking history of 45 pack/years. His medical history also included atrial fibrillation, coronary artery disease that led to coronary artery bypass grafting 10 years ago, goitre and gastroesophageal reflux.

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On clinical examination, he presented normal blood pressure (125/72 mm Hg), tachycardia (95 beats/min), elevated respiratory rate (19 breaths/min) and low oxygen saturation (SaO₂% 88%) on room air. On chest auscultation, lung sounds were diminished uniformly, and bibasilar crackles were found. He presented jugular venous enlargement and mild leg edemas. Cardiac pulse was irregular and loud P2 sound was present. Examination of the abdomen was normal.

Blood cell count and the basic biochemical panel were normal, along with thyroid function. The BNP value was 307 ng/L. Blood gas analysis revealed mild hypercapnia and hypoxemia on room air. Diffusion capacity (D_{LCO}: 25%) was severely diminished, and lung volumes were mildly abnormal (FEV₁: 80%, FVC: 84%, FEV₁%, 72, TLC: 62%, RV: 38%), implying coexistence of restrictive and vascular pathophysiology. 6-minute walking test (6MWT) was 328 m with desaturation from 92% to 84% while receiving oxygen at a flow of 4 lt/min.

Chest X-ray revealed a reticular pattern in the lower lung area bilaterally, and high-resolution computed tomography (HRCT) confirmed new moderate fibrosis of usual interstitial pneumonia (UIP) pattern in the lower lobes (Figure 1). The upper lobes presented emphysema, comprising the diagnosis of combined pulmonary fibrosis and emphysema (CPFE).

Heart ultrasonography revealed an ejection fraction of 50% and diastolic dysfunction of the left ventricle, severe dilatation of the right ventricle with impaired systolic function, moderate insufficiency of the tricuspid valve and an estimated systolic pressure of the right ventricle of 70 mm Hg. Ventilation-perfusion scintigraphy was negative for pulmonary embolism.

Cardiopulmonary exercise testing (CPET) followed in order to discriminate between cardiac and respiratory cause of dyspnea, assess functional capacity, the degree of desaturation and the need for oxygen therapy. The patient had reduced peak oxygen consumption (65% pred), decreased anaerobic threshold (54% pred), elevated ratio of minute ventilation to CO₂ production (46), reduced ventilatory reserve (10lt), and a nadir saturation of 82%. These values were compatible with lowered functional capacity due to respiratory limitation and increased pulmonary vascular resistance.

The patient underwent right-heart catheterization (RHC) revealing combined pre-and post-capillary PH (CpcPH). He had a mean pul-

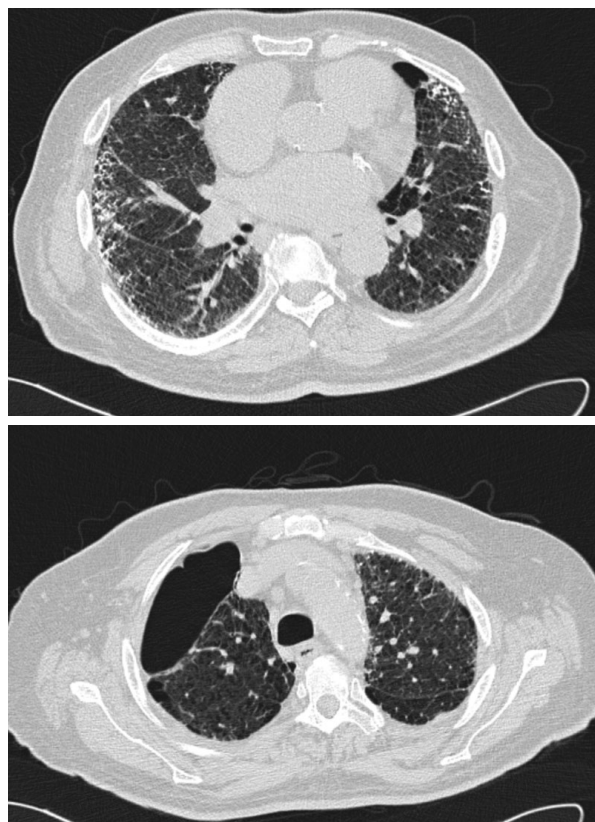


Figure 1. Chest computed tomography

monary pressure (mPAP) of 32 mm Hg, pulmonary wedge pressure (PAWP) of 16 mm Hg, pulmonary vascular resistance (PVR) of 3.2 WI, cardiac index (CI) of 3.5 L/min/m² and a diastolic pulmonary gradient (DPG) of 9 mmHg. According to hemodynamic values, the man was classified as group II-due to heart disease and group III-due to lung disease PH. Current guidelines do not support the use of the approved therapies for pulmonary arterial hypertension (PAH) in these two groups, unless the patient presents with severe pulmonary hypertension (mPAP > 35 mm Hg or CI < 2.0 L/min) with right ventricular dysfunction and is treated in an expert center and preferably in the context of a randomized control trial. Furosemide and continuous oxygen therapy were initiated. The patient was already receiving perindopril, bisoprolol, rivaroxaban, simvastatin, and omeprazole. Low-salt and low-fat intake and mild exercise, as tolerated, were recommended. Moreover, the man received nintedanib, an anti-fibrotic agent as treatment for his lung disease. However, he presented severe gastroesophageal reflux disease that led to immediate discontinuation of treatment. Pirfenidone could not be prescribed as alternative anti-fibrotic treatment due to insurance coverage reasons.

The patient did not present for follow-up and returned deteriorated one year after. His dyspnea occurred in simple tasks, with immediate severe desaturation. We repeated a CT angiography that was negative for pulmonary embolism. Heart ultrasonography presented deterioration with severe enlargement of the right ventricle with flattening of intraventricular septum and a D-shaped left ventricle. The BNP value increased to 897 ng/L. A second RHC revealed an elevated mPAP of 49 mm Hg, PVR of 4.3 WI and normal wedge pressure under diuretic treatment. We decided to initiate sildenafil, a PDE-5 inhibitor, in combination with inhaled iloprost, a prostanoïd analogue, due to the severe impairment of hemodynamics. The patient improved transiently but disease progression led to the unfortunate event of death four months later.

Discussion

The case presented is characterized by challenging complexity. The first RHC revealed CpcPH, as PAWP was > 15 mm Hg and PVR was > 3 WI [1]. Ischemic heart disease explained the post-capillary element of the hemodynamic derangement. The precapillary element was attributed to chronic lung disease, based on the extensive findings on HRCT. The discrimination between group 1 and 3 PH often requires a comprehensive investigation of several criteria, including spirometry, CPET, hemodynamic profile, radiologic findings and PAH risk factors [2]. In our case, the spirometry was not representative of the extent of lung disease and could mistakenly favor the diagnosis of group 1 PAH, as in CPFE, lung volumes appear normal or mildly abnormal due to the opposite effects of expiratory flow and lung volumes [3].

Moreover, at the time of the first RHC, PH was classified as non-severe, and treatment was focused on the underlying lung and heart disease [4]. Currently, the well-established PAH therapies are not approved in groups 2 and 3 PH, as the results from existing studies have been unfavorable [4–7].

Specifically, no multicenter trial exists to support a benefit of vasoactive drugs in group 2 PH [1, 4]. On the contrary, disappointing results from trials testing the efficacy of sildenafil, macitentan, riociguat, epoprostenol and others have accumulated [1]. However, several trials are ongoing to examine the use of these drugs in patients with heart failure with preserved ejection fraction (HFpEF) and CpcPH [1, 8]. A promising signal for this selected subgroup of patients arise

from a few studies on sildenafil and riociguat, encouraging further research [9, 10].

Similarly, the use of vasodilator agents in group 3 PH is generally contraindicated. Endothelin receptor antagonists and riociguat have been deemed harmful, while sildenafil has occasionally been used in group 3 PH with conflicting results [3, 6, 7, 11]. Positive effects have also been reported regarding inhaled iloprost in COPD patients, inhaled and intravenous treprostinil use in patients with severe group 3 PH, with severe right ventricular dysfunction [12, 13].

Existing literature involving the aforementioned group provides heterogeneous results. Brewis *et al* reported an absence of change in 6MWT and FC, and an improvement of BNP levels ($p = 0.015$) after specific PH therapy in 118 patients with severe group 3 PH [5]. Furthermore, the treatment effect was found dependent on lung disease phenotype, with CPFE presenting the worst outcome [5]. However, the study was limited by the absence of a control group that did not receive treatment [5].

Moreover, results from a subgroup of 151 patients of the COMPERA registry with chronic fibrosing interstitial pneumonias and severe PH indicated that PDE5-i long-term use increased 6MWT and functional class in the short term, with unknown effects on survival [14].

Another promising single arm prospective study included 14 patients with severe PH associated with lung disease, 6 of which were diagnosed with CPFE. Repeated cardiac magnetic resonance imaging revealed improvement of right ventricle dilatation and dysfunction after 3 months of treatment with sildenafil, implying potential benefit in this group of patients [15].

Additional trials are currently ongoing to further evaluate long-term efficacy of PAH therapies in severe group 3 PH [7]. Possibly, selected subgroups could be identified to benefit from these drugs, altering therapeutic strategies in the future [7]. To date, recent guidelines and recommendations underline the significance of referral to an expert center for the individualized care of a patient presenting severe hemodynamic derangement with coexisting lung disease [2, 4]. Cautious use of PH specific therapy could be considered, preferably in the context of a randomized control trial, with frequent follow-up assessing treatment effect [4, 7].

Conflict of interest

None declared.

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