



Severe Pulmonary Hypertension Secondary to Concomitant Mitral Stenosis with Veno-occlusive Disease in the Context of Systemic Sclerosis: Importance of Careful and Comprehensive Assessment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Pulmonary Arterial Hypertension (PAH) is a clinical syndrome consisting of physiologic/hemodynamic criteria that are a consequence of several etiologies. Confirmation of pulmonary hypertension is based on right heart catheterization.

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Pulmonary hypertension is a devastating condition that can lead to considerable morbidity and premature mortality. In the last few decades, significant advancement in the pharmacotherapy of pulmonary hypertension has resulted from better understanding of the complex pathogenesis and pathophysiology of this dreaded disease. Despite these accomplishments, pharmacotherapy of pulmonary hypertension is still far from perfect, and the mortality in this modern treatment era is still unacceptably high.

We report a complex clinical presentation characterized by severe pulmonary hypertension secondary to concomitant mitral stenosis with veno-occlusive disease in the context of systemic sclerosis.

Our case highlights the importance of a systematic and comprehensive diagnostic approach to avoid missing an underlying pathology.

Keywords: *Pulmonary arterial hypertension; pulmonary veno-occlusive disease; systemic sclerosis; mitral stenosis; etiological diagnosis; right heart catheterization.*

1. INTRODUCTION

“Pulmonary Arterial Hypertension (PAH) is a clinical syndrome consisting of physiologic/hemodynamic criteria that are a consequence of several etiologies” [1,2]. “Confirmation of pulmonary hypertension is based on right heart catheterization” [3,4,5].

“Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension (PH) characterized by predominantly pulmonary and capillary venous involvement. It may be associated with a connective tissue disease, in particular Systemic sclerosis (SSc)” [3,6,7].

The diagnosis of pulmonary arterial hypertension PAH is based on a rigorous clinical approach comprising 3 stages including the data from the history, the clinical examination and the results of complementary explorations:

- Detection and confirmation of PAH
- Classification of PAH according to the presence or absence of associated pathology
- Evaluation of the severity [4,5].

We report a complex clinical presentation characterized by severe pulmonary hypertension secondary to concomitant mitral stenosis with veno-occlusive disease in the context of systemic sclerosis.

2. CLINICAL CASE

Mr. J. A, 33 years old, with no particular pathological history, presented with a history of aggravation of fatigue and exertional dyspnea associated with palpitations. The clinical examination reveals a diastolic rolling at the mitral focus, a systolic murmur at the tricuspid

focus and a P2 burst at the pulmonary focus, accompanied by jugular turgidity. The clinical examination also found an irregular pulse, congestive signs of heart failure with mild peripheral edema, multiple telangiectasias and Raynaud's phenomenon. Electrocardiogram showed atrial fibrillation and chest X-ray showed significant cardiomegaly.

Transthoracic echocardiography (TTE) was performed, confirming the presence of rheumatic mitral stenosis with a mitral area of 0.8 cm² and mean gradient at 15 mmHg. The left ventricle shows normal systolic function, but the right cavities are dilated. The right ventricle has good function. A systolic pulmonary arterial pressure (PASP) at 121 mmHg. A severe tricuspid regurgitation. A dilation of the pulmonary artery (PA) at 40 mm and its right and left branches is observed.

A thoracic angioscanner revealed signs of pulmonary hypertension with a dilated pulmonary artery of 41 mm as well as its right and left branches, with a diameter ratio of the trunk of the pulmonary artery/aorta of 1.4. significant cardiomegaly depending on the right cavities and the left atrium. Mediastino-hilar lymphadenopathy. Septal thickenings, some pure ground glass micronodules, as well as a dilation of the esophagus, measuring 3.7 cm in anteroposterior diameter. Thoracic angioscanner suggests that PAH is probably secondary to veno-occlusive disease, given the presence of three radiological abnormalities significantly associated with pulmonary veno-occlusive disease: septal thickening, ground-glass opacities and mediastinal lymphadenopathy. A spirometry was performed which objectified the absence of obstructive ventilatory disorder or restrictive syndrome.

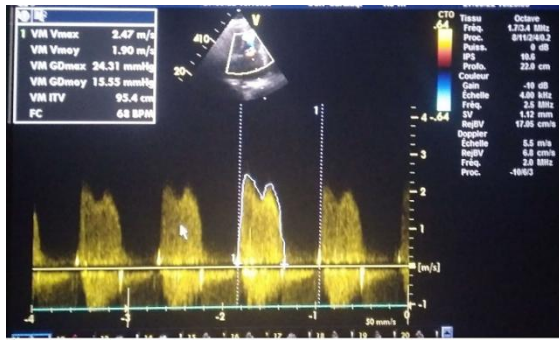


Fig. 1. TTE shows mitral stenosis with a mean gradient at 15 mmHg

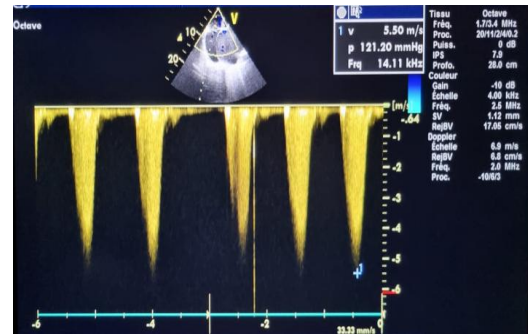
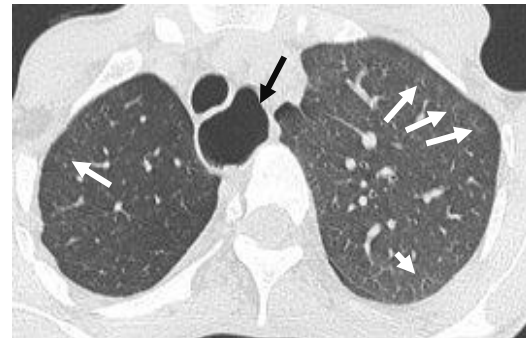
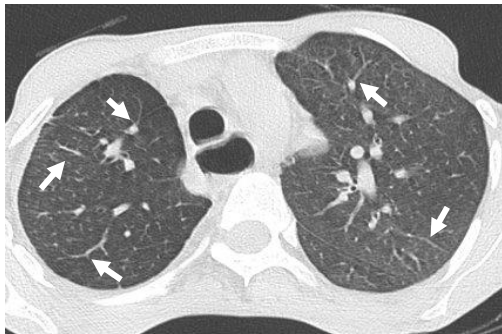


Fig. 2. TTE shows systolic pulmonary arterial pressure at 121 mmHg



Fig. 3. TTE demonstrates a dilated pulmonary artery at 40 mm



Figs. 4,5,6. Thoracic angioscanner shows mediastinum- hilar lymphadenopathy, septal thickenings ↗, some pure ground glass micronodules, as well as a dilation of esophagus ↘



Fig. 7. Thoracic angioscannershowscardiomegaly.

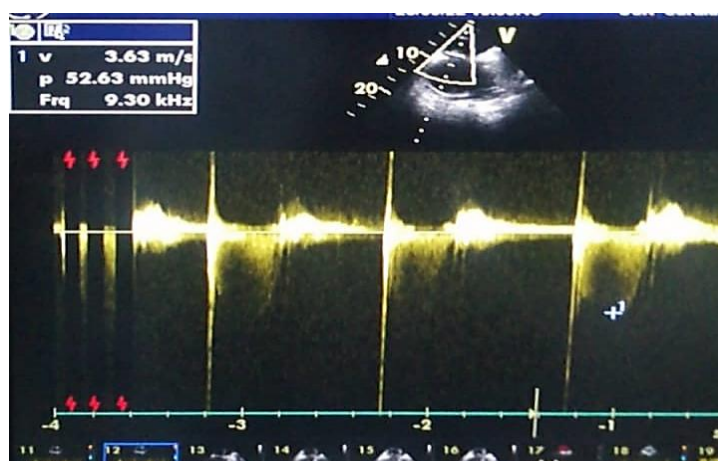


Fig. 8. TTE shows systolic pulmonary arterial pressureafter mitral valve replacement at 52 mmHg

Finally, a right heart catheterization was performed to obtain more precise hemodynamic data, and showed pulmonary arterial pressure (PAP) at 130/25 mmHg and the mean pulmonary artery arterial pressure (mPAP) at 65 mmHg. pulmonary capillary wedge pressure (PCWP) was 22 mmHg. Pulmonary vascular resistance (PVR) (5 Wood Units) was significantly elevated, and cardiac output (CO) significantly decreased (4.2 L/min). The results reveal a combined pre/post-capillary pulmonary hypertension.

In view of the cluster of arguments, the scanographic aspect and the results of right catheter pointing to a veno-occlusive disease and in view of the signs found on clinical examination (Raynaud's syndrome and multiple telangiectasias) as well as the dilatation of the esophagus found on thoracic angioscan, an immunological biological assessment was carried out in search of an associated connective tissue disease. Antinuclear antibodies (ANA) and Autoantibodies against topoisomerase I (anti-Scl

70 antibodies) were positively elevated. According to the results of the blood tests and the classification criteria established by the American College of Rheumatology (ACR), the diagnosis of systemic sclerosis was confirmed in our patient.

To treat mitral stenosis, despite the challenges of surgery and anesthesia due to high-risk pulmonary hypertension (PH), a decision is made to perform mitral valve replacement by Sorin N°33 double-fin mechanical valve. Anesthesia is tailored to minimize the risks associated with high-risk PH. Fortunately, the patient has a good postoperative evolution without major complications.

On subsequent echocardiographic control, a significant improvement in PH was observed, with a PASP measured at 52 mmHg after valve replacement. This decrease in pulmonary arterial pressure indicates a positive response to surgery.

However, control of the chest CT angiography still shows persistent signs in favor of veno-occlusive disease, indicating continued involvement of the pulmonary vessels. The pulmonary artery and its branches still showed dilatation.

To assess hemodynamic status after mitral valve replacement, a new right heart catheterization was performed. The results revealed precapillary pulmonary hypertension this time, with pulmonary arterial pressure (PAP) at 55/18 mmHg and mean pulmonary artery arterial pressure (mPAP) at 33 mmHg. pulmonary capillary wedge pressure (PCWP) was 14 mmHg. Pulmonary vascular resistance (PVR) (3.5 Wood Units) was high, and cardiac output (CO) was at (5 L/min).

The patient has a regular echocardiographic follow-up of his PH with stationary PASP values around 60-70 mmHg. The administration of targeted therapies for PAH is under discussion

because of the major risk of pulmonary edema and the generally poor response.

3. DISCUSSION

Pulmonary hypertension (PH) is defined as :

- An increase in the mean pulmonary artery arterial pressure (mPAP) > 20 mmHg,
- A pulmonary vascular resistance (PVR) of ≥ 3 Wood units (WU),
- "a pulmonary capillary wedge pressure (PCWP) of ≤ 15 mmHg on right heart catheterization (RHC) in the absence of significant Interstitial Lung Disease (ILD)" [8,9].

"PH results in arteriosclerosis, medial hypertrophy with intimal fibrosis and plexiform lesions of pulmonary arteries. The presence of high PVR leads to an increase in the right ventricular pressure causing right ventricle hypertrophy (RVH) and failure of the right side of the heart" [10].

GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
 - 1.1.1 Non-responders at vasoreactivity testing
 - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable
- 1.3 Associated with drug and toxins
- 1.4 Associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1.5 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

GROUP 2 PH associated with left heart disease

- 2.1 Heart failure
 - 2.1.1 With preserved ejection fraction
 - 2.1.2 With reduced or mildly reduced ejection fraction
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

GROUP 3 PH associated with lung diseases and/or hypoxia

- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3. Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

GROUP 4 PH associated with pulmonary artery obstructions

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

GROUP 5 PH with unclear and/or multifactorial mechanisms

- 5.1 Hematological disorders
- 5.2 Systemic disorders
- 5.3 Metabolic disorders
- 5.4 Chronic renal failure with or without haemodialysis
- 5.4 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

Fig. 9. Classification of pulmonary hypertension

Table 1. Hemodynamic classification of pulmonary hypertension

Hemodynamic Classification of PH	Mean Pulmonary artery Pressure (mPAP)	Pulmonary Capillary Wedge Pressure (PCWP)	Pulmonary Vascular Resistance(PVR)
Isolated pre-capillary PH	> 20 mm Hg	< 15 mm Hg	> 3WU
Combined pre- and post-capillary PH	> 20 mm Hg	> 15 mm Hg	> 3 WU
Isolated post-capillary PH	> 20 mm Hg	> 15 mm Hg	< 3 WU

Based on the findings and new recommendations of the European Society of Cardiology/European Respiratory Society on pulmonary hypertension (ESC/ERS), pulmonary hypertension (PH) is classified into five distinct groups, as shown in Fig. 9. The five groups of PH are based on substantiating cause, clinical characteristics, hemodynamic characteristics, and response to therapy [11].

The new guidelines stated the new mean pulmonary arterial pressure (mPAP) of more than 20 mmHg as the cut off for the diagnosis of PH. Accordingly, all patients with mPAP > 20 mmHg will be further differentiated into: precapillary PH, isolated post capillary PH, and combined pre/post capillary PH, based on pulmonary wedge capillary pressure (PCWP) and pulmonary vascular resistance (PVR) (Table 1) [10, 11].

In our case, the initial diagnostic orientation was a post-capillary PH due to mitral stenosis, but in front of the important value of PASP on echocardiography and the dilated pulmonary artery, we decided to complete by a thoracic angioscanner and right catheter in order to eliminate an underlying pathology.

According to the latest recommendations for PH, presented at the ESC Barcelona 2022 congress [11]:

- A right heart catheterization is recommended in case of suspicion of PH in a patient with left heart disease, only if a therapeutic decision follows (class I, C).
- Right heart catheterization is recommended in patients with severe tricuspid insufficiency and with or without known left heart disease before considering an intervention (surgical or percutaneous) (class I, C).
- In case of known left heart disease, but with signs suggestive of precapillary PH and/or right ventricular dysfunction, referral to a PH reference center for

additional assessment is recommended (class I, C).

In our patient, the diagnostic orientation based on a set of arguments (clinical, biological, CT scan and right catheter results) was, in addition to the mitral narrowing, in favor of a veno-occlusive disease associated with a systemic scleroderma.

Pulmonary arterial hypertension (PAH) is a frequent and severe complication of systemic sclerosis (SSc), occurring in 8 to 12% of cases [12,13]. PAH is a manifestation of two of the hallmarks of SSc, vasculopathy and fibrogenesis. Early diagnosis and treatment are highly challenging in SSc-PAH and require referral to an expert PAH centre [14].

Indeed, several mechanisms of PH may occur and coexist in scleroderma, including PAH associated with connective tissue disease (PH group 1.4.1), and PH due to chronic respiratory disease in the context of severe interstitial lung disease (PH group 3). During the course of SSc, PH group 2 (due to heart disease) tends to occur more frequently, mainly through the development of myocardial fibrosis leading to systolic or diastolic left heart dysfunction. Pulmonary veno-occlusive disease (PVOD) can also occur in SSc (PH group 1.5) [9].

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension (PH), first described pathologically by J Hora in 1934 [15]. It can develop in patients with connective tissue diseases (CTD). Most cases have been reported in patients with systemic sclerosis [16]. It is characterized by obliterative fibrosis of the small-caliber pulmonary veins and venules and/or infiltration of the capillaries of the pulmonary interstitium resulting in increased pulmonary vascular resistance leading to right ventricular failure [3,16].

The clinical presentation of PVOD is similar to that of idiopathic pulmonary arterial hypertension (PAH), making the diagnosis difficult; the symptoms are dominated by progressive and often neglected exertional dyspnea, explaining the delay in management. Most patients with PVOD are diagnosed at an advanced stage of the disease (dyspnea in New York Heart Association NYHA functional class III or IV) [3,16,17].

Transthoracic echocardiography (TTE) is useful in screening for PH [18]. There are no specific signs of PVOD on TTE. The features looked for on TTE are the same as for other forms of precapillary PH: dilatation of the right heart cavities, high tricuspid regurgitant velocity, more or less associated with right ventricular dysfunction [3,16]. Echocardiography is neither specific nor sensitive enough to confirm the diagnosis of pulmonary hypertension and right heart catheterization is mandatory in suspected cases.

Lung biopsies are contraindicated in PH and the diagnosis is therefore based on a variety of arguments [5,11]. The diagnosis of PVOD is usually made in the presence of scannographic abnormalities (septal thickening, ground glass opacities and mediastinal lymphadenopathy) [19,20], a collapsed DLCO associated with profound hypoxemia (resting hypoxemia and low carbon monoxide diffusion capacity) [6,17,21]. Right heart catheterization confirms pulmonary hypertension and shows a pre-capillary pulmonary hypertension (PH) pattern with normal pulmonary capillary wedge pressure [3,16].

In the new classification resulting from the latest recommendations of the European Respiratory Society and the European Society of Cardiology on the diagnosis and management of PH, PVOD and/or pulmonary capillary hemangiomatosis are individualized within the group of PAH (group 1) [11].

This disease remains a serious condition. Indeed, despite recent therapeutic advances, there is no curative treatment. The interest of targeted therapies for PAH remains controversial in PVOD because of a lower efficacy than that observed in PAH and a limited tolerance [22,23]. The administration of targeted therapies for PAH should be evaluated on a case-by-case basis because of the major risk of pulmonary edema and the generally poor response [6,17,24].

Due to the poor prognosis of PVOD and limited treatment options, lung transplantation should be considered early in the management of these patients [5,17].

4. CONCLUSION

Pulmonary hypertension is a complication of many conditions. It is crucial to perform a precise etiological diagnosis of pulmonary hypertension to ensure appropriate management. A thorough clinical evaluation, combined with multiple investigations, will help identify the underlying causes of pulmonary hypertension and/or classify it into a specific group.

Our case highlights the importance of a systematic and comprehensive diagnostic approach to avoid missing an underlying pathology.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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