Case study

Severe pulmonary hypertension secondary to concomitant mitral stenosis with veno-occlusive disease in the context of systemic sclerosis: Importance of careful and comprehensive assessment.

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.

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).

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.

Key words : Pulmonary Arterial Hypertension - Pulmonary veno-occlusive disease - Systemic sclerosis - Mitral stenosis - Etiological diagnosis - Right heart catheterization.

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.

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 B2 burst at the pulmonary focus, accompanied by jugular turgidity. Pulmonary auscultation revealed no abnormality. The clinical examination also found an irregular pulse, congestive signs of heart failure with mild peripheral edema, multiple telangiectasias and Raynaud's phenomenon. ECG showed atrial fibrillation and chest X-ray showed significant cardiomegaly.

An echocardiography was performed, confirming the presence of rheumatic mitral stenosis with a mitral area of 0.8 cm². 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 IT. A dilation of the pulmonary artery (PA) and its branches is observed.

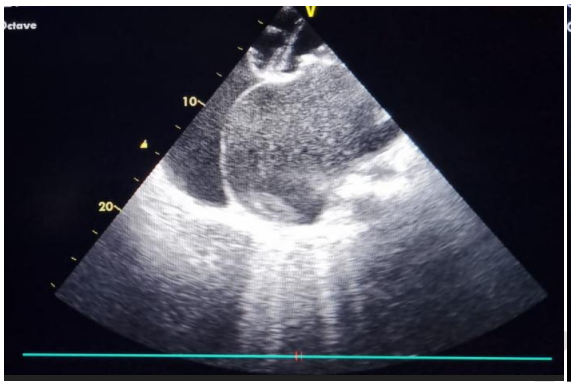

Figure 1. TTE shows mitral stenosis

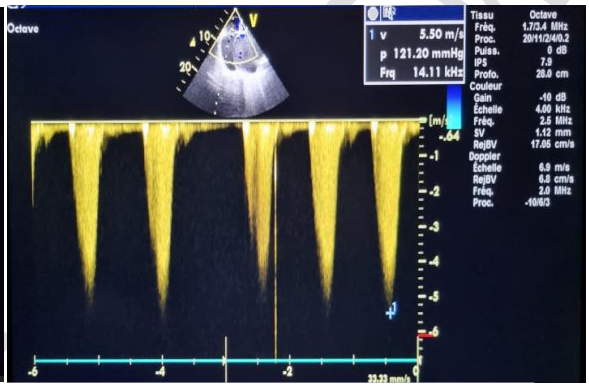

Figure 2. TTE Shows systolic pulmonary arterial pressure at 121 mmHg

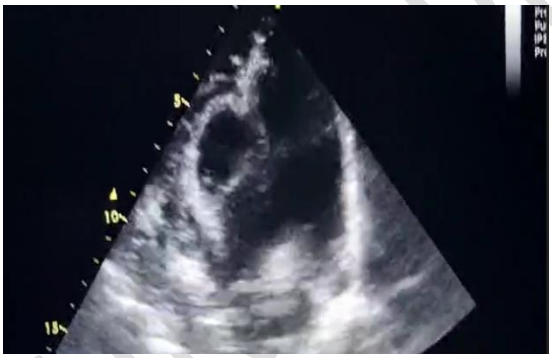

Figure 3. ETT demonstrates a dilated pulmonary artery

A thoracic angioscan revealed signs of pulmonary hypertension with a dilated pulmonary artery of 41 mm as well as these 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. The CT scan suggests PAH probably secondary to veno-occlusive disease.

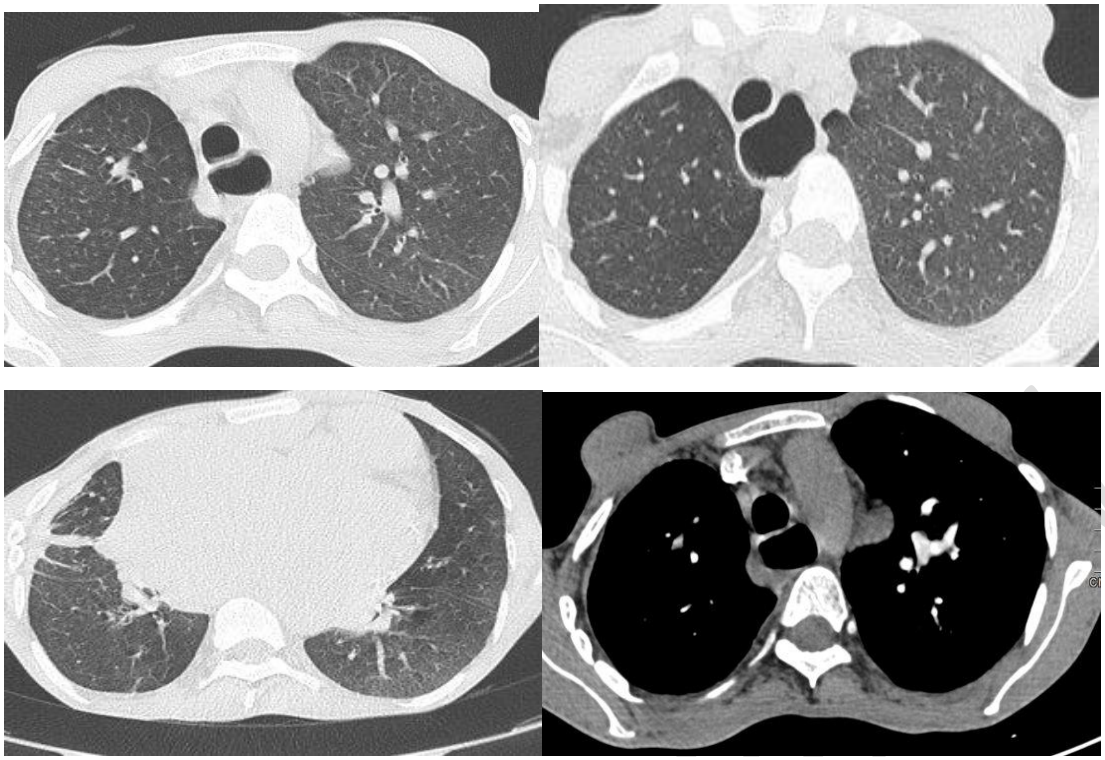

Figure 4,5,6 and 7: Thoracic CT angiogram shows mediastinum-hilar lymphadenopathy, septal thickenings, some pure ground glass micronodules, as well as a dilation of the esophagus.

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) were significantly elevated, and cardiac output (CO) significantly decreased (4.2 L/min). The results reveal a combined pre /post-capillary pulmonary hypertension.

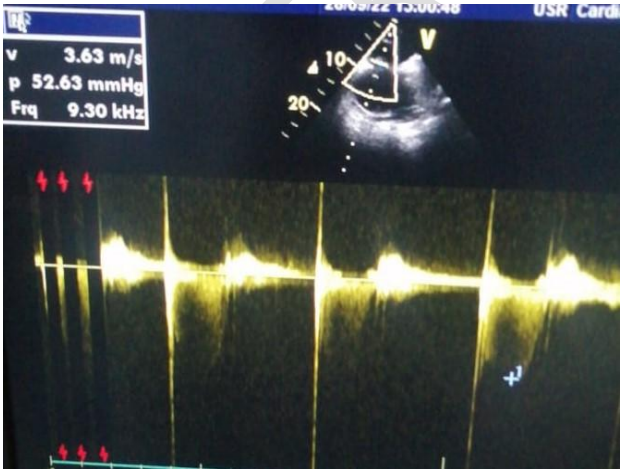

Figure 8. TTE Shows systolic pulmonary arterial pressure

after mitral valve replacement at 121 mmHg

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 angioscanner, an immunological biological assessment was carried out in search of an associated connective tissue disease. Antinuclear antibodies (ANA) and 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. 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).

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 ≥ 3Wood 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].

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 Figure 1. The five groups of PH are based on substantiating cause, clinical characteristics, hemodynamic characteristics, and response to therapy [11].

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[a]
- 1.3 Associated with drugs and toxins[a]
- 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 features of venous/capillary (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[b]
- 2.2 Valvular heart disease
- 2.3 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 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

GROUP 4 PH associated with pulmonary artery obstructions
- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions[c]

GROUP 5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders[d]
- 5.2 Systemic disorders[e]
- 5.3 Metabolic disorders[f]
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

Figure 9. Classification into 5 groups of pulmonary hypertension

The new guidelines stated the new mean pulmonary arterial pressure (PAPm) of more than 20 mmHg as the cut off for 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].

Table 1. Hemodynamic classification of PH.

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

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 latestrecommendations 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 veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension (PH), first described pathologically by J Hora in 1934 [12]. It can develop in patients with connective tissue diseases (CTD). Most cases have been reported in patients with systemic sclerosis [13]. 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 [3,13].

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 NYHA functional class III or IV) [3,13,14].

Transthoracic echocardiography (TTE) is useful in screening for PH [15]. 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 [3,13]. 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) [16,17], a collapsed DLCO associated with profound hypoxemia (resting hypoxemia and low carbon monoxide diffusion capacity) [6,14,18]. Right heart catheterization confirms pulmonary hypertension and shows a pre-capillary pulmonary hypertension (PH) pattern with normal pulmonary capillary wedge pressure [3,13].

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 [20,21]. 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 [6,14,19].

Due to the poor prognosis of PVOD and limited treatment options, lung transplantation should be considered early in the management of these patients [5,14].

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.

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