

# Case Report

## Pulmonary veno-occlusive disease: diagnostic and therapeutic alternatives\*

Doença veno-oclusiva pulmonar: alternativas diagnósticas e terapêuticas

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### Abstract

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension. Surgical biopsy has typically been required for diagnostic confirmation. However, the morbidity, mortality and limited benefit of this procedure have generated discussion regarding noninvasive diagnostic techniques. We present the case of a female patient with progressive dyspnea, hypoxemia and pulmonary hypertension, the last diagnosed via catheterization. Computed tomography revealed septal thickening and diffuse micronodules. Bronchoalveolar lavage revealed occult alveolar hemorrhage. Treatment with an endothelin antagonist was started, resulting in symptomatic and functional improvement. Occult alveolar hemorrhage differentiates PVOD from idiopathic pulmonary hypertension. We believe that this finding, in combination with characteristic tomographic findings, is sufficient to establish a diagnosis of PVOD.

**Keywords:** Hypertension, pulmonary; Pulmonary veno-occlusive disease; Bronchoalveolar lavage; Receptors, endothelin/antagonists & inhibitors.

### Resumo

A doença veno-oclusiva pulmonar (DVOP) é uma causa rara de hipertensão pulmonar. A biópsia cirúrgica era usualmente necessária para seu diagnóstico; entretanto, sua morbidade, mortalidade e seu impacto limitado levantou a discussão sobre o diagnóstico não-invasivo. Apresentamos um caso de uma paciente com dispnéia progressiva, hipoxemia e hipertensão pulmonar no cateterismo. A tomografia computadorizada revelou espessamento septal e micronódulos difusos. O lavado broncoalveolar revelou hemorragia alveolar oculta. Iniciou-se tratamento com antagonista da endotelina, que resultou em melhora clínica e funcional. A hemorragia alveolar oculta é uma característica da DVOP capaz de diferenciá-la da hipertensão pulmonar idiopática. Acreditamos que sua presença, associada à tomografia característica, seja suficiente para o diagnóstico de DVOP.

**Descritores:** Hipertensão pulmonar; Pneumopatia veno-oclusiva; Lavagem broncoalveolar; Receptores de endotelina/antagonistas e inibidores.

### Introduction

Pulmonary hypertension is a complex clinical condition that can result from any one of a number of distinct processes; extensive investigation is therefore required in order to make an accurate diagnosis and institute the correct treatment.<sup>(1)</sup> Among the various forms of pulmonary hypertension is pulmonary veno-occlusive disease (PVOD),<sup>(2)</sup> which is characterized by the fact that it primarily affects the venous compartment of the pulmonary vascular system. The definitive diagnosis of PVOD is made through surgical lung biopsy.<sup>(3)</sup> However, the morbidity and mortality associated with performing biopsies in this population of patients,

together with the fact that the diagnosis has only a limited impact on the long-term treatment plan, have motivated the development of new diagnostic tools that involve less invasive procedures, such as the combination of bronchoalveolar lavage and computed tomography of the chest.

### Case report

A 58-year-old, previously healthy, female patient present with a 4-year history of dyspnea on great exertion and cyanosis of the extremities. The symptoms progressed

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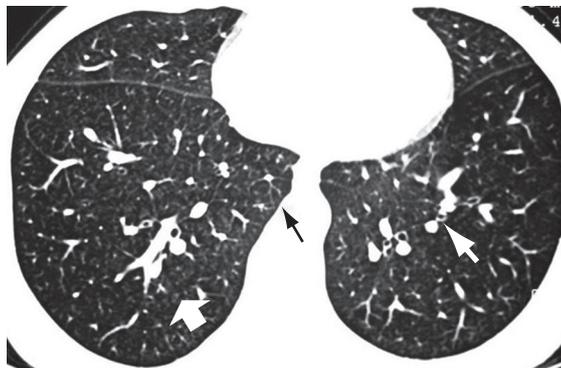
within the preceding 18 months, and, within the last 6 months, the patient had experienced dyspnea on minimal exertion (functional class III). She stated that she had not presented upper-limb edema, chest pain or syncope. By her own admission, she was a former smoker, with a 24 pack-year history, although she had quit smoking 26 years prior. The physical examination revealed cyanosis, regular cardiac rhythm with hyperphonestosis of the second heart sound, normal breath sounds and peripheral oxygen saturation ( $\text{SpO}_2$ ) at 84% on room air.

A chest X-ray revealed prominence of the medial pulmonary artery, and a computed tomography scan of the chest showed dilation of the arterial branches, with an artery-bronchus ratio of  $> 1$ , septal thickening and diffuse micronodules (Figure 1). The pulmonary function tests results showed that airflow and lung volumes were normal, but that there was a significant reduction in the diffusing capacity of the lung (30% of predicted). An echocardiogram revealed dilated right heart chambers and pulmonary artery systolic pressure estimated at 84 mmHg. The patient was submitted to the six-minute walk test (6MWT), and the distance covered was 375 m. Tests for connective tissue diseases, HIV infection, portal hypertension and chronic pulmonary embolism were all negative.

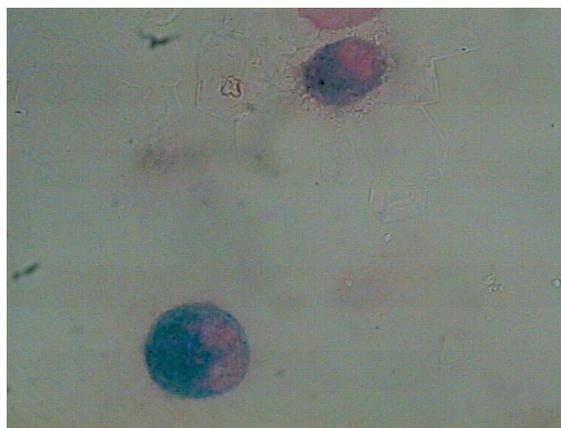
Right heart catheterization was performed, and the findings confirmed the diagnosis of pulmonary hypertension: mean pulmonary artery pressure, 48 mmHg; right atrial pressure, 6 mmHg; pulmonary wedge pressure, 8 mmHg; cardiac output, 2.6 L/min; and pulmonary vascular resistance, 15.3 Woods units (unresponsive to nitric oxide).

Based on the tomographic findings, we decided to investigate PVOD using bronchoscopy and bronchoalveolar lavage (BAL). The cytological analysis revealed a predominance of macrophages (89% of the total number of cells), 50% of which were hemosiderin-laden (Figure 2). Therefore, the presumptive diagnosis was PVOD.

Full anticoagulation with warfarin was started, together with specific treatment of the pulmonary hypertension using the endothelin receptor antagonist bosentan, at 125 mg/day for four weeks and at 250 mg/day thereafter. After 6 months of follow-up, the patient presented significant functional improvement, evolving to functional class II, with an  $\text{SpO}_2$  of 90% on room air and covering 500 m on the 6MWT.



**Figure 1** - Tomography scan of the chest showing septal thickening (black arrow), artery-bronchus ratio  $> 1$  (narrow white arrow) and diffuse micronodules (broad white arrow).



**Figure 2** - Photomicrograph of the bronchoalveolar lavage showing heavily hemosiderin-laden macrophages (magnification,  $\times 1,000$ ).

## Discussion

Pulmonary hypertension is rarely caused by PVOD, which accounts for only 10% of all cases initially considered idiopathic.<sup>(3,4)</sup> Prior to 2003, PVOD was classified as venous pulmonary hypertension. However, it is currently included in the arterial hypertension category, since it presents clinical characteristics similar to those of idiopathic pulmonary arterial hypertension and has the same risk factors.<sup>(2)</sup> Although PVOD is most often seen in children and young adults, it can appear as early as the first year and as late as the seventh decade of life; among adult patients, it occurs predominantly in males (at a ratio of approximately 2:1).<sup>(1,5)</sup>

The cause of PVOD is unknown. It might represent an idiopathic process or a common pathological response to various injurious stimuli.<sup>(3)</sup> Among the potential etiologies are genetic factors (familial cases of PVOD related to mutation of the bone morphogenetic protein receptor II gene having been reported),<sup>(6)</sup> autoimmune diseases and infections,<sup>(3)</sup> It remains unknown whether smoking plays a role. From an anatomopathological point of view, PVOD is characterized by the following<sup>(3)</sup>: intimal fibrosis and medial hypertrophy, together with thrombi, in the pulmonary veins and venules; medial hypertrophy, albeit without plexiform lesions, in the arteries; and interstitial edema, accompanied by hemosiderosis, in the parenchyma.

In PVOD, the clinical profile resembles that of pulmonary hypertension resulting from other causes, including progressive dyspnea on exertion, with or without signs of *cor pulmonale*.<sup>(7)</sup> The diagnosis should be based on the clinical presentation and on any radiological alterations suggestive of pulmonary edema, such as septal lines, basal reticular opacities and pleural effusion.<sup>(3,5)</sup> Specifically, characteristic findings on tomography scans of the chest include smooth septal thickening, diffuse micronodules and ground-glass opacities.<sup>(8)</sup> Pulmonary function tests typically show a reduction in the diffusing capacity of the lung.<sup>(5)</sup>

In catheterized patients, an increase in pulmonary artery pressure can be seen, although pulmonary wedge pressure remains normal.<sup>(9-11)</sup> Typically, PVOD patients do not respond to vasodilators and can even develop acute pulmonary edema when treated with prostacyclin, a reaction considered strongly suggestive of a diagnosis of PVOD.<sup>(12)</sup> Nevertheless, in the largest case-series study of PVOD to date, 10 PVOD patients received vasodilators, and 8 of those patients presented a favorable response, whereas only one developed pulmonary edema. Despite such suggestive clinical, radiological and hemodynamic characteristics, diagnostic confirmation can only be obtained through surgical lung biopsy.<sup>(3)</sup>

Due to the predominance of the postcapillary component, occult alveolar hemorrhage, as evidenced by hemosiderosis, is considered another characteristic of PVOD.<sup>(3)</sup> It has recently been demonstrated that the quantification of hemosiderin-laden macrophages in BAL fluid can be used as a means of differentiating between patients with PVOD and those with idiopathic pulmonary hypertension

Since such patients present functional limitation, and since surgical lung biopsy implies considerable morbidity and mortality, a presumptive diagnosis of PVOD should be made based on the combination of suggestive tomographic findings and BAL-proven occult alveolar hemorrhage.

There have been no controlled studies of treatments for PVOD. There have been only a few, isolated reports of clinical and functional improvement brought about through the use of medications, such as nifedipine and prostacyclin.<sup>(9,11)</sup> However, prostacyclin and its derivatives should be used with extreme caution due to the risk of pulmonary edema resulting from the preferentially arterial vasodilation. Lung transplantation is currently considered the only treatment capable of significantly increasing survival.<sup>(3)</sup> Without treatment, the prognosis is poor, and the majority of patients die within two years after diagnosis.<sup>(4)</sup>

In the case presented here, we opted to treat the patient with an endothelin receptor antagonist, since its antiremodeling effect tends to overpower its vasodilator effect,<sup>(14-16)</sup> thereby reducing the risk of hemodynamic complication as well as slowing the progression of the disease. We believe this to be the first case of PVOD to present a favorable clinical response to this class of drug.

The case presented here highlights the possibility of making a presumptive diagnosis of PVOD using a noninvasive technique (bronchoscopy), as well as the potential benefit of endothelin receptor antagonists in treating PVOD. This combination can have advantages for patients not only in that it offers a therapeutic option but also in that it can obviate the need for surgical lung biopsy.

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