

Scientific Letters

The First Experience of Pulmonary Venocclusive Disease Treatment With Macitentan and Sildenafil**Experiencia única con macitentan y sildenafil en el tratamiento de la enfermedad venooclusiva pulmonar****To the Editor,**

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary arterial hypertension. PVOD shares many characteristics with idiopathic pulmonary arterial hypertension, making it very difficult to distinguish between these conditions. Accurate diagnosis is essential because PVOD has a worse prognosis, and treatment with specific vasodilators can trigger acute pulmonary edema. Currently, the only effective treatment is lung transplantation.¹

We present the case of a 74-year-old woman who was initially diagnosed with pulmonary arterial hypertension and was treated with macitentan and sildenafil. The patient showed significant improvement with this treatment, even though subsequent diagnosis revealed that she very likely had PVOD.

The patient's medical history included Sjögren syndrome, diagnosed several years previously based on presentation with dry eyes and a positive antinuclear antibody test.

The patient was first admitted in January 2015 with a diagnosis of severe congestive heart and respiratory failure secondary to atrial flutter with a rapid ventricular response. On admission, echocardiography revealed evidence of severe pulmonary hypertension and right ventricular dysfunction, whereas left cavity dimensions and function were normal (left atrium anteroposterior diameter, 33 mm). Symptoms improved substantially with diuretic therapy and reversion to sinus rhythm, and the patient was discharged. She was readmitted 1 month later with similar symptoms, but this time in sinus rhythm. The decision was taken to conduct the battery of diagnostic tests recommended for the study of pulmonary hypertension: abdominal ultrasound, serology for hepatotropic and human immunodeficiency viruses, respiratory function tests, lung computed tomography with contrast, and ventilation-perfusion scintigraphy.^{2,3} These tests revealed no major involvement. The study was completed with a right-side catheterization that revealed severe pulmonary arterial hypertension (pulmonary artery occlusion pressure, 7 mmHg), with highly elevated pulmonary arterial resistance and severely impaired cardiac output (Table). A nitric oxide vasodilation test conducted during the same

catheterization was positive according to current guidelines,^{2,3} and treatment was therefore commenced with calcium antagonists. The patient showed a good initial response to increasing doses of amlodipine; however, at the end of May she was readmitted with congestive heart failure.

A diagnostic review revealed that the patient had limited systemic sclerosis (calcinosis, telangiectasias, microstomia, Raynaud phenomenon, and positive tests for anti-centromere, anti-sp100, and anti-pM-scl antibodies). The worsening condition was attributed to the nonresponsiveness of patients in this subgroup, and the decision was taken to start treatment with macitentan at 10 mg/d.

The response over the following months was clearly satisfactory, albeit insufficient. In September 2015 sildenafil was added at a dose of 20 mg/8 h, and a few weeks later the patient was once again admitted with worsening breathlessness and congestive heart failure. A cardiac nuclear magnetic resonance examination showed no signs of left heart disease and indicated acceptable right ventricle function. Repeat right heart catheterization confirmed clear improvement in cardiac output and pulmonary artery resistance (Table). Even after administration of 500 mL physiological saline solution, the pulmonary artery occlusion pressure remained below 17 mmHg at all times, definitively excluding a combination of heart failure with preserved ejection fraction.

A high-resolution lung computed tomography scan was requested and demonstrated a centrilobular distribution of nodular ground-glass opacities, mediastinal lymphadenopathies of up to 3.8 cm diameter, and septal thickening (Figure). In repeat tests, all respiratory functions were normal except for extremely low lung carbon monoxide diffusion capacity (DLCO) after adjustment for alveolar volume (DLCO/AV 44%) and severe chronic hypoxemia. Together, these findings very strongly suggested that the patient had PVOD associated with systemic sclerosis.

Today, more than 1 year after symptom onset, the patient is in dyspnea functional class II/IV. Her condition shows no sign of deterioration, her brain natriuretic peptide concentration is normal, her 6-minute walk distance is about 325 m, and her echocardiography-measured right-ventricular function parameters and cavity size are also within the normal range. Her situation is thus stable and satisfactory (Table) and given the risk of complications we have no plans to intensify treatment.

Diagnostic confirmation of PVOD requires histological analysis; however, lung biopsy is contraindicated in most patients. Lung computed tomography is currently considered a major diagnostic tool, and the 3 radiological signs found in our patient together give

Table
Prognostic Variables Before and After Treatment With Macitentan and Sildenafil

	WHO-FC	No. admissions	TAPSE	S	FSRV area	RVEF (MR)
Before	III	5	11 mm	7 cm/s	25%	
After	II	1	22 mm	12 cm/s	47%	47%
	6MWD	CI	PVR	PAPm	RAP	BNP
Before	144 m	1.9 L/min/m ²	12 WU	36 mmHg	4 mmHg	2791 pg/mL
After	325 m	3.28 L/min/m ²	6.4 WU	42 mmHg	8 mmHg	87 pg/mL

BNP, brain natriuretic peptide; CI, cardiac index; FSRV area, fractional shortening of right ventricular area; PAPm, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; RVEF (MR), right ventricular ejection fraction measured by magnetic resonance; S, systolic tricuspid annular velocity measured by Doppler tissue imaging; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class; WU, Wood units; 6MWD, 6-minute walk distance.

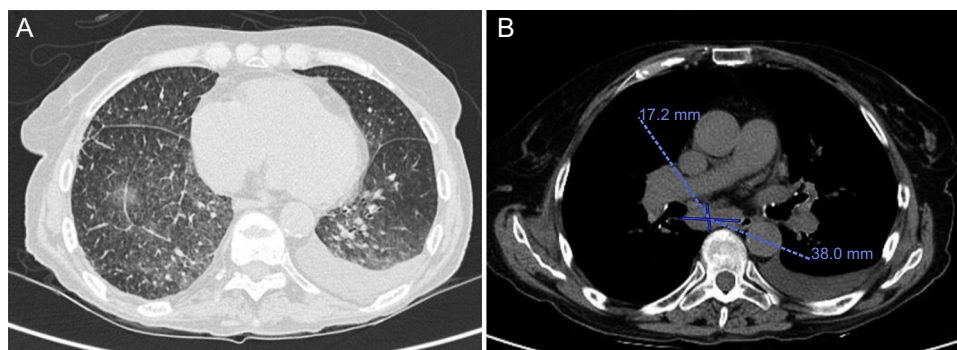


Figure. High-resolution lung computed tomography. A, Nodular ground-glass opacities with a centrilobular distribution and thickening of interlobular septa. B, Subcarinal mediastinal adenopathy, with a diameter up to 38 mm.

a specificity of up to 100%.² In addition, a DLCO below 55% has a specificity of 89.5%, and the diagnosis is further strengthened by the right-side catheterization data and the respiratory failure.

The initiation of specific treatment in PVOD patients carries a recognized risk of acute pulmonary edema. Nonetheless, improvements with these therapies have been documented in small series and individual cases, the vast majority with low dose epoprostenol. To date, only minor and transient improvements have been documented with oral vasodilators,⁴ and there is only 1 reported positive experience with combined treatment.⁵ This is thus the first report of a clear improvement with combined oral therapy and a beneficial effect of macitentan in the treatment of PVOD.

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Late Detachment of an Aortic Prosthetic Valve and Reactivation of Takayasu Arteritis



Dehiscencia tardía de prótesis valvular aórtica y reactivación de arteritis de Takayasu

To the Editor,

Takayasu arteritis (TA) is a chronic autoimmune disease that affects the aorta and proximal segments of arteries arising from the aortic arch, especially the left subclavian artery. The pulmonary artery, its branches, and sometimes the coronary circulation may also be involved. The disease causes dilatation of the affected vessels with or without the formation of aneurysm, and stenosis or occlusion, accompanied by vessel wall thickening and calcification.¹

The incidence of significant aortic regurgitation is estimated to be between 13% and 25% in patients with TA. The etiology has been associated with aortic root dilatation,¹ as well as with aortic valve

leaflet inflammation.² Aortic regurgitation, hypertension, and, sometimes, coronary lesions are the main factors associated with the onset of heart failure.¹ Aortic valve surgery entails a significant risk of prosthetic valve detachment and the formation of pseudoaneurysms along the suture line.^{1,3,4}

We present the case of a male patient with TA who had received an aortic valve replacement. The immunosuppressive therapy was discontinued, TA reappeared, and late valve detachment then occurred.

The patient was diagnosed with TA and hypertension in 2001, at the age of 16 years. Magnetic resonance imaging showed damage to the ascending aorta, aortic arch and descending thoracic aorta, and stenosis of the left subclavian artery. The ultrasound study revealed mild aortic regurgitation and moderately depressed systolic function. The patient was treated with corticosteroids, methotrexate and antihypertensive medication. In 2003, he had symptoms of heart failure. An echocardiogram showed severe aortic regurgitation, moderately reduced systolic function, and dilatation of the ascending aorta. The patient