Occlusive Venopathy Phenotype in Hereditary Pulmonary Arterial Hypertension

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A 33-year-old male with severe hereditary pulmonary arterial hypertension had a confirmed diagnosis of occlusive venopathy and microvasculopathy. He remained stable for three and a half years on oral sildenafil, 75 mg t.i.d. (six-minute walked distance of 375 m *vs* 105 m at baseline), but required addition of bosentan (125 mg b.i.d.), subsequently. Despite the fatal outcome at five years post-diagnosis, the observations suggest a potential usefulness of vasodilators as a bridge for lung transplant in selected cases with significant venous/capillary involvement. The occurrence of veno-occlusive and capillary lesions in the familial form of pulmonary arterial hypertension reinforces the difficulties with the current classification of the disease.

Introduction

Hereditary transmission of pulmonary arterial hypertension (PAH) has been identified in 6% to 10% of PAH subjects. Bone morphogenetic protein type-2 receptor (BMPR2) gene mutations have been reported in 50% to 90% of families with PAH[1]. Pulmonary occlusive venopathy (POV, formerly pulmonary veno-occlusive disease) is a rare form of histological presentation of PAH, found in approximately 5% of biopsies from patients with unexplained pulmonary vascular disease[2,3]. Even less frequent is the familial presentation of POV. One single family report, with BMPR2 mutation detected[4], led to the inclusion of POV (and pulmonary microvasculopathy, formerly pulmonary capillary hemangiomatosis) in the first diagnostic category of pulmonary hypertension (namely, PAH). One striking characteristic of POV is the poor outcome, in some cases, following vasodilator administration (particularly epoprostenol), with development of massive pulmonary edema and death[5,6]. We report a case of confirmed POV associated with microvasculopathy, with familial history of PAH, that remained stable for five years on oral vasodilator therapy, without development of pulmonary edema.

Keywords

Pulmonary hypertension; pulmonary occlusive venopathy; microvasculopathy; hereditary pulmonary arterial hypertension; sildenafil.

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Case report

A 33-year old male was admitted in October 2002, with recent and progressive dyspnea, edema and ~10 kg weight loss. Two sisters of his had died of "primary pulmonary hypertension" at the ages of 11 and 14 years. There were no further data suggesting specific cardiac, respiratory or infectious diseases, joint or skin abnormalities or use of appetite suppressants. On physical examination he had a "weak" (undernourished) appearance (weight 60 kg; height 1.82 m), mild liver enlargement and lower limb edema. A loud pulmonic valve closure sound was heard on the precordium. Lung examination revealed mild rhonchi and fine rales on both sides, which disappeared completely following diuretic administration. Complementary imaging and laboratory tests for heart liver and lung disease, chronic thromboembolism, schistosomiasis, human immunodeficiency virus infection and connective tissue disorders were negative. DNA sequencing methodologies revealed no mutations in the coding region of the patient's BMPR2 gene. Right heart catheterization data were compatible with pulmonary arterial hypertension. Both inhaled nitric oxide and oral sildenafil were effective in reducing pulmonary vascular resistance. A marked elevation of the wedge pressure was registered during nitric oxide inhalation (Table 1). Open-lung biopsy confirmed the suspicion of pulmonary occlusive venopathy and depicted the concomitance of microvasculopathy (Figure 1).

During the first two years of oral sildenafil therapy (75 mg t.i.d.), there was a sustained improvement in the six-minute walked distance (105 m and 399 m, respectively at baseline and 2 years) associated with an increase in Doppler-echocardiographic estimate of pulmonary (and systemic) flow (pulmonary systolic flow velocity-time integral of 0.10 m and 0.19m, respectively). Pulmonary edema was never observed. The clinical status deteriorated from three and a half to 4 years (walked distance 375 m to 261 m); bosentan was added (125 mg b.i.d., orally, final dose), and the patient was listed for lung transplantation. He died at five years post-diagnosis, despite the use of the combined therapy. Autopsy findings confirmed the initial diagnosis.

Discussion

The present case adds elements to the discussion on the familial presentation of POV. First, since we do not have histological data from other family members (especially those who died of "primary pulmonary hypertension"), we cannot affirm that the phenotype of the other PAH subjects was really POV. The same point was mentioned by Runo et al[4] and co-workers in their family report. Thus, it remains

Table 1 - Baseline hemodynamics and acute pulmonary vasodilator test

		Baseline	10 ppm NO* (10 min)	Interval	75 mg Sildenafil†
Heart rate (bpm)		89	74	92	81
Systemic pressure (mmHg)	systolic	94	94	97	95
	diastolic	68	66	66	62
	mean	78	78	79	76
Pulmonary pressure (mmHg)	systolic	90	75	99	78
	diastolic	48	36	49	32
	mean	61	48	65	44
	wedge	8	29	9	15
Cardiac index (l/min/m^2)		1.9	2.3	2.2	2.6
Systemic vascular resistance (dyn•s•cm^{-5})		3,156	2,746	2,726	2,522
Pulmonary vascular resistance(dyn•s•cm^{-5})		2,230	661	2,035	892

** Inhaled nitric oxide. † Measurements performed one hour after oral administration.*

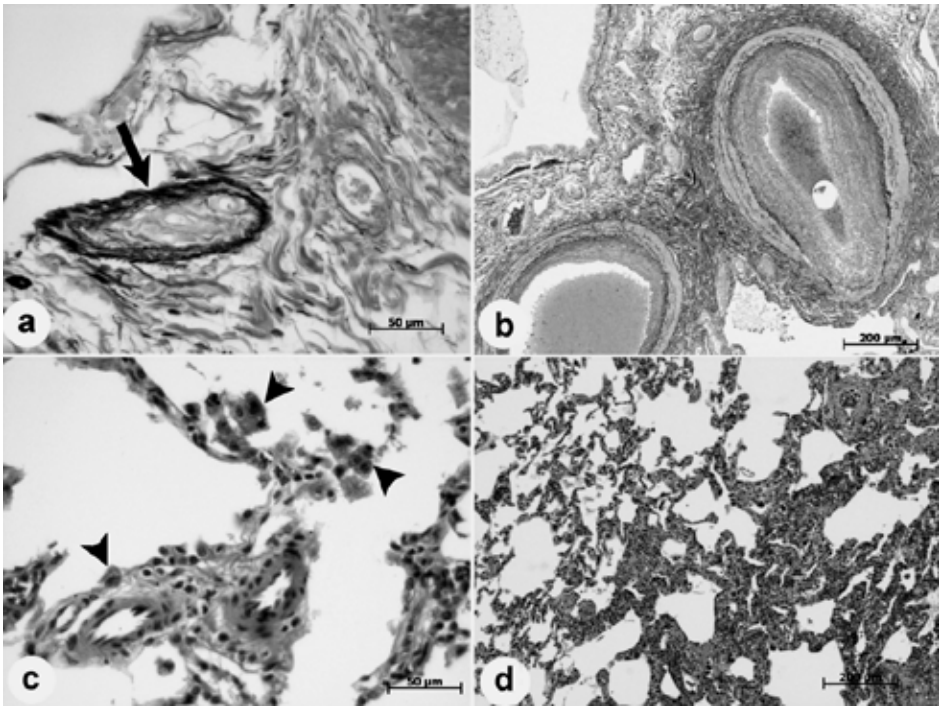

Figure 1 - *Photomicrographies of the lung biopsy showing in: A) a venule with fibrotic luminal occlusion (arrow); B) severe intimal proliferative lesions in pre-acinar arteries; C) Hemosiderin-laden macrophages in the alveoli lumens (arrow heads) and hypertrophy of small intra-acinar arterioles; D) a focus of the so-called "microvasculopathy" (formerly capillary hemangiomatosis), characterized by proliferation of capillaries within alveolar septa (right lower corner). The final histopathological diagnosis was pulmonary occlusive venopathy, concomitant with microvasculopathy. Hematoxylin-eosin stain in "c" and "d" and Miller´s elastic stain in "a" and "b". Objective magnifications 20X (for panels "c" and "d") and 5X (for panels "a" and "b").*

to be clarified whether POV is an individual expression of pulmonary vascular disease in these families or affects all family members. Furthermore, the frequent concomitance of occlusive venopathy and microvasculopathy foci in lung tissue has brought the possibility that they represent a morphological spectrum of the same entity. Second, since we did not analyze other genes of the TGF-beta superfamily, we cannot exclude mutations in these genes as a possible explanation for the familial character of the disease in the present report. Alternatively, the possibility remains that POV with familial PAH presentation is related to genes other than the TGF-beta family. Anyway, the concomitance of POV/microvasculopathy

and familial presentation reinforces the limitations of the current classification of pulmonary hypertension, where these conditions appear separately in the first diagnostic category (pulmonary arterial hypertension)[7].

Another point to be discussed is the relatively stable clinical course on vasodilator therapy. High-dose sildenafil was administered from the beginning, since treatment was started far before the publication of the SUPER-1 study[8]. Despite the evidence of the beneficial effects of sildenafil and bosentan in PAH, there have been no reports on the use of these drugs in rare conditions, as is the case of POV/microvasculopathy. One possible explanation for the non-occurrence of pulmonary edema in the present case is the presence of markedly obstructive lesions at the arterial side of pulmonary circulation (Figure 1). On the other hand, preliminary observations in the catheterization laboratory suggested that sildenafil, in particular, may have different effects on the pulmonary venous circulation as compared with other vasodilators, such as inhaled nitric oxide[9]. This is in agreement with our initial observations of mild elevation of pulmonary wedge pressure following sildenafil (single dose) administration and points toward the need for controlled studies to investigate the effects of this drug (as well as other vasodilators) in the setting of PAH with significant venous involvement.

Conclusions

Pulmonary occlusive venopathy and microvasculopathy may occur concomitantly in hereditary PAH. In selected cases, chronic oral therapy with sildenafil may be of help as bridge to lung transplantation. Controlled studies are obviously needed in this way. However, the rare character of the disorder is a clear limitation to the analysis of large series.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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