Multiple Peripheral Pulmonary Artery Stenoses in Adults: A Rare Cause of Severe Pulmonary Hypertension Necessitating Lung Transplantation

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Stenoses of multiple peripheral pulmonary artery branches represent a rare cause of pulmonary hypertension in children, but the prognosis is very poor for such patients. Herein we describe 2 patients with multiple peripheral pulmonary artery stenoses (MPPAS) presenting with severe pulmonary arterial hypertension in adulthood, which has only once been described previously. Both patients lived without significant health problems for decades; however, after onset of symptoms, their medical condition declined rapidly, necessitating lung transplantation several months after the diagnosis despite vasodilator therapy. Because MPPAS mimics chronic thromboembolic pulmonary hypertension, this entity may be underdiagnosed, decreasing the possibility of adequate therapy. J Heart Lung Transplant 2005; 24:1984–7. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

Stenoses of the pulmonary artery branches represent a rare cause of pulmonary hypertension (PH) in children,1,2 but this condition is often associated with congenital syndromes.3–7 Clinical presentation, prognosis and treatment depend on number, location and extension of the lesions, as classified by Gay and French.1,8,9 In contrast to more proximally located stenoses of the pulmonary artery branches, multiple peripheral pulmonary artery stenoses (MPPAS; corresponding to Class III according to Gay and French) are rarely accessible to curative therapeutic reconstructive strategies, such as balloon angioplasty,1,3 and few symptomatic children reach adulthood. Herein we report, for the first time, 2 adult patients with MPPAS that led to severe PH. Both underwent successful lung transplantation shortly after symptom onset.

CASE 1

A 21-year-old man was referred for evaluation of lung transplantation due to PH. His mother was known to have suffered from newly acquired rubella infection in the first trimester of pregnancy. The patient’s medical history began shortly after birth, when the work-up of a crescendo–decrescendo heart murmur over his pulmonary ejection tract revealed elevated pulmonary artery pressures by right-heart catheterization and constricted peripheral pulmonary arteries in the upper and lower right lobe, with complete occlusion of the segmental pulmonary arteries in the left middle lung field. Although he was weaker than his peers from early childhood on, he lived well until his late teens, when his exercise capacity rapidly decreased. At 21 years of age, he was referred for lung transplantation because of progressing New York Heart Association (NYHA) Grade III or IV dyspnea due to severe PH.

Physical examination revealed a slender young man (175 cm, 65 kg) with palpable right ventricular heave and a systolic–diastolic flow murmur over the right upper lung field, but no signs of overt right-heart failure. His arterial oxygen saturation was 98%, desaturating to 93% during exercise. Echocardiography showed an elevated right ventricular systolic pressure of 85 mm Hg above the right atrial pressure without stenoses of the pulmonary valve or the main pulmonary artery. The right-heart chambers were enlarged, although left-heart size and function were normal. Thoracic computed tomography confirmed an enlarged right ventricle and diluted central pulmonary arteries; the lung parenchyma was normal without signs of interstitial lung disease. Ventilation–perfusion scan of the lung revealed decreased perfusion of the right lung (right to left: 10% to 90%).

Pulmonary angiography demonstrated two segmental arteries of the right upper lobe, one of which was completely occluded 1.5 cm from its outlet and the other showed multiple peripheral tapering stenoses of its segmental and sub-segmental branches, resulting in
almost complete absence of peripheral vascular structures of the upper right lobe (Figure 1). The segmental arteries of the right middle and lower lobes showed multiple sub-segmental and peripheral tapering pulmonary artery stenoses. Although the left pulmonary arteries were technically difficult to observe, several randomly distributed tapering stenoses of the intermediate and peripheral pulmonary arteries could be demonstrated with sufficient clarity. There were no angiographic signs of chronic thromboembolic vessel-wall disease such as bands, webs, irregular intimal surface, round or pouch-like termination of segmental branches, odd-shaped pulmonary arteries or post-stenotic dilation. A normal aortic arch was observed during the late phase of the examination with multiple dilated bronchial arteries going off the descending aorta as pulmonary collaterals. Due to these angiographic features and distribution pattern, along with the reported pulmonary angiographic results shortly after birth, MPPAS was diagnosed as cause of this patient’s severe PH.

The patient underwent successful lung transplantation a few months later. Macroscopic examination of the explanted lungs revealed marked wall thickening of pulmonary arterial vessels with multiple yellow plaques and luminal narrowing seen in the proximal arteries (Figure 2). There were no macroscopic signs of pulmonary thromboembolic disease such as thread-like fibrous residues (webs) in the pulmonary arterial branches. Histologic examination showed extensive arteriosclerotic plaques in the greater vessels with wall thickening and almost complete occlusion of peripheral vessels without crescent-like intimal thickening as seen in thromboembolic disease. Hypertensive pulmonary vascular disease with plexiform lesions was seen (Figure 3). Two years after lung transplantation the patient required hospitalization due to severe bronchiolitis obliterans. An increase of immunosuppressive therapy and intravenous immunoglobulins could not stop the disease process and the patient died 2 months later due to disseminated aspergillosis.

CASE 2

A 47-year-old woman with typical malformations of the upper extremities due to thalidomide intake by her mother during early pregnancy was referred for further evaluation due to recently diagnosed severe pulmonary arterial hypertension. At 45 years of age, oral anti-coagulation was started due to intermittent atrial fibrillation. When the patient reached 46 years of age, her exercise capacity declined rapidly. Work-up of dyspnea in this slender woman (167 cm, 60 kg) revealed no signs of right-heart failure or clubbing, and arterial blood saturation was 93%. Lung function test revealed a mildly restrictive ventilation pattern with a severe reduction in CO₂ diffusion capacity. PH was diagnosed by echocardiography and right-heart catheterization with the following values: mean pulmonary arterial pressure, 41 mm Hg; right atrial pressure, 9 mm Hg; pulmonary artery occlusion pressure, 11 mm Hg; cardiac index, 1.9 liters/min/m²; and pulmonary vascular resistance, 750 dyn/s/cm–5.6

Ventilation-perfusion lung scan revealed inhomogeneous lung perfusion in all normally ventilated lobes with a perfusion disequilibrium toward the right lung (60:40%). Pulmonary angiography showed multiple, randomly distributed, sub-segmental tapering vessel narrowing and disruptions without bands, webs or post-stenotic vasodilation, as well as marked rarefaction.
of peripheral lung vessels compatible with MPPAS (Figure 4). Together with the clinical presentation and history, the patient was diagnosed as having severe PH due to MPPAS, possibly associated with thalidomide embryopathy.

The patient's medical condition worsened rapidly. Combination therapy with bosentan, inhaled iloprost and diuretics only transiently stabilized her clinical condition. While waiting for lung transplantation, iloprost had to be switched to a continuous intravenous administration and oral sildenafil was added until successful transplantation several months later. Histopathologic examination of her explanted lung was similar to Case 1.

DISCUSSION

Congenital stenoses of the pulmonary artery and its branches are usually detected in early childhood during investigation of pathologic cardiac murmurs, respiratory symptoms or failure to thrive. They are often associated with other cardiac anomalies, which usually account for the overall prognosis. In most cases, the main pulmonary arteries are involved (Class I or II by Gay and French). Multiple peripheral stenoses of small pulmonary arteries alone (Class III) or in conjunction with central stenoses (Class IV) are rare. A few cases of an association with maternal rubella, one case of an association with maternal thalidomide use during pregnancy, and some cases associated with other congenital syndromes have been reported. In both of our cases, one of these associations was found (maternal rubella primary infection in pregnancy in Case 1 and thalidomide embryopathy in Case 2). In contrast to our cases, most congenital pulmonary artery stenoses are located in the main or proximal segmental pulmonary artery branches, and therefore may be treated successfully with surgery or balloon angioplasty. MPPAS is usually not amenable to this therapeutic option and only rarely do the affected children reach adolescence.

MPPAS in adult patients without a history of major cardiopulmonary symptoms is extremely rare. Only one comparable, but less severe case not requiring lung transplantation has been reported previously. The clinical presentation of MPPAS in adults differs from the common pediatric presentation, with rapidly progressive, exertional dyspnea in previously relatively healthy individuals, accompanied by multiple segmental lung ventilation-perfusion mismatches and progressive PH leading to right-heart failure. MPPAS may mimic chronic thromboembolic pulmonary hypertension and both disorders may co-exist, as stenotic peripheral small pulmonary artery branches are prone to superimposed thromboembolism.

Although MPPAS and chronic thromboembolic pulmonary hypertension (CTEPH) may share some angiographic features, the classic signs with preponderant affection of the upper lung lobes and random distribution pattern of mainly tapering stenoses in MPPAS—as

Figure 3. (a) Branching elastic artery with occlusion by fibrotic tissue and stenosis by fibrosis and smooth muscle cells in the intima on the right side. (b) Muscular pulmonary artery with plexiform lesion.

Figure 4. Pulmonary digital subtraction angiography of a 27-year-old woman (Case 2) showing bilateral pruning of the pulmonary arteries with stenoses (arrowheads) and paucity of peripheral branches.
compared with abrupt vessel disruption commonly affecting several adjacent pulmonary arteries in mainly lower lung lobes in CTEPH together with patient history (time course of symptoms onset, absence of thromboembolic events in medical history and previous oral anti-coagulation as in our Case 2)—should permit the diagnosis of MPPAS. Nevertheless, some overlap may exist and definitive diagnosis may not be achieved until histopathologic examination of explanted lung tissue with typical features of pulmonary artery stenoses (vessel narrowing due to extensive fibrous plaques, intimal thickening), complex lesions due to secondary pulmonary arterial hypertension (plexiform and dilation lesions, intimal and medial hypertrophy) and absence of thromboembolic residues (thread-like fibrous webs, semi-lunar intimal thickening in small peripheral pulmonary artery branches).

Both cases presented emphasize the crucial role of pulmonary angiography in the diagnostic work-up of PH because other contrast-enhanced imaging techniques, such as computed tomography and magnetic resonance imaging, have not yet been able to provide comparable sensitivity to examine distal pulmonary artery vessels. Our observations suggest that MPPAS should be considered a rare cause of pulmonary hypertension in adults requiring lung transplantation. The condition may be underdiagnosed and should be included in the differential diagnosis of patients evaluated for lung transplantation due to rapidly worsening pulmonary hypertension. Clinical suspicion and early detection of MPPAS may help to diminish secondary pulmonary thromboembolism in these high-risk patients with severe disease and may expand therapeutic possibilities to include surgery, endovascular dilation or stenting, which have so far been reserved for more proximally located stenoses. As shown in our cases, lung transplantation is presently a viable therapeutic option after failure of medical treatment.

REFERENCES