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CASE STUDY

Pulmonary arterial hypertension masquerading as severe refractory asthma

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ABSTRACT: Once the diagnosis of pulmonary arterial hypertension is established, wheezing and chronic cough are rarely described during the course of the disease.

The present study reports on two nonsmoking patients with severe pulmonary arterial hypertension, confirmed by right-heart catheterisation, who developed chronic cough, wheezing and irreversible obstructive lung disease masquerading as adult-onset severe refractory asthma.

In both cases, extrinsic proximal airway obstruction by dilated pulmonary arteries was demonstrated by fibreoptic bronchoscopy and computed tomography of the chest.

The present observations add dilatation of the central pulmonary arteries with compression of the mainstem bronchi to the list of masqueraders of asthma in patients with pulmonary arterial hypertension.

KEYWORDS: Asthma, compression of the mainstem bronchi, congenital heart diseases, obstructive airway disease, Ortner's syndrome, pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a severe condition characterised by a progressive remodelling of small pulmonary arteries leading to elevated pulmonary vascular resistance and right ventricular failure. Despite several studies showing asymptomatic airway obstruction in patients with PAH [1, 2], asthma-like symptoms have been rarely reported during the course of the disease [3, 4]. The present study reports on two nonsmoking patients with severe PAH, confirmed by right-heart catheterisation, who developed cough, wheezing and irreversible obstructive lung disease masquerading as adult-onset severe refractory asthma. In both cases, extrinsic proximal airway obstruction by dilated pulmonary arteries was demonstrated by fibreoptic bronchoscopy and computed tomography of the chest. The present observations add dilatation of the central pulmonary arteries with compression of the mainstem bronchi to the list of masqueraders of asthma in patients with PAH.

CASE 1

A 34-yr-old nonsmoking male was referred to the present authors' institute in July 2002 for management of PAH. He had no personal or familial history of allergy, rhinitis, asthma, wheeze or chronic cough. At 3 yrs of age, he underwent a mesenterico–caval shunt for a portal cavernoma, and a diagnosis of mild PAH was made at 16 yrs of age. PAH-specific therapy was not initiated at that time. In 2002, the subject was in functional class III of the New York Heart Association (NYHA) classification and his 6-min walk distance (6MWD) was 580 m with a Borg index of dyspnoea of 3. Mean pulmonary arterial pressure ($\bar{P}_{pa}$) was 52 mmHg, cardiac index (CI) was 3.84 $L \cdot min^{-1} \cdot m^{-2}$, indexed total pulmonary resistance (R_iTR) was 13.5 $mmHg \cdot L^{-1} \cdot min^{-1} \cdot m^{-2}$, and mixed venous oxygen saturation (S_{V,O_2}) was 75%. Pulmonary artery wedge pressure was normal and there was no acute vasodilator response to inhaled nitric oxide (NO). Pulmonary function tests (PFTs) showed irreversible obstructive lung disease: forced expiratory volume in one second (FEV1) was 2.29 L (52% predicted); forced vital capacity (FVC) was 3.48L (65% pred); FEV1/FVC ratio was 57%; residual volume (RV) was 3.07 L (162% pred); total lung capacity (TLC) was 7.07 L (94% pred); and the RV/TLC ratio was 162% (fig. 1a). Blood gases showed mild hypoxaemia (arterial oxygen tension (P_{a,O_2}) of 10.7 kPa) and hypocapnia (arterial carbon dioxide tension (P_{a,CO_2}) of 3.95 kPa). Computed tomography of the chest showed significant dilatation of the pulmonary arteries. Medical treatment was initiated with warfarin and bosentan, a dual endothelin receptor antagonist. Regular monitoring demonstrated

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good clinical and haemodynamic response until 2004, when the patient presented with an acute episode of wheezing upon exertion and a chronic dry cough. Asthma was clinically suspected. There was no atopy on skin prick tests. PFTs confirmed irreversible airway obstruction but neither inhaled steroids nor bronchodilators improved respiratory symptoms or lung function (fig. 1a). Pulmonary haemodynamics and 6MWD remained stable. However, there was a marked deterioration in dyspnoea with a Borg index of 5 and audible wheezing during exercise. Computed tomography of the chest showed a thrombosed aneurysm of the proximal pulmonary arteries with bronchial compression (fig. 1b). Fibreoptic bronchoscopy revealed significant stenosis of the right mainstem bronchus and difficulty advancing the bronchoscope. A diagnosis of bronchial compression by massively dilated proximal pulmonary arteries was established. In June 2006, the patient was hospitalised for an acute myocardial infarction due to extrinsic stenosis of the left main coronary artery, without evidence of other coronary artery disease. This was consistent with a diagnosis of left coronary arterial extrinsic compression by the aneurysmal pulmonary arteries. In the context of worsening dyspnoea due to bronchial compression, along with coronary compression and myocardial infarction, the patient was listed for heart–lung transplantation and subsequently transplanted (fig. 2). Examination of the explanted lungs showed major bilateral dilatation of the proximal pulmonary arteries and a thrombosed aneurysm of the right pulmonary artery with severe small vessel pulmonary plexiform arteriopathy. No atherosclerotic coronary lesions were found. There was no bronchial inflammation or remodelling suggestive of asthma.

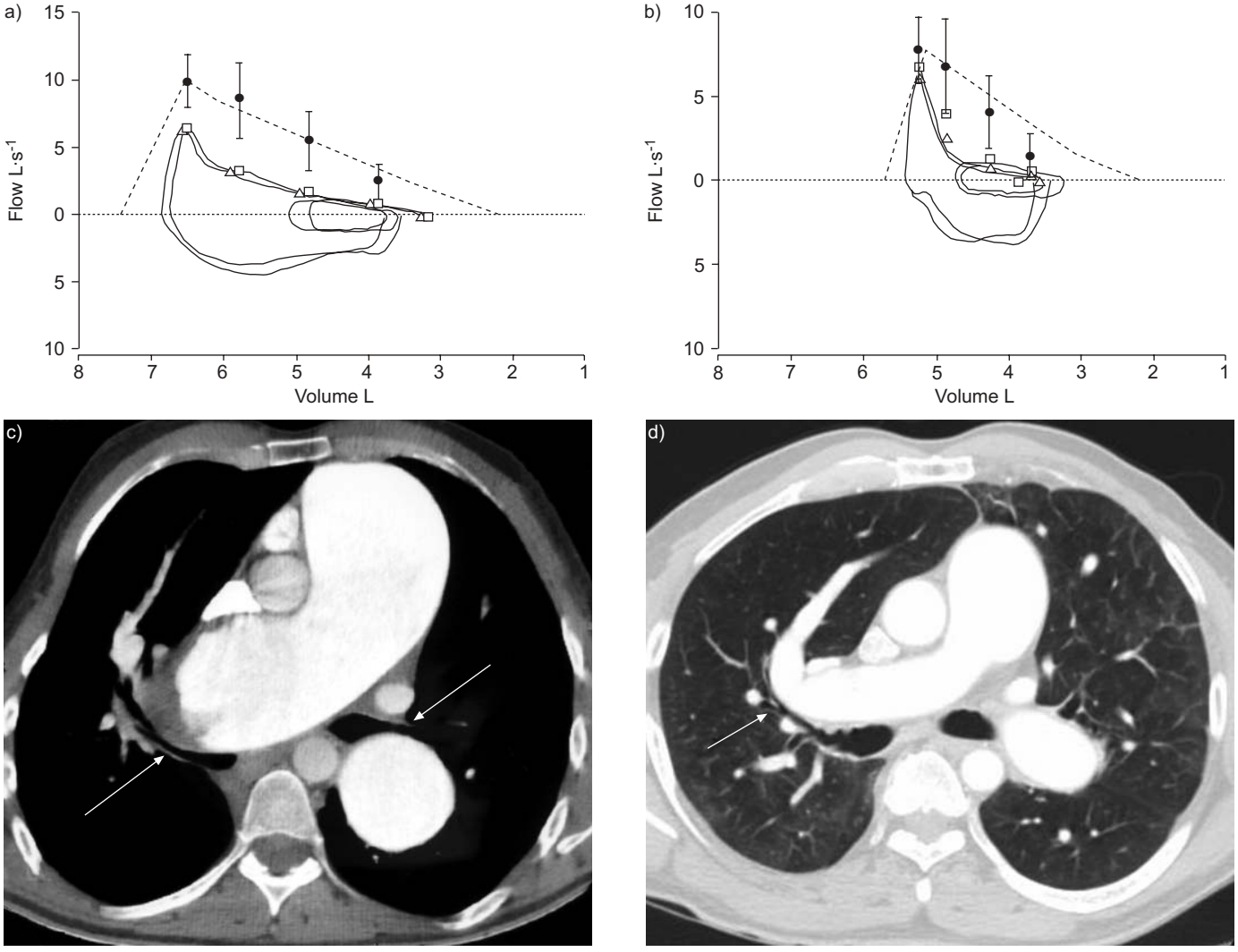

FIGURE 1. Pulmonary function tests and computed tomography of the chest in two patients with compression of the mainstem bronchi by dilated pulmonary arteries masquerading as severe asthma. Patient 1: a) pulmonary function tests showed a moderately severe irreversible airway obstruction; and c) computed tomography of the chest demonstrated a pulmonary trunk to aortic diameter ratio of >2 and compression of right and left mainstem bronchi (arrows) by a partially thrombosed aneurysmal dilatation of the proximal pulmonary arteries. Patient 2: b) pulmonary function tests showed moderately severe irreversible airway obstruction; and d) computed tomography of the chest demonstrated pulmonary trunk to aortic diameter ratio of >1.5 and compression of right mainstem bronchus (arrow) by dilated pulmonary artery. ●: predicted theoretical values presented as median±SD; □: pre-bronchodilator values; △: post-bronchodilator values; – – –: % predicted flow–volume; ·····: 0 L·s^{-1} flow.

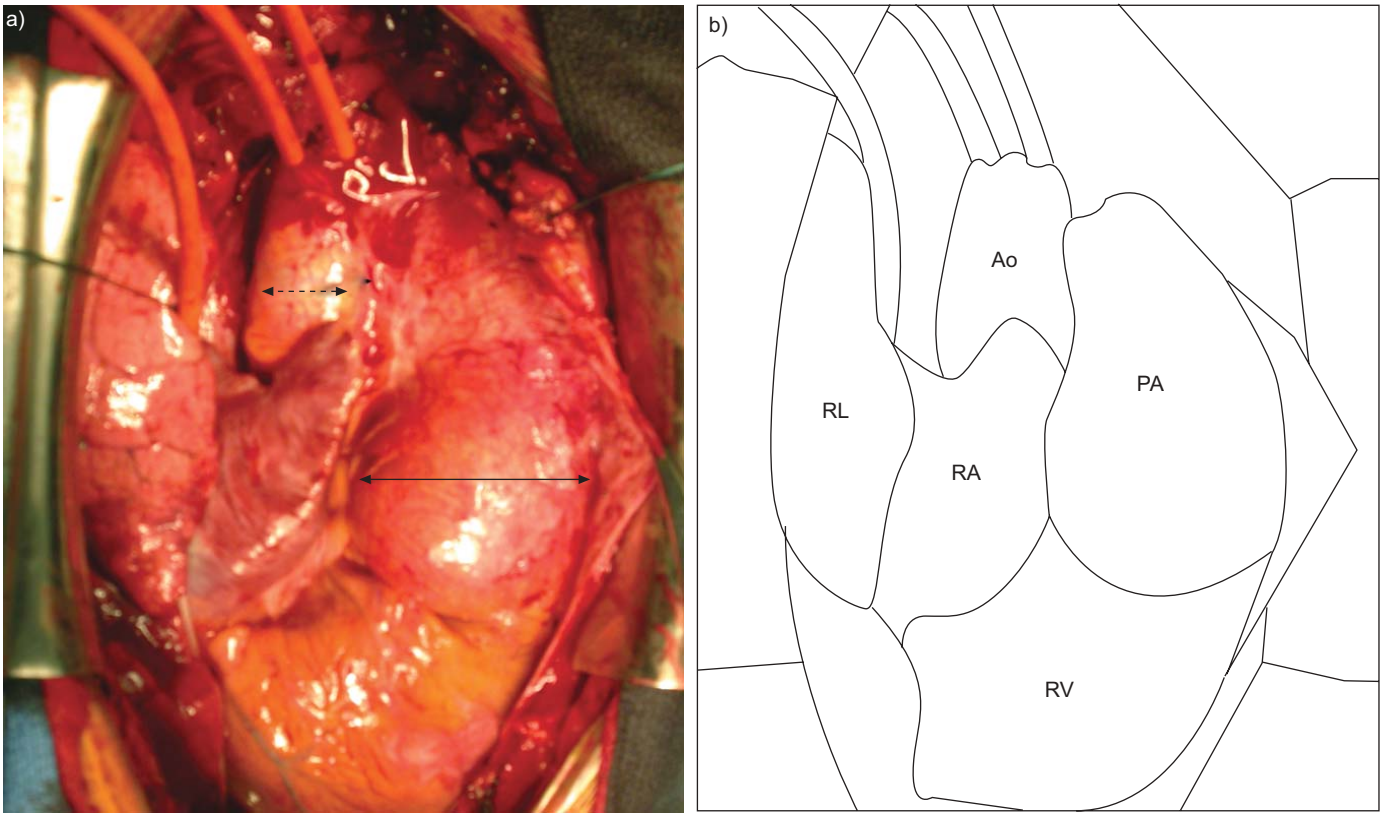

FIGURE 2. a) Operative view and b) schematic representation of patient 1 at the time of heart-lung transplantation showing major pulmonary artery dilatation (arrow) which is more than twice as large as the aorta (dotted arrow) Ao: aorta; PA: pulmonary artery; RA: right atrium; RL: right lung; RV: right ventricle.

CASE 2

A 56-yr-old nonsmoking male with PAH related to an atrial septal defect was referred to the present authors' institute in December 2001. He had no personal or familial history of allergy, rhinitis, asthma, wheeze or chronic cough. He was in NYHA functional class III and had a 6MWD of 450 m with a Borg index of dyspnoea of 1. Haemodynamic evaluation revealed severe precapillary pulmonary hypertension, $\bar{P}_{pa}$ was 60 mmHg, CI was 2.29 $L \cdot min^{-1} \cdot m^{-2}$, R_{iTR} was 14.5 $mmHg \cdot L^{-1} \cdot min^{-1} \cdot m^{-2}$, S_{V,O_2} was 82% and there was a 36 mm atrial septal defect with bidirectional shunting. Pulmonary artery wedge pressure was normal and there was no acute vasodilator response to inhaled NO. PFTs showed a restrictive and obstructive pattern: FEV_1 was 1.24 L (43% pred); FVC was 1.72 L (47% pred); FEV_1/FVC ratio was 72%; TLC was 4.19 L (72% pred); RV was 2.11 L (101% pred); and RV/TLC was 143%. Blood gases showed hypoxaemia (P_{a,O_2} of 8.55 kPa) and hypocapnia (P_{a,CO_2} of 4.25 kPa). Computed tomography of the chest showed marked dilatation of the pulmonary arteries. Bosentan therapy was initiated, and regular monitoring demonstrated good clinical and haemodynamic response until 2005. In April 2005, he complained of chronic cough and wheezing especially upon exertion. Asthma was again clinically suspected. There was no atopy on skin-prick tests. PFTs showed irreversible airway obstruction but neither inhaled steroids nor bronchodilators improved respiratory symptoms or lung function (fig. 1c). Pulmonary haemodynamics were stable, although there was a decline in 6MWD with a worse Borg index of dyspnoea of 3 and audible wheezing on exercise. After 6 months, he complained of hoarseness and underwent flexible bronchoscopy, which showed reduced mobility of the left vocal cord, compatible with Ortner's syndrome (cardiovocal syndrome) due to left recurrent laryngeal nerve palsy. In addition, there was an extrinsic compression of the right mainstem bronchus. Computed tomography of the chest showed bilateral bronchial compression, predominantly of the right mainstem bronchus, by dilated proximal pulmonary arteries (fig. 1d).

DISCUSSION

The present observations add dilatation of the central pulmonary arteries and compression of the mainstem bronchi to the list of masqueraders of late-onset asthma in patients with severe PAH. When airflow obstruction is irreversible, as it was in the present patients, an alternative diagnosis to asthma should be sought. Interestingly, both patients developed other symptoms due to compression by dilated proximal pulmonary arteries, including hoarseness (left recurrent laryngeal nerve palsy) [5] and myocardial infarction (extrinsic compression of the left main coronary artery) [6–8]. In patients with PAH complicating congenital heart diseases, compression by enlarged pulmonary arteries is common; narrowing of the left main coronary artery by extrinsic compression may be detected in 44% of patients with atrial septal defects [9] and in 26% of patients with pulmonary trunk to aortic diameter ratios $\geqslant 1.21$ [10].

Extrinsic airway compression may explain chronic cough, wheezing and obstructive lung disease in PAH patients. In that setting, it is useful to perform computed tomography of the chest, fibreoptic bronchoscopy and magnetic resonance imaging [11–13]. Interestingly, computed tomography of the chest has demonstrated pulmonary arteries that were consistently enlarged and could be aneurysmal, causing bronchial compression and atelectasis in patients with PAH associated with congenital heart diseases [14, 15].

Although wheezing and chronic cough are uncommon in PAH patients, several studies have demonstrated small airways disease in PAH. RASTOGI *et al.* [1] found distal small airway obstruction in 59% of paediatric PAH cases with no prior history of asthma or atopy, and a bronchodilator response was seen in 78% of patients with an obstructive baseline pattern. The FEV_1/FVC ratio is inversely correlated with $\bar{P}_{pa}$, whereas RV, TLC and the RV/TLC ratio positively correlated with $\bar{P}_{pa}$. SPIEKERKOETTER *et al.* [16] found a normal FEV_1 in all patients with idiopathic PAH, whereas flow–volume curves, mean expiratory flow at 50% and 25% of vital capacity ($MEF_{50\%}$ and $MEF_{25\%}$, respectively) showed peripheral airflow obstruction. In a cross sectional study of 171 adult patients with idiopathic PAH, MEYER *et al.* [2] demonstrated peripheral airway obstruction with a reduced FEV_1/FVC, end-expiratory airflow limitation and moderate lung hyperinflation. RV/TLC ratio correlated with $\bar{P}_{pa}$ and was more elevated in patients with a $\bar{P}_{pa} > 56$ mmHg. Due to the proximity of the small pulmonary arteries and the peripheral airways, it was suggested that peripheral airway obstruction may reflect structural bronchial changes secondary to the underlying pulmonary vascular disease. In favour of this hypothesis, FERNANDEZ-BONETTI *et al.* [17] showed peripheral airway obstruction and narrowing of the small airways with thickened walls, infiltrated by lymphocytes, plasma cells and polymorphonuclear leukocytes, on lung samples from pulmonary arterial hypertension patients. However, it remains unclear whether small airway obstruction in PAH is the consequence of mechanical distal airway compression by remodelled small pulmonary arteries, structural airway abnormalities related to PAH or to the vasoconstrictive/bronchoconstrictive mediator imbalance characteristic of PAH (decreased NO and increased endothelin-1 production).

In summary, chronic cough, wheezing and obstructive airway disease may complicate the course of pulmonary arterial hypertension. These asthma-like symptoms are refractory to usual asthma therapy, such as steroids and bronchodilators, and may be due to compression of the mainstem bronchi by dilated pulmonary arteries. The present authors conclude that pulmonary arterial hypertension should be added to the list of conditions masquerading as severe refractory asthma.

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