

Advanced interstitial lung fibrosis with emphysema and pulmonary hypertension with no evidence for interstitial lung disease on high resolution CT

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Abstract

The diagnosis of idiopathic pulmonary arterial hypertension (iPAH) is complex and, besides invasive hemodynamic evaluation, includes several diagnostic steps to exclude any underlying diseases. The role of a decreased diffusion capacity of the lung for carbon monoxide (DLCO) is a matter of discussion. Here, we present a 76-year-old man with a smoking history of 30 pack-years who was diagnosed with iPAH after chronic thromboembolic pulmonary hypertension was excluded based on a negative perfusion scan, an underlying heart disease was excluded based on echocardiography and right heart catheterization, and a significant lung disease was excluded based on lung function test (FVC = 101% predicted, FEV1 = 104% predicted, FEV1/FVC = 77, TLC = 97% predicted) and thin-slice computed tomography (CT) scan. Just DLCO was reduced to 40% predicted, suggesting a possible structural lung disease. Postmortem examination demonstrated severe interstitial lung fibrosis combined with microscopic emphysema. This indicates that both CT imaging and pulmonary function test may be insensitive to a diffuse peripheral combined pattern of fibrosis and emphysema and that DLCO may be the only sensitive marker of this significant lung pathology.

Keywords

DLCO, idiopathic pulmonary arterial hypertension, high-resolution lung CT, lung histology

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Case description

A 76-year-old male patient was referred to our outpatient clinic for further evaluation of an elevated systolic pulmonary arterial pressure (sPAP) in the transthoracic Doppler echocardiogram. He was suffering from progressive dyspnea (World Health Organization functional class [WHO FC] III) without chest pain on exertion. He had no recent episodes of cough or fever. The physical examination revealed no pathological findings except a loud p2 heart sound and some minor inspiratory rales over the posterolateral basal parts of the lung. His medical history included arterial hypertension, type 2 diabetes mellitus, obesity, and thrombendarterectomy of the left femoral artery. He had been a cigarette smoker (30 pack-years) and quit 40 years ago. His medical treatment included lercanidipine, enalapril,

bisoprolol, hydrochlorothiazide, simvastatin, aspirin, allopurinol, and metformin. The laboratory results showed normal C-reactive protein (CRP) and leucocyte count, mild renal impairment (creatinine = 1.36 mg/dL, glomerular filtration rate [GFR] = 50 mL/min), elevated NT-proBNP (1323 pg/mL, normal range <150 pg/mL), and mild IgG4 elevation (2.50 g/L, normal range = 0.03–2.01 g/L). Spirometry and bodyplethysmography revealed normal values for FEV1/FVC with 77%, and % predicted values of FVC, FEV1, PEF, and TLC of 101, 104, 95, and 97, respectively, and mild decreases in MEF 50 and MEF 25

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with % predicted values of 81 and 68, respectively, while DLCO was significantly impaired (DLCOcSB = 2.89 mmol/min/kPa, 40% predicted). The flow-volume loop is depicted in Fig. 1a. The arterial blood gas analysis revealed severe hypoxemia despite compensatory hyperventilation ($pO_2 = 47.5$ mmHg, $pCO_2 = 26.4$ mmHg, $pH = 7.42$, $BE = -6.6$ mmol/L) on room air. A high-resolution computed tomography (CT) scan of the chest showed mild emphysema of the right upper lobe with a small nodule, mild infracarinal lymphadenopathy, and no signs of interstitial lung disease (Fig. 1b–d). There were also no signs of pulmonary veno-occlusive disease. V/Q scintigraphy revealed no signs of acute or chronic pulmonary embolism.

Echocardiography showed concentric left ventricular (LV) hypertrophy and E/e' suggested mild diastolic LV dysfunction with preserved ejection fraction, and no pericardial effusion. The right atrium and right ventricle were significantly enlarged and a paradoxical interventricular septal motion was observed. There was a mild tricuspid valve insufficiency where a sPAP of $70 + 5$ mmHg could be estimated. TAPSE was normal (21 mm). The 6-min walking distance was 327 m (BORG Dyspnoea Index 4) and significant desaturation (oximetry $SpO_2 = 60\%$) was recorded at the end of the walk. Right heart catheterization (RHC) revealed a moderately increased mean pulmonary arterial pressure (mPAP) of 36 mmHg, increased pulmonary vascular resistance (PVR; 5.8 WU), a normal right atrial pressure (RAP; 4 mmHg), and pulmonary arterial wedge pressure (PAWP; 8 mmHg). Cardiac index (CI) was in the lower normal range (2.5 L/min/m²) and a normal mixed venous oxygen saturation ($venSO_2 = 70.2\%$) on 2.5 L/min of oxygen was observed. Autoantibody screening was negative.

In agreement with current recommendations,^{1,2} the diagnosis of idiopathic pulmonary arterial hypertension (iPAH) was made and the patient was started on an endothelin receptor antagonist. His clinical condition improved in the first month, but then deteriorated within two weeks including syncope and progressive leg edema. He was admitted to a general internal medicine ward where diuretic therapy was intensified; he was discharged home symptomatically improved after one week. Two months later he developed a pleural effusion and progressive signs of cardiac decompensation. He was admitted to our ward and increasing doses of diuretics were administered. The high-resolution chest CT control showed very mild reticulation in the basal areas of the lung (Fig. 1e–g) but no signs of right ventricular (RV) decompensation. Based on these findings, the ERA was stopped and a short-term therapy with oral prednisolone was started. This led to a significant improvement in oxygenation; after three weeks, the patient was discharged home on 12.5 mg prednisolone o.d. Two weeks later, we were informed that the patient had decompensated at home with circulatory shock, had been admitted to the ICU, and died within 24 h.

Postmortem examination showed that the heart was enlarged (500 g), with dilatation of the right atrium and

ventricle, slight increase of the RV wall thickness (6 mm) and significantly increased thickness of the LV wall (22 mm), and middle to high-grade atherosclerosis with significant stenosis of all major coronary arteries.

Histological analysis of the lung revealed architectural distortion of the lung parenchyma in all samples taken from all lung lobes. Unevenly distributed, diffuse interstitial fibrosis with some lymphocytic infiltration was present in the subpleural and central lung areas. This was slightly more pronounced around the blood vessels, with cicatricial organizing pneumonia (Fig. 1h–j). Centroacinar emphysema was also evident. Most arteries showed intimal and medial hypertrophy, with congestion and intra-alveolar edema. In the intra-alveolar space, there was an increased number of macrophages and siderophages. Anthracotic pigments as well as focal pulmonary ossifications were also present. Histological findings were consistent with advanced interstitial lung fibrosis with organizing pneumonia pattern at different stages of organization, smoking-induced changes (emphysema and anthracosis), and severe pulmonary vasculopathy, complicated by acute on chronic lung edema. A timeline is shown in Fig. 1k.

This study was approved by the Ethical Committee of the Medical University Graz (23-408 ex 10/11).

Discussion

We present a case of severely decreased gas exchange capacity and significant pulmonary hypertension (PH), which was classified as iPAH based on a normal PAWP in the RHC and non-significant changes in the pulmonary function test and thin-slice CT as well as perfusion scintigram and autoantibody screening. Postmortem examination revealed advanced structural distortion of the lung architecture with advanced interstitial fibrosis and centrilobular emphysema and a significant biventricular hypertrophy and coronary heart disease. Although the patient did not meet the diagnostic criteria for systolic or diastolic left heart failure, it is possible that his significant structural heart disease contributed to the adverse events like pleural effusions. Some of the interstitial changes may have developed in the two months between the last high-resolution CT of the lung and death but certainly not all. Organizing pneumonia might be a response to an infectious or inflammatory injury to the lung.

This suggests that CT imaging and pulmonary function test were insensitive to a diffuse combined pattern of microscopic fibrosis and emphysema while DLCO was more sensitive for these pathologies. Combined pulmonary fibrosis and emphysema (CPFE) has been suggested as a distinct entity, characterized by apical emphysema and basal fibrosis and a pulmonary vasculopathy.^{3–5} This case highlights the importance and difficulty in discriminating PAH from PH due to CPFE. Based on this case and a case series from Amsterdam with iPAH patients presenting with significantly lowered DLCO,⁶ we suggest broadening the understanding

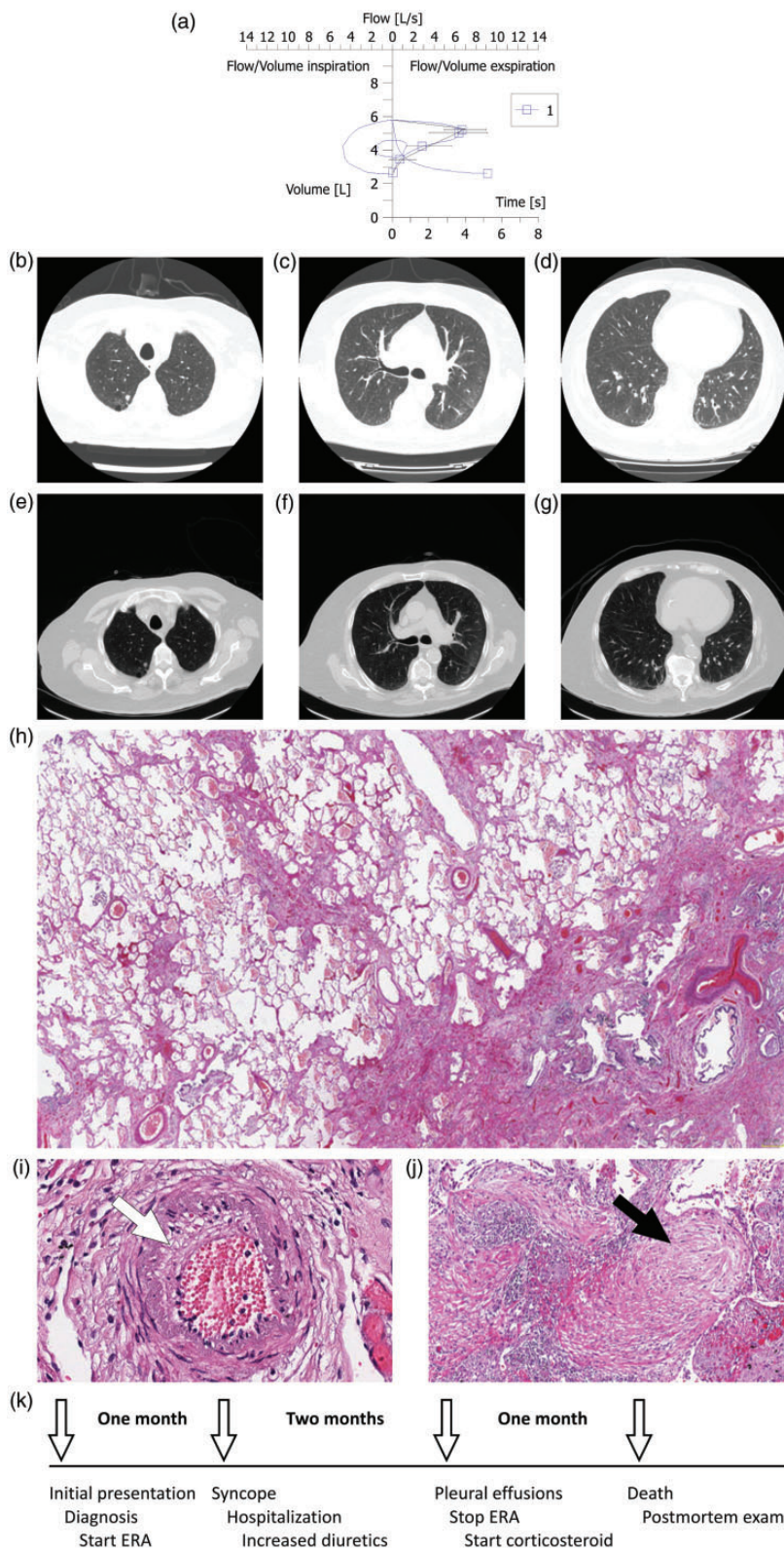


Fig. 1. Flow-volume loop at initial presentation (a). High-resolution chest CT of the upper lobes (b), middle lobe (c), and lower lobes (d) at the initial presentation and at follow-up (e-g). Area of lung parenchyma with pulmonary arterial wall hypertrophy and lung parenchyma showing severe interstitial fibrosis (h). Histologic presentation of myointimal proliferation (white arrow) (i) and cicatricial organizing pneumonia (black arrow) (j). Timeline of the events in the patient (k).

of this combined disease by including patients with severe pulmonary vasculopathy and low DLCO and severe hypoxemia, who present with near normal pulmonary function test and minimal findings in the high-resolution CT.

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Conflict of interest

The author(s) declare that there is no conflict of interest.

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