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Case report

A diffuse lung emphysema, severe pulmonary hypertension and lack of airflow limitation

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ABSTRACT

Pulmonary veno-occlusive disease is characterized by remodeling of pulmonary arteries, capillaries and venules. We report a case of diffuse lung emphysema and pulmonary veno-occlusive disease with the characteristic of having no airflow limitation. A very low diffusing capacity for carbon monoxide and results of high-resolution computed tomography of the chest suggested pulmonary veno-occlusive disease. The diagnosis was confirmed on histological analysis after lung transplantation. The combination of results of the computed tomography of the chest and the histological analysis suggested a relationship between diffuse lung emphysema and remodeling of pulmonary vessels. A distinctive pattern of mild-to-moderate airflow limitation in patients with chronic obstructive pulmonary disease and severe pulmonary hypertension has been described. This observation of the combination of diffuse emphysema, pulmonary veno-occlusive disease and no airflow limitation supports further pathophysiological studies on severe pulmonary hypertension in chronic obstructive pulmonary disease.

1. Introduction

Severe pulmonary hypertension (PH) is a possible but infrequent complication of chronic obstructive pulmonary disease (COPD) [1]. These patients have a distinctive pattern of mild-to-moderate airflow limitation, severe hypoxemia, and a low diffusing capacity for CO (DL_{CO}) [1–5]. Almost all patients in these studies [1,2,4] had significant pulmonary emphysema on computed tomography (CT). Recently, Adir et al. [6] reported three cases of severe PH with marked diffuse lung emphysema but normal spirometry results.

No study has reported the pathological assessment in this disease. In the present case report, we describe a patient with a similar pattern of pulmonary emphysema and severe PH who then received a lung transplant. Pathology of the explanted lung showed pulmonary veno-occlusive disease (PVOD). This case provides new insights into the pathophysiology of this uncommon disorder. The clinical and radiological description of this clinical case also underlines the non-invasive diagnostic algorithm and methods of treatment of PVOD [7].

2. Case report

A 61-year-old male ex-smoker with a 20 pack-year history was admitted with progressive worsening of dyspnea on exertion. He had no personal or family medical history and was a manager in the tertiary sector. The patient had been experiencing syncope on exertion and reported NYHA functional class IV. An examination revealed notable cyanosis, hepatomegaly and edema of the lower limbs. An echocardiography showed normal left-ventricular function, a dilated right ventricle, and a systolic pulmonary-artery pressure of 85 mmHg.

A ventilation/perfusion lung scan excluded a chronic thromboembolic PH. Pulmonary function tests showed an increase in all

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pulmonary volumes including forced expiratory volume in 1 s (FEV_1). Forced vital capacity, FEV_1 and total lung capacity were 144 of the predicted value (% pred.), 130% pred. and 133% pred., respectively. Diffusing capacity for carbon monoxide was very low, 27 of % pred. High-resolution CT of the chest showed major diffuse centrilobular emphysema, patchy ground-glass opacities, few septal lines, and mediastinal and hilar lymphadenopathies (Fig. 1). Arterial blood gases assessed under stable condition revealed severe hypoxemia (PaO_2 46 mm Hg) and hypocapnia ($PaCO_2$ 23 mm Hg). Serum level of alpha1-antitrypsin was in the normal range (130 mg/mL).

Right-sided heart catheterization showed severe pre-capillary pulmonary hypertension with a mean pulmonary artery pressure of 45 mm Hg and a pulmonary artery wedge pressure of 6 mm Hg. Cardiac output was 2.3 L/min (cardiac index = 1.3 L/min/m^2). Test for acute pulmonary vasodilation with inhaled nitric oxide was negative. PVOD was strongly suspected; therefore, we cautiously started upfront dual therapy with continuous i.v. epoprostenol at low doses and bosentan (62.5 mg p.o. twice daily). The patient then presented with pulmonary edema whose evolution was resolved after increasing the diuretic dose. Oxygen therapy and warfarin were also prescribed. Afterwards PAH-drug specific therapy doses were increased progressively.

Due to an overall insufficient response to medical treatment, the patient was placed on a lung-transplant waiting list, which was successfully performed seven months later. Histology of the explanted lungs showed pre- and post-capillary lesions involving pulmonary arteries, pulmonary veins, and pre-septal venules, leading to partial occlusion of the lumen (Fig. 2). Vein and venular remodeling showed paucicellular intimal fibrosis. There was patchy distribution and abnormal multiplication of capillaries along the alveolar walls, which corresponded to pulmonary capillary hemangiomatosis. Small arteries and arterioles showed eccentric intimal fibrosis. This histological examination was consistent with PVOD. However, uncommonly for PVOD, emphysematous loss of alveoli and moderate interstitial and bronchiolar lymphocytic infiltrates were observed, sometimes in close association with pulmonary vascular lesions.

3. Discussion

PVOD is 10-to-20 times less frequent than idiopathic pulmonary arterial hypertension (PAH) and is subcategorized as group 1′ within the current PH classification [8]. Because of its rarity and similarity with idiopathic PAH, diagnosis of PVOD is challenging and can only be confirmed by a histopathological examination. It is crucial to distinguish PVOD from idiopathic PAH because PVOD has a much poorer prognosis under drug-specific PAH therapy and carries a risk of severe pulmonary edema [7,9]. Since lung biopsy carries life-threatening risks in PVOD, a non-invasive diagnostic procedure has been developed [10].

In the present case, a chest high-resolution CT showed all three signs in favor of PVOD that differentiate PVOD from PAH, i.e., mediastinal lymph nodes, septal lines, and centrilobular ground-glass opacities (Fig. 1) [7,11]. The patient also had a very low DLCO, and severe hypoxemia, which also strongly suggested PVOD.

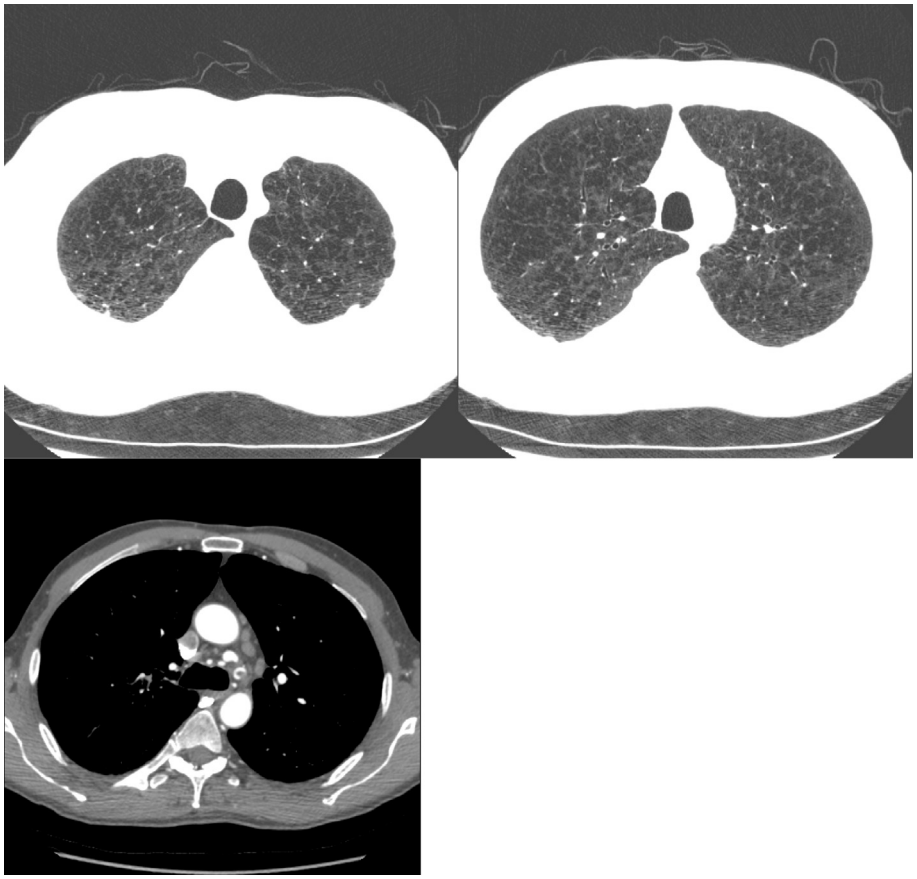

Fig. 1. High-resolution computed tomography of the chest with major diffuse centrilobular emphysema, characteristic signs of pulmonary veno-occlusive disease and no evidence of pulmonary fibrosis: patchy ground-glass opacities, and few septal lines; and mediastinal and hilar lymphadenopathies. Note the presence of significant development of arteries in the mediastinum from the systemic circulation.

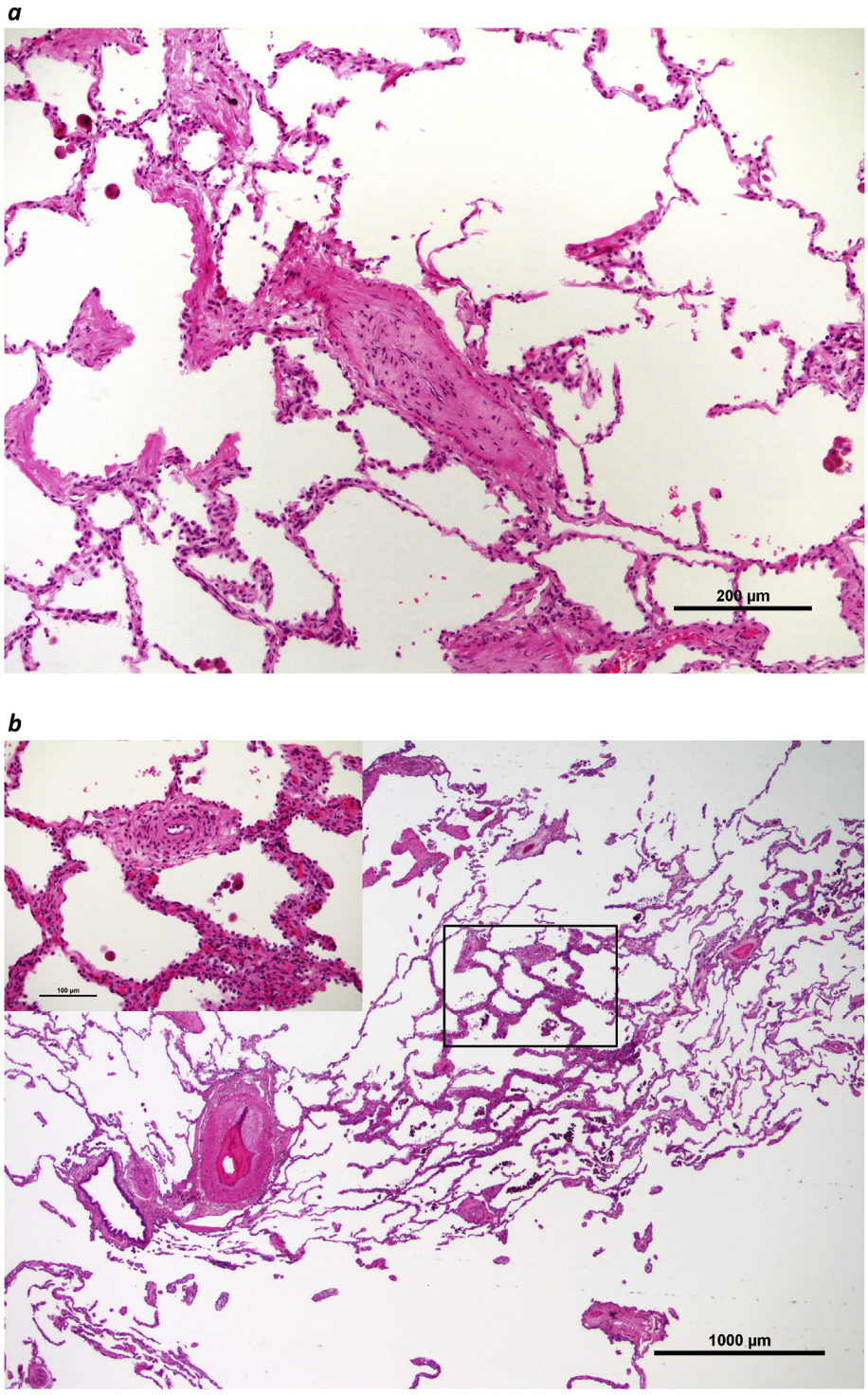

Fig. 2. Lung histology of samples obtained after lung transplantation. As typically seen in pulmonary veno-occlusive disease (PVOD), small pulmonary veins and venules are partially or completely occluded by paucicellular fibrous thickening of the intimal layer (a). In addition, pulmonary arteries (b, bottom left) display eccentric wall-thickening. Also, focal broadening of the alveolar walls with multiplication of alveolar capillaries is observed (b, inset center), corresponding to pulmonary capillary hemangiomatosis, a feature that is typically observed in PVOD, these patchy foci are frequently associated with muscularized microvessels (b, inset top). Note the areas with emphysematous loss of alveoli (b, top and bottom).

However, in the presence of pulmonary emphysema, the decrease in DLCO to distinguish a PAH from an MVOP may be difficult to interpret. Since we excluded a combined pulmonary fibrosis and emphysema we considered that the patient belonged to group 1′ of the clinical classification of PH [12]. These results prompted us to apply guidelines for the diagnosis and treatment of PH published in 2009 [12] expecting a clinical improvement up to the possibility of carrying out a lung transplantation. Therefore, we started PAH-drug specific therapy at very progressive doses. Also of note is that the histology showed signs of both PVOD and pulmonary capillary

hemangiomatosis: this overlap is consistent with previous reports [13,14].

Two points of this case report appear interesting to discuss. Firstly, the association of severe emphysema and severe PH. Secondly, the lack of airflow limitation in a patient with diffuse lung emphysema.

The present case report clearly shows diffuse pulmonary parenchymal involvement linked with pulmonary vascular lesions at the pathological level (Figs. 1 and 2). The combination of emphysema and pulmonary vascular disease may not be a simple coincidence. The inhibition of Vascular Endothelial Growth Factor (VEGF) [15,16] and nitric oxide/soluble Guanylate Cyclase-cGMP signaling [17] can lead to the development of both, lung emphysema and pulmonary hypertension in experimental models. Another argument for the role of VEGF is the major development of the systemic circulation noticeable on the High-resolution CT of the chest (Fig. 1). While we have no direct evidence in the present case report of such a mechanism, a common pathophysiological link between emphysema and PVOD deserves further investigation.

Of particular interest was the association of severe diffuse pulmonary emphysema and the lack of airflow limitation. Several studies showed that COPD with severe PH is paradoxically associated with moderate airflow obstruction [1–5]. In the report of the fifth world symposium on PH devoted to chronic lung diseases it is underlined that the mechanisms of disproportionate appearance of pulmonary hypertension in lung diseases is unknown. Important mechanisms that limit airflow in emphysema are the loss of lung elastic-recoil forces and collapse of the distal airway during expiration [18]. In our patient and in published reports on severe PH in patients with COPD [1–4,19], we hypothesize that pulmonary vascular remodeling prevented airway collapse and restored, at least partially, some of the elastic-recoil forces. This mechanism seems possible because of the anatomical connections between the distal airways and pulmonary arteries of small caliber (Fig. 2). Decrease in total respiratory compliance in pulmonary vascular disease due to pulmonary vascular stiffness without spirometric abnormalities was shown previously [20]. Our hypothesis is also supported by Coste et al. [21], who recently observed using CT a specific increase in total cross-sectional area and an increase in the number of small vessels (<5 mm^2) in COPD patients with severe PH compared to COPD patients without severe PH.

4. Conclusion

The combination of lung function test, CT abnormalities and pathological analysis in the present case supports to investigate the relationship between pulmonary vascular remodeling and lung mechanics in chronic lung diseases with severe PH. Such yet to come pathophysiological studies will help to explain the paradoxical association between severe pulmonary hypertension and mild-to-moderate airflow limitation and better understand the relationship between PH and emphysema [2–5,19].

Conflict of interest statements

All authors have no conflict of interest.

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