

Pathological characteristics in idiopathic nonspecific interstitial pneumonia with emphysema and pulmonary hypertension

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Abstract

A 75-year-old man was admitted to our hospital complaining of a 4-year history of persistent dry cough and progressive dyspnea on exertion. Chest computed tomography images revealed diffuse reticular opacities and traction bronchiectasis in the bilateral lower lobes and emphysema predominantly in the upper lobes. He was treated with inhaled N-acetylcystein therapy, oral corticosteroids, and pirfenidone in addition to oxygen administration. However, his symptoms and oxygenation gradually deteriorated. In addition, echocardiography showed that estimated pulmonary arterial pressure was 109 mm Hg, sildenafil was started. Twenty months later, he suddenly died of decompensated right heart failure. The autopsied lungs demonstrated a diffuse fibrotic nonspecific interstitial pneumonia (NSIP) pattern with emphysema (combined pulmonary fibrosis and emphysema) and widespread severe intimal and medial thickening ranging from proximal elastic to distal muscular pulmonary arteries. To our knowledge, little has been reported on clinicopathological characteristics of idiopathic NSIP associated with emphysema and severe pulmonary hypertension.

Introduction

Pulmonary hypertension (PH) is a common complication of interstitial lung diseases (ILDs), which is associated with deterioration on the functional status and poor survival [1]. Although Hallowell et al. [2] reported recently that severe PH can occur in idiopathic nonspecific interstitial pneumonia (NSIP), little has been reported focusing on clinicopathological characteristics of idiopathic NSIP associated with emphysema and PH.

Case Presentation

A 75-year-old man was admitted to our hospital complaining of a 5-year history of persistent dry cough and progressive dyspnea on exertion. He had a smoking history of 110 pack-year and no exposure to dusts. He was initially diagnosed as having combined pulmonary fibrosis and emphysema (CPFE) associated with idiopathic pulmonary

fibrosis (IPF) at the age of 70, and treated by inhaled N-acetylcysteine twice daily (352.4 mg per day), oral administration of corticosteroids (20 mg per alternate-day), and pirfenidone (1800 mg per day). Despite the initiation of these treatments, his condition gradually worsened (World Health Organization functional class IV).

Results of arterial blood gas analysis were pH: 7.42; PaCO₂:33.2 Torr; and PaO₂:55.4 Torr on room air. The pulmonary function test revealed normal vital capacity of 3.19 L (96.7% of predicted) with decreased diffusing capacity of 21.4% of predicted. Chest computed tomography (CT) images revealed diffuse reticulation and honeycombing admixed with ground glass opacity, as well as prominent traction bronchiectasis with bilateral lower lobes predominance. In addition, there was upper lobe-predominant centrilobular and paraseptal emphysema (Fig. 1). Echocardiography showed that estimated pulmonary arterial pressure was 109 mm Hg, with flattening of the interventricular septum, right ventricular dilatation,

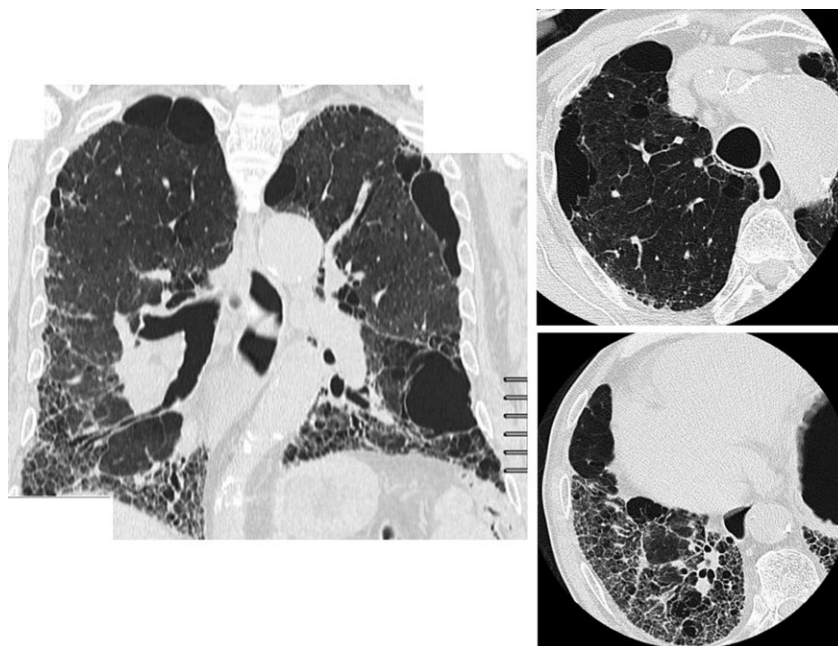


Figure 1. Chest computed tomography images reveal diffuse reticulation and honeycombing admixed with ground glass opacity, as well as prominent traction bronchiectasis with bilateral lower lobes predominance. In addition, there is upper lobe-predominant centrilobular and paraseptal emphysema.

and moderate tricuspid regurgitation. CT pulmonary angiography and venous Doppler were negative for thromboembolism. After the initiation of sildenafil treatment and supplement of oxygen, his clinical condition remained unchanged. Twenty months later, he suddenly died of decompensated right heart failure. Macroscopic appearance at autopsy of the bilateral lungs revealed multiple bullae with upper lobes predominance, uniformly enlarged air-space with thick walls and prominent traction bronchiectasis with bilateral lower lobes predominance (Fig. 2a). Histological examination revealed fibrotic NSIP pattern in addition to paraseptal and centrilobular emphysema (Fig. 2b). There were widespread small pulmonary arteries with intimal fibrosis and medial hypertrophy, as well as small pulmonary veins with intimal fibrosis in fibrotic lesions, resulting in marked luminal narrowing (Fig. 2c,d). On the other hand, the obstruction of small muscular pulmonary arteries and diffuse alveolar capillary multiplication were present in areas of relatively normal lung (Fig. 2e). Macroscopic reconstruction appearance of the left lower pulmonary artery (A8) demonstrated varying degrees of luminal narrowing and thickened walls (Fig. 2f). Histologically, the hilar pulmonary arteries showed mild atherosclerotic lesions (Fig. 2g). Furthermore, obviously intimal fibrosis and medial hypertrophy were found from proximal elastic pulmonary arteries to distal muscular type pulmonary arteries (Fig. 2h,i). There was no evidence of plexiform and angiomatoid lesions.

Discussion

PH is a common complication of ILDs including IPF, connective tissue disease such as systemic scleroderma, pulmonary Langerhans cell histiocytosis, and sarcoidosis, which is associated with worse function impairment and survival [1]. Furthermore, Mejía *et al.* [3] recently reported that 31 (28%) of 110 patients with IPF also had emphysema and that patients with IPF complicated by emphysema had a higher mortality rate than those with IPF alone. Although the present patient was treated with sildenafil for 1 year, New York Heart Association functional class or pulmonary hemodynamics were deteriorated. In particular, it is known that several medications approved for PH are not available for PH out of proportion to parenchymal lung disease [2]. To our knowledge, little has been reported focusing on clinicopathological characteristics of idiopathic NSIP associated with emphysema and PH. It is difficult to ascertain on chest CT whether subpleural cystic changes in the areas of fibrosis in the lower lobes are due to emphysema, honeycombing, bronchioloectasis, or a combination of these entities. However, the present case was histologically proven as fibrotic NSIP.

The onset of secondary PH in patients with IPF is considered to be associated with vessel ablation or a reduction of the pulmonary vascular bed caused by fibrosis of alveolar septa and with hypoxic pulmonary artery spasm. The apparent lack of correlation between the degree of

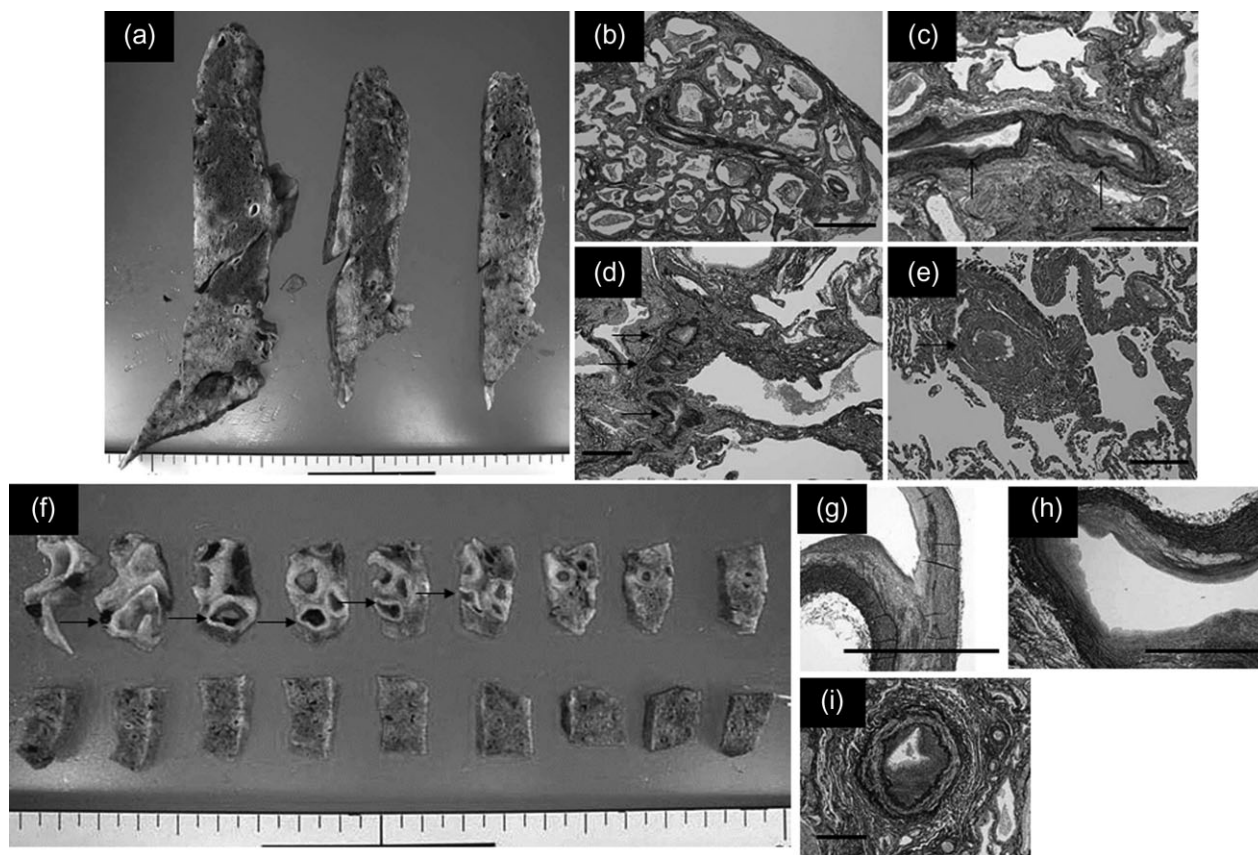


Figure 2. (a) Macroscopic appearance at autopsy of the bilateral lungs reveals multiple bullae measuring up to 5 cm with upper lobe predominance, marked anthracosis, subpleural grayish-white zonal lesions, and volume loss of both lower lobes. Various sized thin-walled cysts are seen slightly apart from pleura in the bilateral upper lobes. The uniformly enlarged airspace with thick walls, partially small-size honeycomb change, and prominent traction bronchiectasis are evident predominantly in the bilateral lower lobes (1 scale = 5 mm). (b) Low-magnified microscopic appearance of both basal lobes showing diffuse and temporally uniform interstitial fibrosis. The fibrosis is collagenous with collapse of alveoli and also contained mild chronic inflammation, in which there is no evidence of fibroblastic foci (fibrotic NSIP pattern; Elastic van Gieson stain; 1 scale bar = 1 mm). (c) High-magnified microscopic appearance of the fibrotic area indicated in Figure 2b. There are widespread small pulmonary arteries with intimal fibrosis and thickened muscular media (arrows; Elastic van Gieson stain; 1 scale bar = 250 mm). (d) High-magnified microscopic appearance of both upper lobes. Note small pulmonary veins with intimal fibrosis in fibrotic lesions, resulting in marked luminal narrowing (arrows; Elastic van Gieson stain; 1 scale bar = 250 mm). (e) High-magnified microscopic appearance of areas in the relatively normal lung lesion showing the thickened muscular layer of a small pulmonary artery (arrow). Note the obviously increased muscular area and diffuse alveolar capillary multiplication (hematoxylin-eosin stain; scale bar = 100 mm). (f) Macroscopic reconstruction appearance of the left lower pulmonary artery (A8) shows varying degrees of luminal narrowing and thickened walls (1 scale = 5 mm). (g) Microscopic appearance of hilar large pulmonary artery showing thickened intimal atherosclerotic lesions (Elastic van Gieson stain; 1 scale bar = 5 mm). (h) Microscopic appearance of proximal elastic type pulmonary artery showing moderate intimal fibrosis and medial muscular hypertrophy (Elastic van Gieson stain; 1 scale bar = 1 mm). (i) High magnified microscopic appearance of distal muscular type pulmonary artery. Note the markedly luminal narrowing with intimal fibrosis and medial muscular hypertrophy (Elastic van Gieson stain; 1 scale bar = 100 mm).

fibrosis and the prevalence and severity of PH in IPF indicates that factors other than fibrosis contribute to the development of PH. Recently suggested mechanisms of its onset include vascular remodeling because of overexpression of cytokines and growth factors such as transforming growth factor- β , platelet-derived growth factor, and vascular endothelial growth factor [1].

Few reports are available on histopathological features of patients with CPFE associated with PH such as the

present case [4]. It was demonstrated using pulmonary arterial reconstruction that the pulmonary vascular lesions such as luminal narrowing and/or occlusion were continuously located from large elastic to small muscular pulmonary arteries. As Colombat et al. [5] described previously, pulmonary vascular lesions in patients with end-stage IPF, similarly in the present case the pulmonary vascular lesions were evident in both pulmonary arteries and veins within fibrotic areas, whereas the obstruction of small

muscular pulmonary arteries and alveolar capillaries multiplication were present in relatively normal areas. This alveolar capillaries multiplication is known to be usually relevant to the increase of the pressure in the pulmonary vein [5].

In summary, idiopathic fibrotic NSIP with emphysema can be associated with severe PH because of prominent pulmonary vascular lesions. Therefore, further studies are needed to ascertain the pathophysiology of CPFE with PH including mechanisms of vascular remodeling and/or PH out of proportion.

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Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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