Broad and heterogeneous vasculopathy in pulmonary fibrosis and emphysema with pulmonary hypertension

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Abstract
A 69-year-old man with progressive dyspnea was referred to our hospital in Oct 2010. The patient was clinically diagnosed with combined pulmonary fibrosis and emphysema (CPFE) and pulmonary hypertension (PH). Sildenafil and bosentan were used for the treatment of progressive PH, and dyspnea and pulmonary hemodynamics improved at 3 months follow-up. However, the patient died of respiratory failure 1 year later. Autopsy identified marked intimal and medial thickening of the pulmonary arteries/arterioles, and modest but broad fibrous obstruction of the veins/venules and capillary multiplication. Also, immunohistochemical study showed positive staining for the target proteins of the PH-specific vasodilators, sildenafil and bosentan, on the diseased vessels. The present autopsy report is the first to pathologically document the diseased pulmonary vasculature and how PH-vasodilators can ameliorate pulmonary hemodynamics in a patient with CPFE and PH.

Introduction
Combined pulmonary fibrosis and emphysema (CPFE) is an emerging clinical entity characterized by dyspnea, hypoxemia, relatively preserved lung function, low diffusing capacity of the lung (DLCO), and findings on lung computed tomography (CT) of concomitant fibrosis and emphysema [1, 2]. Pulmonary hypertension (PH) often develops in CPFE [1], but the underlying pathophysiology of the vasculopathy remains unknown. In addition, optimal treatment strategies for PH in CPFE have yet to be established.

We recently published the clinical courses of four patients with group 3 PH who responded favorably to pulmonary artery hypertension (PAH)-specific vasodilators [3]. One of the four patients later died of respiratory failure, and the present report documents the autopsy findings from that case with CPFE and PH. Findings of an immunohistochemical study for expression of the target proteins/receptors of PAH-specific vasodilators are also presented.

Case Report
The clinical course of the patient was introduced in our recent report [3]. In brief, the patient was a 69-year-old man with progressive dyspnea and advanced hypoxemia whose chest CT and pulmonary function test findings were consistent with a diagnosis of CPFE. Right heart catheterization (RHC) showed increased mean pulmonary arterial pressure (PAP) (47 mmHg) and pulmonary vascular resistance (PVR) (987 dyn/s/cm5). Under a clinical diagnosis of CPFE with advanced PH, PAH-specific vasodilators comprising sildenafil (60 mg/day) and bosentan (125 mg/day) were administered. At the follow-up assessment 3 months later, he noted less dyspnea at rest but 6-min walk distance test was not conducted due to remaining short breath and hypoxia. Plasma brain-type natriuretic peptide concentration reduced from 1390 pg/ml at baseline to 32.8 pg/ml, and cardiac magnetic resonance-derived right ventricular ejection fraction also improved from 26% to 44%. RHC showed a reduction in mean PAP (43 mmHg) and a 35% decrease in PVR (to 645 dyne/s/cm5). The patient was...
discharged but, 1 year later, he experienced exacerbations of dyspnea and hypoxia and was rehospitalized. With a suspicion of microbial infection and/or progression of interstitial pneumonia, we treated him with antibiotics and steroids but he died of respiratory failure in January 2012.

Autopsy showed intimal thickening and medial hypertrophy of the pulmonary arteries/arterioles in the emphysematous upper lobes of the lungs (Fig. 1A, B). Pulmonary capillary multiplication was also evident (Fig. 1A, C), and showed positive staining for CD34 (Fig. 1D). Also, fibrous obstruction of the veins/venules was noted (Fig. 1E). In the preserved lung area without obvious emphysematous or fibrotic changes, modest remodeling of the arterial and venous trees and capillary multiplication were observed. In
the lower lobes where fibrotic changes dominated, obstruction of the arteries/arterioles due to thickened fibrous intima was observed (Fig. 1F). There was modest venopathy, but no obvious capillary changes were identified. Complex vascular lesions including plexiform lesions were not observed. Also, there were no findings suggestive of acute progression of interstitial pneumonia or of left heart failure. These vascular changes in the emphysematous, preserved or fibrotic areas of the lungs are summarized in Table 1.

Immunohistochemical examination showed slight but positive staining for phosphodiesterase (PDE)-5, endothelin receptor (ER)-A and -B, and prostaglandin (PG) I2 receptor in the diseased pulmonary arterial/arteriolar walls (Fig. 2).

Figure 2. Immunohistochemical study of lungs. Slight staining for phophodiesterase-5 (A), endothelin receptor-A (B), endothelin receptor-B (C), and prostaglandin I2 (D) receptor was observed on diseased pulmonary arteries. All antibodies used were provided by Abcam, Cambridge Science Park, UK.

Table 1. Summary of the vascular changes in the emphysematous, preserved or fibrotic areas of the lungs.

|                     | Arterial/arteriolar remodeling | Capillary multiplication | Venous/venular remodeling | Plexiform lesions | Vasculitis |
|---------------------|--------------------------------|--------------------------|---------------------------|------------------|-----------|
| Emphysematous area  | ++                             | +                        | +                         | –                | –         |
| Preserved area      | +                              | +                        | +                         | –                | –         |
| Fibrotic area       | +                              | –                        | +                         | –                | –         |

Neutrophil accumulation in right lower lobe, No diffuse alveolar damage.
Discussion

In this autopsy, pathological evaluations were performed with a particular focus on evaluation of three pulmonary vascular components of a patient with CPFE and PH: arteries/arterioles; capillaries; and veins/venules. Associations between vascular changes and background lung parenchymal lesions were also carefully evaluated.

As summarized in Table 1, broad and heterogeneous vasculopathies of the arteries/arterioles, veins/venules, and capillaries were noted throughout the lungs. Among these, changes to the arteries/arterioles were the most noticeable and were considered to play a central role in the development of PH. Regarding the venules and capillaries, the extent of changes was modest but distributed prevalently. These venous and capillary changes, along with arterial/arteriolar changes, were likely to have contributed to the development of not only PH, but also low DLco and hypoxia.

Heterogeneous vascular changes have been reported in other types of PH. For example, systemic sclerosis (SSc)-associated PH has been reported to exhibit heterogeneous vasculopathy of arteries, veins and small vessels of the lungs [4]. Also, arterial, venular and capillary changes were documented in a recent histopathological study on the explanted lungs from idiopathic pulmonary fibrosis (IPF) patients [5]. These publications indicate that broad/heterogeneous vasculopathy is not necessarily specific to PH that occurs in CPFE.

Idiopathic PAH (IPAH)-type vasculopathy has been hypothesized to employ in the pathogenesis of PH in CPFE. However, the vascular changes observed in the present case differed somewhat from IPAH-type vasculopathy. Most importantly, arteriopathy was evident in the emphysematous and fibrotic areas, but was observed only mildly in the preserved lung area. The arteriopathy would have been more homogeneous if IPAH-type vasculopathy represented the primary process. Also, plexiform lesions were not observed in our case.

It seems that the vasculopathy seen in the present study differs from the typical vascular changes of COPD. In COPD, vasculopathy usually develops in small arteries through arterioles in mild to moderate COPD [6] as well as in advanced COPD [7]. Also, the degree of these changes appears to parallel the extent of emphysema and small airways disease [6]. In the present case, there was a broad and heterogeneous vasculopathy that developed irrespective of the background lung parenchymal changes, which was not consistent with the typical vasculopathy of COPD.

Previous studies have shown increased vascular expression of PDE-5 in PAH patients. Also, increased vascular expression of ER receptors (ERs) has been documented in PH associated with congenital heart disease. The results of the immunohistochemical investigations in the present report were in line with those observations. Of note, however, is that the present report verified these findings in a case which favorably responded to sildenafil and bosentan before the pathological evaluation.

In conclusion, the present autopsy case report demonstrated broad and heterogeneous vasculopathy of the lungs that presumably caused advanced PH and some clinical features of CPFE. The presence of the target proteins of sildenafil and bosentan also partly explained how the two vasodilators could improve pulmonary hemodynamics. However, the pathogenesis of PH in CPFE may be heterogeneous, depending on the specific case. Further studies are thus needed to better elucidate the pathophysiology and optimal treatment strategy for PH patients with CPFE.

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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