Combined Unclassifiable Interstitial Pneumonia and Emphysema: A Report of Two Cases

Nobuhiko Nagata, Kentaro Watanabe, Michihiro Yoshimi, Hiroshi Okabayashi, Katsuo Sueishi, Kentaro Wakamatsu, Hiroyuki Kumazoe and Yoshinori Nagamatsu

Abstract

We herein report two cases of combined pulmonary fibrosis and emphysema (CPFE), whose histological patterns of lung pathology could not be categorized into any subset of idiopathic interstitial pneumonias (IIPs). Case 1 was a 62-year-old man, who presented with dyspnea on exertion and cough. Case 2 was a 51-year-old man with a dry cough. The CT findings of both cases fit the definition of CPFE. Surgical lung biopsies of both patients revealed alveolar septal widening due to collagen deposition, with emphysema and respiratory bronchiolitis mainly in the subpleural parenchyma. These cases suggest that the fibrosis of CPFE includes smoking-related interstitial fibrosis other than the known histological patterns of IIPs.

Key words: interstitial pneumonia, pulmonary fibrosis, pulmonary emphysema, smoking

(Intern Med 52: 2337-2341, 2013)  
(DOI: 10.2169/internalmedicine.52.0840)

Introduction

The term ‘unclassifiable interstitial pneumonia’ is assigned if the histology of fibrosis does not fit any subset of the existing classification of idiopathic interstitial pneumonias [IIPs (1)]. Combined pulmonary fibrosis and emphysema (CPFE), originally described by Cottin et al. (2), is defined by imaging findings. There is a well-established relationship between smoking and CPFE, but the histological patterns of its fibrosis have not been fully examined. We herein report two patients with CPFE whose fibrotic lungs were biopsied, but the histological patterns could not be categorized into any existing IIPs subset.

Case Reports

Case 1

In January, 2008, a 62-year-old man visited our hospital presenting with gradually increasing dyspnea on exertion and a cough that had lasted for five years. He had smoked two packs of cigarettes a day for 42 years and was obese (height, 162 cm; weight, 91.1 kg). Chest auscultation revealed fine crackles in both lung bases. Neither cyanosis nor clubbing was noted. Blood tests showed mild increases in the WBC count (11.4×10⁹ cells/L) and the CRP (0.68 mg/dL), KL-6 (865 IU/mL), SP-D (176 ng/mL) and SP-A (264 ng/mL) levels. The results of an arterial blood gas analysis were normal, with a PaO₂ of 90.4 torr, a PaCO₂ of 40.6 torr and a pH of 7.433. Pulmonary function tests showed a decreased diffusing capacity for carbon monoxide (DLco and DLco/VA of 78.1% and 79.5% of the predicted values, respec-
the 3D visualization system (AZE Virtual Place, Fujin) was age of emphysema of whole lung field on CT measured by areas of both lung bases (Fig. 4, left column). The percentage of emphysematous parenchyma (Fig. 2, right panel). Four years after the initial visit to our hospital, his chest X-ray and pulmonary function test revealed no deterioration.

Case 2

In March 2012, a 51-year-old man visited our hospital presenting with a four-month history of a persistent dry cough. He had smoked two packs of cigarettes a day for 31 years. Fine crackles were audible in both lung bases. Neither cyanosis nor clubbing was noted. Blood tests were unremarkable, with a normal KL-6 (407 IU/mL) level and a normal SpO₂ (97%). Pulmonary function tests showed a normal VC (106.2% of predicted value) and FEV1. Chest X-rays showed hyperlucency in both upper lung fields and reticular shadows in both lower lung fields (Fig. 1). High-resolution computed tomography (HRCT) confirmed low-attenuation areas primarily in the outer zones of both upper lung fields, and diffuse reticular and ground-glass opacities in the subpleural areas of both lung bases (Fig. 2, left column). The percentage of emphysema of the whole lung field on CT measured by a 3D visualization system (AZE Virtual Place, Fujin AZE Ltd., Tokyo, Japan) was 3.7%. Surgical lung biopsy of the left S2 and S8 was performed by video thoracoscopy. The histological findings revealed alveolar septal widening due to collagen deposition with emphysema and respiratory bronchiolitis. Fibrosis was present in the subpleural parenchyma, and surrounded not only the enlarged airspaces, but also the non-emphysematous parenchyma (Fig. 2, right panel). Four years after the initial visit to our hospital, his chest X-ray and pulmonary function test revealed no deterioration.

Figure 1. A chest X-ray of Case 1 showing hyperlucency in both upper lung fields and reticular shadows in both lower lung fields.

Discussion

Although diseases consistent with CPFE had been reported in case reports and series in the past (3-5), it began to attract attention when Cottin et al. described CPFE in 61 patients with both emphysema in the upper zones and diffuse parenchymal lung disease with fibrosis in the lower zones of the lungs on chest CT (2). The nature of the fibrosis was not determined, in those cases, because the pathological features were examined in only eight patients, five of whom had been reported to have usual interstitial pneumonia (2). Based on the pathological analyses of resected lungs from smokers with lung cancer who showed no signs or symptoms related to fibrosis, pathologists have found that interstitial fibrosis in smokers is histologically distinct from that of IIPs. These findings were classified as airspace enlargement with fibrosis (6), smoking-related interstitial fibrosis (SRIF) (7) or respiratory bronchiolitis-associated interstitial lung disease with fibrosis (8) by different pathologists. Most importantly, these lesions show a stable clinical course, rather than deteriorating, as does idiopathic pulmonary fibrosis. The relationship of these lesions with CPFE is unknown.

The CT findings of our two cases fit the definition of CPFE; however, the histological patterns of fibrosis did not fit any IIP subset. They differed from the usual interstitial pneumonia (UIP) histological patterns because there was no patchwork pattern, temporal heterogeneity of fibrosis or remodelling of the lung architecture, such as honeycombing and scarring. They also differed from nonspecific interstitial pneumonia (NSIP), because the fibrosis was localized in the subpleural lung parenchyma, rather than the more diffuse fibrosis in NSIP, and because the fibrosis surrounded the enlarged airspaces, and little inflammatory infiltration was seen in the fibrously thickened alveolar septa. The pathological features of the two cases reported here are similar to the smokers’ fibrosis described above, but are more likely to fit the definition of SRIF, as reported by Katzenstein et al. (6). Although desquamative interstitial pneumonia and respira-
Figure 2. A chest high-resolution computed tomography image (left column) and photomicrograph of the biopsied lung tissue (right column) from Case 1. The upper lung fields showed low-attenuation areas primarily in the subpleural area (upper left), while diffuse reticular and ground-glass opacities were noted in the subpleural area of both lung bases (lower left). The photomicrograph revealed alveolar septal widening due to collagen deposition, with emphysema and respiratory bronchiolitis. The fibrosis is seen in the subpleural parenchyma, and surrounds not only the enlarged airspaces, but also the non-emphysematous parenchyma. The right lower photomicrograph shows a higher magnification of the boxed area of the right upper one photograph (Hematoxylin and Eosin staining, original magnification: right upper, 14×; right lower, 56×).

Figure 3. A chest X-ray from Case 2 showing hyperlucency in both upper lung fields and reticular shadows in both lower lung fields.

tory bronchiolitis-associated interstitial lung disease are subsets of IIPs (1) with characteristic clinical symptoms and signs, SRIF has not yet been recognized as a clinically-established interstitial pneumonia with symptoms or impaired respiratory function.

SRIF was proposed based on a pathological study of lobectomy specimens excised for neoplasm from cigarette smokers with no clinical evidence of interstitial lung disease (7), and its clinical significance is unknown at present. Both patients in this report visited the hospitals because of subjective symptoms such as dyspnoea on exertion and cough (Case 1) or dry cough (Case 2). Moreover, Case 1 had impairment of the diffusing capacity and elevation of the levels of KL-6, SP-A and SP-D. The possibility that the patients’ symptoms and impaired diffusing capacity were solely caused by emphysema and the fibrous pathology that we reported to only represent trivial fibrotic lesions in smokers cannot be completely ruled out. However, the attending physicians in our cases diagnosed the patient’s illness as interstitial lung disease as the primary diagnosis, and performed surgical lung biopsy or lobectomy for the diagnosis of interstitial lung disease. Therefore, we think that the fibrotic lesion noted in our patients contributed at least
partly to the patients’ clinical features. Yousem reported similar pathology in terms of respiratory bronchiolitis-associated interstitial lung disease with fibrosis from the study of nine cases with clinical and radiological chronic interstitial lung disease (8).

The chest X-rays and pulmonary function tests in Case 1 revealed no deterioration during the four years after lung biopsy, and the chest CT of Case 2 did not show worsening of the interstitial opacities during the 1.5 year follow-up period before lung biopsy. These clinical features are inconsistent with idiopathic pulmonary fibrosis and fibrosing NSIP.

In this report, we showed that SRIF is a pathological counterpart of pulmonary fibrosis in CPFE. In addition to the CT findings, the histological patterns in the lower lobes associated with CPFE are various and complicated, especially in patients with concomitant emphysema. Further studies are needed to clarify the histological nature of the fibrosis in CPFE and the clinical significance of SRIF. There may be other features, in addition to SRIF, in the lungs with CPFE, which cannot be classified as known histological patterns of IIPs. We therefore believe that the histology of the reported cases is one of the variety of smoking-related interstitial lung diseases.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
This study was partly supported by a grant to the Diffuse Lung Diseases Research Group from the Ministry of Health, Labour and Welfare, Japan.

References


© 2013 The Japanese Society of Internal Medicine

http://www.naika.or.jp/imonline/index.html