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Heterogeneous clinical features in patients with pulmonary fibrosis showing histology of pleuroparenchymal fibroelastosis

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ABSTRACT

Background: The histological pattern of pleuroparenchymal fibroelastosis (PPFE) is well defined, but its clinical features remain unclear.

Methods: We retrospectively examined the predominantly involved lung-fields (based on abnormal opacities on computed tomography [CT] images), and the initial value and annual decline of respiratory function in patients with pulmonary fibrosis presenting with histologically confirmed PPFE.

Results: Thirteen female and nine male subjects were included. Eleven interpreters independently analyzed 231 CT image series. One-third of the CT series (78/231) was interpreted as demonstrating equal involvement of the upper and lower lung fields, i.e., six out of 21 patients had equal involvement of the upper and lower lung fields, based on a majority decision of the interpreters. The residual volume/total lung capacity (RV/TLC) was increased and correlated inversely with forced vital capacity (FVC) at the initial measurement. FVC followed two patterns of decline over time: a gradual decline over a follow-up period of more than 6 years (−55 mL/year, R^2=0.799), and a relatively rapid decline over a shorter period (−364 mL/year, R^2=0.855) as determined by mixed-effect linear regression.

Conclusions: The predominantly involved sites seen on CT images of PPFE were not limited to the upper lobes. In some cases, upper lung fields were predominantly involved, but in other cases, both upper and lower lung fields were equally involved. Two patterns of FVC decline exists: a rapid decline over a short period and a slow decline over a longer period, suggesting that the disease follows a heterogeneous clinical course.

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1. Introduction

In 2013, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) updated the international multidisciplinary classification of idiopathic interstitial pneumonias (IIPs) [1]. According to this classification, idiopathic pleuroparenchymal fibroelastosis (PPFE) is one of the rare IIPs.

The concept of idiopathic PPFE overlaps with that of idiopathic pulmonary upper lobe-localized fibrosis (IPUF) proposed by Amitani (Amitani disease) [2] and that of pulmonary upper lobe-dominant fibrosis [3–5]. Currently, idiopathic PPFE is the globally accepted nomenclature for these fibroses with unknown etiology. However, the worldwide accumulation of case series of PPFE has led to evolution of this concept [6–15], although some issues remain unclear. Despite the defined nature of the histological pattern of PPFE, the clinical manifestation seems to be heterogeneous. The histological pattern of PPFE is found with a variety of conditions, such as repeated infections, autoimmune diseases, a family history of interstitial pneumonias, asbestos exposure, and in response to anticancer chemotherapeutic agents, including cyclophosphamide [6,7,10,14,15], while transplantation-associated PPFE was also reported recently [9,12,13,16]. This complicates the assessment of PPFE pathogenesis. Although the PPFE imaging pattern is thought to represent upper lobe fibrosis [1], PPFE may be a more diffuse process that is not limited to the upper lobes [14], and no convincing imaging studies have been published showing upper lobe predominance.

This fibrotic disease may progress irreversibly to end-stage fibrosis [1], but its prognosis is unclear. Amitani disease is a slowly progressive fibrosis with a presentation of 10–20 years [2].

PPFE is a “rare” pulmonary fibrosis, and the number of patients in the case-series studies reported in the past has been fewer than 20. Here, we present the clinical, imaging, and physiological characteristics of 22 patients with pulmonary fibrosis and histologically proven PPFE.

2. Patients and methods

2.1. Patient selection

We reviewed the medical files of all patients who were hospitalized in the Departments of Respiratory Medicine at the Fukuoka University Hospital, Omuta National Hospital, Fukuoka Higashi Medical Center, Hamanomachi Hospital, and Kyushu University Hospital, from 2000 to 2014, and found 23 patients with pulmonary fibrosis and histologically proven PPFE who had undergone surgical lung biopsy (SLB) and/or autopsy. We excluded a case of PPFE that occurred in transplanted lungs [16], because an estimation of the predominantly involved sites was not possible in the transplanted lower lobes. After excluding this patient, 22 patients were eventually enrolled.

2.2. Clinical data

We reviewed the patients' clinical records for age at onset, sex, smoking status, steroid treatment, symptoms, crackles, and body mass index (BMI). Comorbidities, past history (including pneumothorax), and occupational history were also examined. The follow-up interval from the onset of symptoms to the last date of follow-up was determined, and information on the prognosis of the patients was recorded.

2.3. Histological and imaging findings

Histological specimens from SLB were obtained for 15 patients. Autopsy samples were obtained for four patients. The remaining three patients who had undergone SLB underwent left lung resection for lung transplantation and/or autopsy at a later stage. Histological specimens, stained with hematoxylin and eosin and with Elastica van Gieson, were reviewed by KW, NN, and KN. PPFE was histologically diagnosed based on the following criteria: (1) increased elastic fibers with septal elastosis in the subpleural area, (2) intra-alveolar collagen deposition associated with septal elastosis, and (3) collagenous thickening of the visceral pleura. When all three or the first two criteria were met, a histological pattern of PPFE was recognized [10,17].

Conventional or high-resolution computed tomography (HRCT) images of the chest were reviewed for all but one patient (it was unavailable for patient #7). We evaluated all of the abnormal patterns identified in the lung parenchyma and pleura, including nodules, consolidation, ground-glass opacities, reticulation, honeycombing, and cysts, seen on chest CT images in the patients who presented with PPFE histology. Such CT patterns were divided into three groups, based on the primary involved site: upper lung field predominance, lower lung field predominance, and equal involvement of upper and lower lung fields. All authors, except for KN, interpreted all the CT images of the 21 patients, independently. To decide on the predominantly involved sites, the 11 interpreters read the first series of CT images available for each patient, totaling 231 series (11 interpreters × 21 patients). If consensus could not be reached, the involved sites were decided based on majority decision. An extended kappa value was calculated for the level of agreement between the 11 interpreters.

Abbreviations: BMI, body mass index; DLco, diffusing capacity of carbon monoxide; FRC, functional reserve capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; IPUF, idiopathic pulmonary upper lobe fibrosis; NTM, nontuberculous mycobacteria; PPFE, pleuroparenchymal fibroelastosis; RV, residual volume; TLC, total lung capacity; UIP, usual interstitial pneumonia

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