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ORIGINAL ARTICLE

Pleuroparenchymal fibroelastosis as a histological background of autoimmune diseases

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Abstract

Patients with autoimmune disease–related interstitial lung disease (AID-ILD) occasionally develop radiologic pleuroparenchymal fibroelastosis (PPFE)–like lesions. However, the significance of AID as an etiology of PPFE has not been fully elucidated. The aim of this study is to verify the increase of elastic fibers in AID-ILD patients and evaluate the prevalence of histological PPFE in patients with AID-ILD. We selected cases of clinically diagnosed AID-ILD and idiopathic pulmonary fibrosis (IPF), in which an autopsy had been performed or in which the patient had undergone pneumonectomy for lung transplantation. We quantified the collagen fibers and elastic fibers in each lobe as the percentage of the non-aerated lung area (collagen fiber score and elastic fiber score, respectively) in histological specimens from a total of 73 patients (AID-ILD, $n = 24$; IPF, $n = 49$). There were no significant differences in the collagen fiber scores of the AID-ILD and IPF groups. Meanwhile, the elastic fiber scores of the AID-ILD group were significantly greater than those of the IPF group in the whole lung (17.3 ± 7.70 vs 11.6 ± 4.55), and the upper (16.6 ± 8.11 vs 11.2 ± 5.18), and lower (18.0 ± 9.68 vs 12.0 ± 5.55) lobes (all $p < 0.01$). Histological PPFE pattern was found in 12 of 24 AID-ILD patients (50%), and histological PPFE pattern as a dominant pattern of fibrosis was found in 2 of the 24 patients (8%). Thus, PPFE can be a manifestation of AID-ILD.

Keywords Pleuroparenchymal fibroelastosis · Elastic fibers · Vasculitis · Usual interstitial pneumonia · Connective tissue disease

Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a unique clinicopathological entity that consists of elastofibrosis involving the lung parenchyma and pleura with an upper lobe predominance [1–3]. Histologically, PPFE shows subpleural intra-alveolar fibrosis accompanied by alveolar septal elastosis [1, 4–6]. The increase of elastic fibers within the fibrotic tissue is one of the histological features of PPFE [7, 8]. PPFE is categorized as either idiopathic or secondary [6]. Possible etiologies of secondary PPFE include radiation, bone marrow or stem cell transplantation, lung transplantation, dust exposure (asbestos and aluminum), infection (*Aspergillus* and *Mycobacterium avium-intracellulare complex*), drugs, and chronic hypersensitivity pneumonia [4, 9–12]. Some investigators reported PPFE in patients with autoimmune disease (AID), including connective tissue disease (CTD) [6, 13, 14] and vasculitis [15, 16]. However, the significance of AID as an etiology of PPFE has not been fully elucidated. The aim of this study is to verify the increase of elastic fibers in histological specimens and evaluate the prevalence of the histologic PPFE pattern in patients with autoimmune disease–related interstitial lung disease (AID-ILD).

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Materials and methods

Subjects

We retrospectively reviewed the medical records of patients who had been autopsied or who underwent pneumonectomy for lung transplantation from 1974 to 2018. We then selected

consecutive patients who were diagnosed with "interstitial pneumonia" and "autoimmune disease" (CTD or vasculitis in the present study). We excluded cases in which the upper or lower lobe was not available for histological evaluation. CTD and vasculitis were diagnosed based on the current diagnostic criteria [17–23], or the previous criteria at the time of the diagnosis. Finally, 24 patients with AID-ILD were selected for the present study.

In addition, we selected consecutive patients with a clinical diagnosis of idiopathic pulmonary fibrosis (IPF) ($n = 49$) who had been autopsied or who had undergone pneumonectomy for lung transplantation. We also selected consecutively autopsied patients ($n = 5$) who had died of non-pulmonary diseases for comparison. The clinical diagnosis of interstitial pneumonia was made based on a multidisciplinary approach. IPF was diagnosed when the cases were judged as either "IPF" or "probable IPF" according to the current consensus classification criteria [1, 24, 25]. The Fukuoka University Hospital Institutional Review Board approved the study protocol and waived the requirement for informed consent (approval number, 16-1-12).

Clinical, imaging, and respiratory function data

Clinical data were abstracted from the medical records. The respiratory function parameters had been measured less than a year prior to the histological examination. The forced vital capacity (FVC) was obtained using spirometry. The predicted value for FVC (FVC %pred.) was calculated using the reference spirometry values for Japanese individuals [6].

Histological patterns of fibrosis

The histological diagnoses of usual interstitial pneumonia (UIP) (definite UIP or probable UIP) and non-specific interstitial pneumonia (NSIP) were based on the guidelines of the American Thoracic Society and the European Respiratory Society [25, 26]. In this study, the criteria for a histological diagnosis of PPFE were as follows: (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 at least the first two criteria were met, a histological pattern of PPFE was recognized [1, 4–6, 8, 27]. When the dominant histological findings did not fit with any of the single histological subsets (i.e., UIP, NSIP, or PPFE), the case was labeled as unclassifiable fibrosis. When we did not determine the histological subset because of end-stage fibrosis, superimposed acute lung injury, or end-stage infection, the case was labeled as undetermined fibrosis. The histological findings were independently evaluated by three observers (KW, YK, and KN), and disagreements were resolved by consensus.

The quantification of elastic fibers/collagen fibers

Samples were fixed in 10% formalin and embedded in paraffin. Staining was performed on 4-μm-thick tissue sections mounted on a glass microscope slide. Hematoxylin-eosin, Elastica van Gieson, and Masson's trichrome staining were performed on each section. As we described previously [8], we assessed the elastic and collagen fiber scores in at least one histological specimen from each of the upper and lower lobes. In short, Elastica van Gieson– and Masson's trichrome–stained slides were scanned and converted to a whole-slide image, also known as a virtual slide, with a NanoZoomer 2.0-RS (Hamamatsu Photonics, Hamamatsu, Japan). The areas of elastic fiber were measured with the ImageJ 1.49v software program (National Institutes of Health, Bethesda, MD, USA) using the same threshold. We defined the number of pixels of the elastic fiber/collagen fiber divided by the number of pixels of non-aerated lung specimens and multiplied by 100 as the elastic fiber/collagen fiber score (Fig. 1). The scores of each specimen were averaged separately for the upper and lower lobes.

Intralobular distribution of elastosis in AID-ILD

To examine the intralobular distribution of elastosis (subpleural distribution or diffuse distribution) in greater detail in AID-ILD patients, we selected 22 AID-ILD patients whose elastic fiber scores in the whole-lung analysis were higher than the mean value of elastic fiber scores in the normal lung; we defined these patients as AID-ILD patients with elastosis. We histologically divided these patients into two groups: one group with upper lobe-predominant elastosis (group A) and the other with lower lobe-predominant elastosis (group B), based on the ratio of the elastic fiber score for upper lobe/lower lobe (≥ 1 or more, group A; < 1, group B) (Fig. 2a). We then examined the intralobular distribution of elastosis (subpleural distribution or diffuse distribution) in the lobes with predominant elastosis.

Statistical analyses

Continuous data are shown as the group means (standard deviation) and categorical data are shown as the number (percentage) in the group. Fisher's exact test was used to compare categorical variables. The differences in the mean values of parametric data were assessed using Student's t test for unpaired data. p values of < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the R software program (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria).

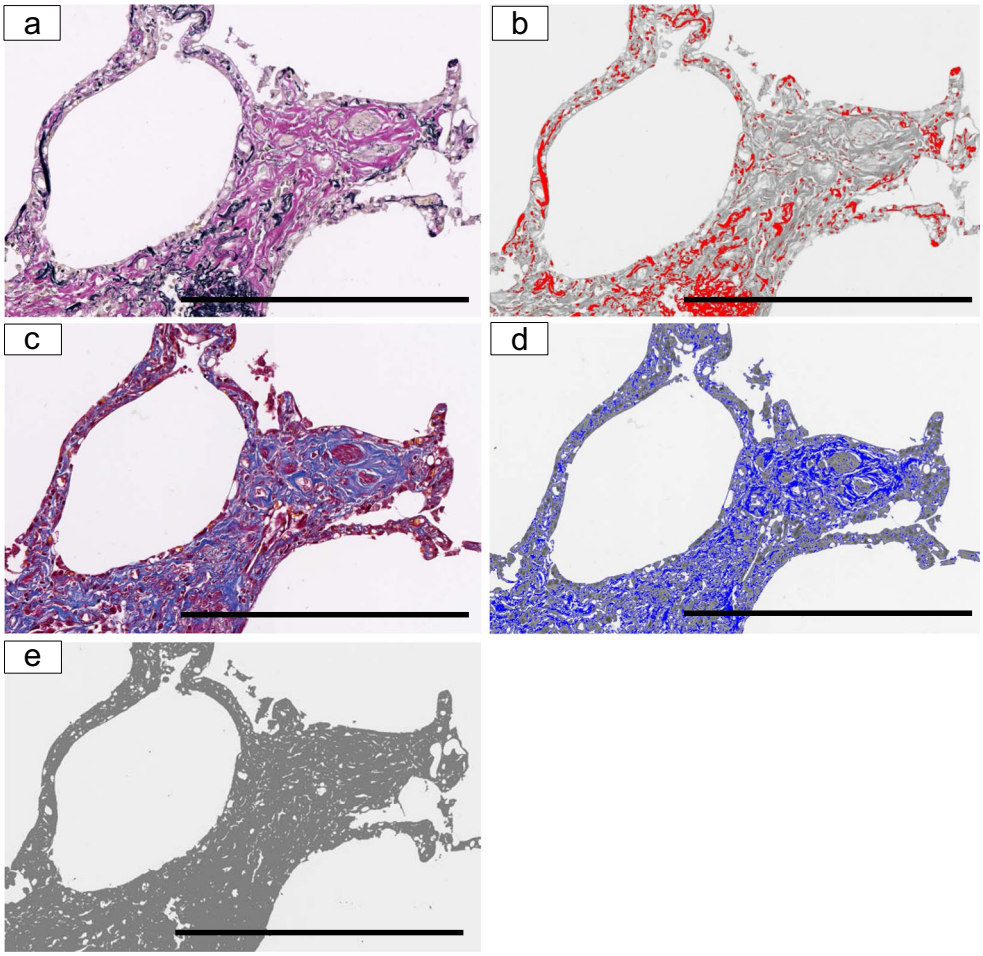

Fig. 1 An Elastica van Gieson–stained section (**a**) was converted to grayscale and binarized (**b**). The red field in (**b**) shows elastic fibers. A Masson's trichrome-stained section (**c**) was converted to grayscale and binarized (**d**). The blue field in (**d**) shows collagen fibers. The Elastica van Gieson–stained section (**a**) was converted to grayscale and binarized (**e**). The gray field in (**e**) shows the non-aerated area. In this case, the elastic fiber score (elastic fiber area/non-aerated area) was calculated to be 25.4, and the collagen fiber score (collagen fiber area/non-aerated area) was calculated to be 36.9. Scale bar = 300 μm

Results

Patient characteristics

A total of 24 patients with AID-ILD were eligible for this study: rheumatoid arthritis ($n = 8$), polymyositis and dermatomyositis ($n = 6$), microscopic polyangiitis ($n = 4$), systemic sclerosis ($n = 3$), systemic lupus erythematosus ($n = 2$), and Sjögren's syndrome ($n = 1$). The patient characteristics are summarized in Table 1. The percentage of female patients in the AID-ILD group (45.8%) was higher than that in the IPF group (18.4%), and steroids were frequently administered to the AID-ILD group (66.7%) than to the IPF group (38.8%). The smoking rate of the IPF was significantly higher than that of AID-ILD group. In the AID-ILD group, the mean body mass index was relatively lower and the mean FVC %pred. was relatively larger in comparison to the IPF group. The prevalence of other parameters was comparable between the two groups.

Dominant histological patterns of fibrosis

A mean of 9.33 paraffin blocks per patient were available for histological examination. In the AID-ILD group, a UIP pattern (definite UIP or probable UIP) was found in 13 of 24 patients (51.2%), and an NSIP pattern was found in four of 24 patients (16.7%). Five of 24 cases (20.1%) were classified as undetermined fibrosis ($n = 2$) or unclassifiable fibrosis ($n = 3$). Two of 24 patients (8.3%) with AID-ILD showed a PPFE pattern: one patient had polymyositis/dermatomyositis; the other had microscopic polyangiitis (Fig. 3).

Histologic PPFE finding

Histologic PPFE pattern was observed in 12 of 24 patients (50%) with AID-ILD. However, in 10 of the 12 patients, the predominant pattern of fibrosis was non-PPFE. In addition, histologic PPFE pattern was observed in 11 of 49 patients (22.4%) with IPF. The prevalence of histologic PPFE pattern in AID-ILD was significantly higher than that in IPF ($p = 0.03$).

Fibrosis scores

The fibrosis scores are summarized in Table 2. The collagen fiber scores of the AID-ILD group were higher than those of the IPF group in both the whole-lung analysis and the individual lobe analyses; however, none of the differences reached

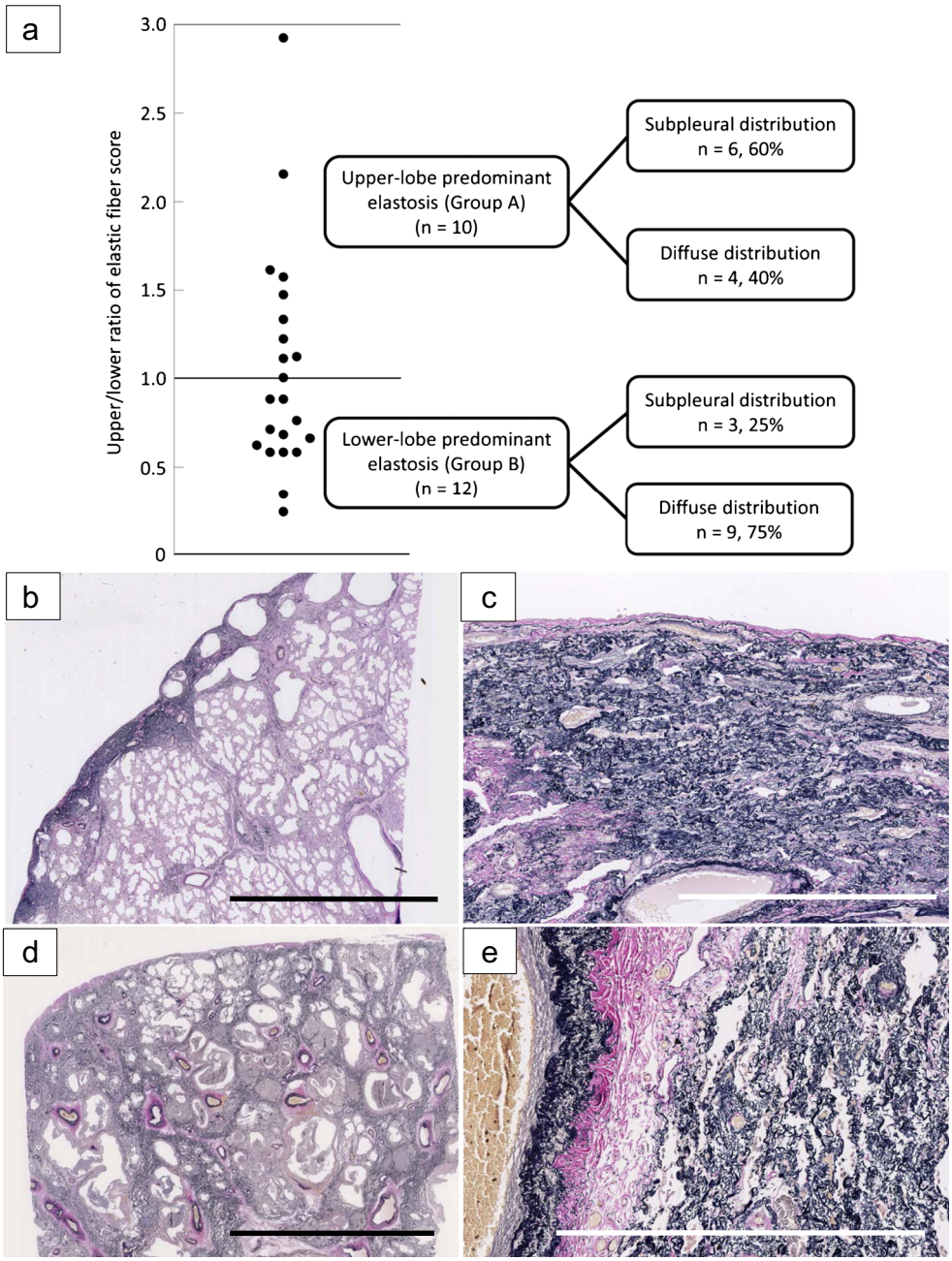

Fig. 2 AID-ILD patients with elastosis were divided into two groups based on the ratio of the elastic fiber score for the upper lobe/lower lobe (group A, ≥ 1; group B, < 1): group A had upper lobe-predominant elastosis; group B had lower lobe-predominant elastosis. We then examined the intralobular distribution of elastosis (subpleural distribution or diffuse distribution) in the lobes with predominant elastosis (**a**). An Elastica van Gieson–stained section (**b**) obtained from the upper lobe of a patient with microscopic polyangiitis showed subpleural-predominant elastosis. A higher magnification view of (**b**) showing the dense accumulation of elastic fibers (**c**). Meanwhile, an Elastica van Gieson–stained section (**d**) that was obtained from the lower lobe of a patient with polymyositis and dermatomyositis, showing the diffuse distribution of elastosis. A higher magnification view of (**d**) showing the dense accumulation of elastic fibers (**e**).Scale bar = 10 mm in panels (**b** and **d**), scale bar =1 mm in panels (**c** and **e**)

statistical significance. Meanwhile, the elastic fiber scores in the AID-ILD group were significantly higher than those in the IPF group in the whole-lung analysis (17.3 ± 7.70 vs 11.6 ± 4.55), the upper lobe analysis (16.6 ± 8.11 vs 11.2 ± 5.18), and the lower lobe analysis (18.0 ± 9.68 vs 12.0 ± 5.55) (all $p < 0.01$). The upper/lower ratios of elastic fiber scores were comparable between the groups (1.07 ± 0.60 vs 1.03 ± 0.47, $p = 0.78$).

The intralobular distribution of elastosis in AID-ILD

In the whole-lung analysis, 22 of 24 patients with AID-ILD had elastic fiber scores above the mean value (8.22) of normal lung (i.e., AID-ILD patients with elastosis). Among the 10 patients of group A, six patients showed a subpleural distribution of elastosis (Fig. 2b, c) and four patients showed a diffuse distribution of elastosis (Fig. 2d, e). Meanwhile, in 12 patients of group B, only three patients showed a subpleural distribution of elastosis and nine patients showed a diffuse distribution of elastosis. The nine cases which showed a lower-lobe predominance and a diffuse distribution of elastic fibers were classified histologically as UIP in five cases, NSIP in two, and undetermined fibrosis in two.

Table 1 Clinical characteristics

Factor	AID-ILD ($n = 24$)	IPF ($n = 49$)	p value
Age (years)	67.3 (15.1)	69.4 (12.0)	0.54
Gender, male/female	13/11	40/9	0.024
BMI (kg/m^2)	19.5 (4.05)	21.2 (4.21)	0.11
Smoking history, current/former/never	4/9/11	26/14/9	< 0.01
Serum KL-6 levels (U/mL)[a]	1250 (1569)	1200 (697)	0.88
Cause of death, respiratory failure/others	19/3	35/13	0.74
Respiratory function parameters[a]			
FVC (ml)	1894 (897)	1616 (909)	0.36
FVC %pred.	64.9 (27.2)	49.3 (27.6)	0.11
Pharmacotherapy			
Corticosteroids	16 (66.7)	19 (38.8)	0.045
Immunosuppressants	9 (37.5)	11 (22.4)	0.26

The data are expressed as the group mean (standard deviations) or n (%)

AID-ILD, autoimmune disease–related interstitial lung disease; *IPF*, idiopathic pulmonary fibrosis; *BMI*, body mass index; *KL-6*, Kerbs von Lungren-6 antigen; *FVC*, forced vital capacity

[a] These parameters were measured less than 1 year prior to death or pneumonectomy for lung transplantation

Discussion

The present study showed that the elastic fiber scores of AID-ILD patients were significantly higher than those of IPF patients. In this cohort, histologic PPFE pattern was found in 12 of the 24 patients (50%) with AID-ILD, and two patients (8%) had PPFE as a predominant histological pattern. Thus, an autoimmune predisposition seems to be a trigger for the increase of elastic fibers, possibly leading to secondary PPFE.

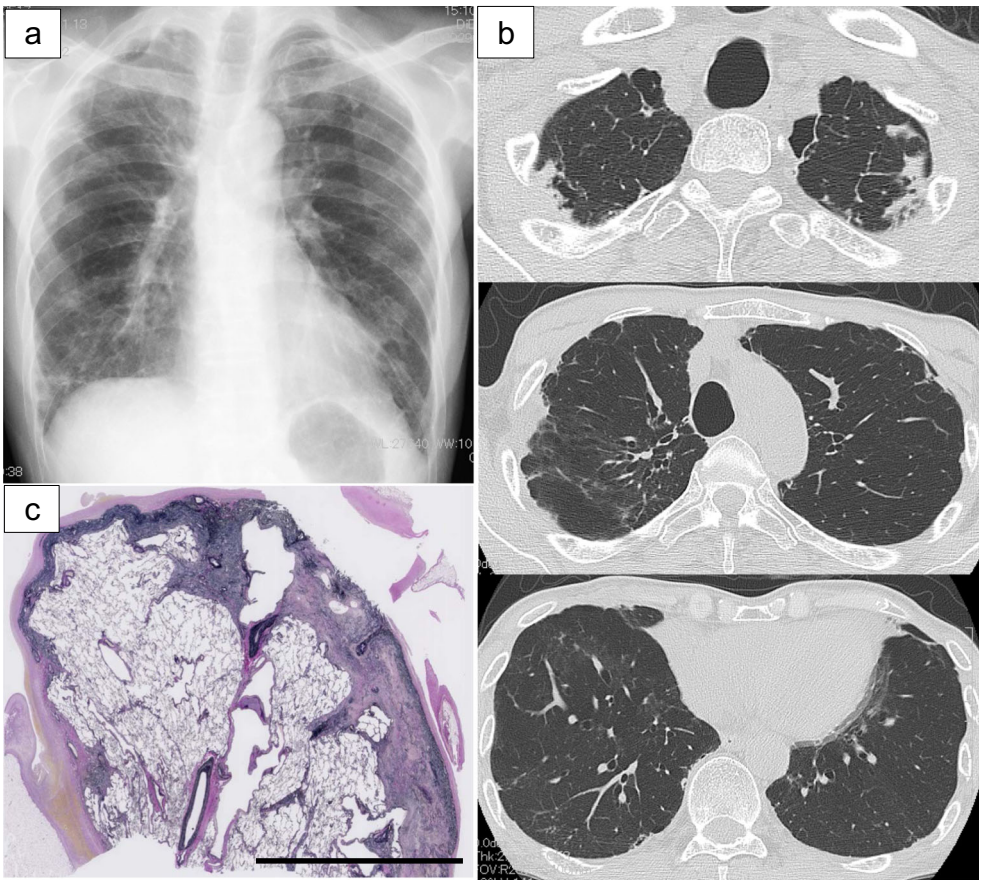

Fig. 3 Chest radiography and high-resolution computed tomography of a 76-year-old man diagnosed with microscopic polyangiitis demonstrating wedge-shaped alveolar consolidation in the subpleural region of the upper lobes (**a**) and (**b**). An Elastica van Gieson–stained section of the upper lobe showed pleural fibrosis and subpleural band–like and wedge-shaped intra-alveolar elastosis and fibrosis (**c**). Scale bar = 10 mm

Table 2 Fibrosis scores

Factor	Normal lung ($n = 5$)	AID-ILD ($n = 24$)	IPF ($n = 49$)	P value[a]
Collagen fiber score				
Whole lung	6.85 (0.98)	19.2 (11.2)	16.4 (6.78)	0.18
Upper lobes	5.11 (1.70)	18.6 (10.0)	15.7 (7.30)	0.17
Lower lobes	8.60 (1.99)	19.8 (14.8)	17.0 (8.66)	0.30
Upper/lower	0.63 (0.27)	1.11 (0.61)	1.10 (0.60)	0.95
Elastic fiber score				
Whole lung	8.22 (2.31)	17.3 (7.70)	11.6 (4.55)	< 0.01
Upper lobes	7.23 (1.10)	16.6 (8.11)	11.2 (5.18)	< 0.01
Lower lobes	9.22 (3.52)	18.0 (9.68)	12.0 (5.55)	< 0.01
Upper/lower	0.84 (0.19)	1.07 (0.60)	1.03 (0.47)	0.78

The data are expressed as the group means (standard deviations)

AID-ILD, autoimmune disease–related interstitial lung disease; *IPF*, idiopathic pulmonary fibrosis

[a] p values were calculated for the comparison of autoimmune disease–related ILD and IPF patients

Few reports have been published on the prevalence of PPFE among patients with AID-ILD. Enomoto et al. showed that radiologic PPFE-like lesions were found in 21 of 113 (19%) patients with connective tissue disease–related interstitial lung disease (CTD-ILD) [14]. Apical cap or upper lobe subpleural fibrosis in IPF might be included in the radiologic PPFE-like lesions in their study because a histological examination was only performed in approximately one third of the cases [8]. However, their conclusion suggests the possibility that a histological pattern of PPFE is commonly found in patients with CTD-ILD. In our whole-lung histological investigation, we demonstrated that half of the patients with AID-ILD had PPFE pattern, and two patients (8%) had PPFE as a predominant histological pattern of fibrosis. Thus, whatever mechanisms are responsible for the development of autoimmune diseases could also be responsible for the occurrence of a histological pattern of PPFE.

Fibrosis is a common feature of many CTDs and affects not only the skin but also the internal organs [28, 29]. The excess synthesis and deposition of collagen fiber and elastic fiber in the lung is sometimes seen in CTD-ILD [29–31]. Felicio et al. histologically examined the collagen/elastic fibers in patients with idiopathic NSIP and CTD-NSIP using lung biopsy specimens and demonstrated that patients with CTD-NSIP showed significant increase of collagen and elastic fiber in comparison to those with idiopathic NSIP [30]. We quantified collagen and elastic fibers in greater detail throughout the lung. Although their method of sample collection and quantification was different, the results of our study support their conclusion.

Meanwhile, it is important to notice that the increase of elastic fibers in AID-ILD is not necessarily connected with clinical PPFE. The subpleural and upper lobe distribution of elastofibrosis is a typical phenotype of clinical PPFE [6]. We examined the intralobular distribution of elastosis in 22 AID-ILD patients with elastosis. Among the 10 AID-ILD patients with upper lobe-predominant elastosis, the subpleural distribution of elastosis in the upper lobes was found in six patients, which is consistent with a histological prototype of PPFE [32]. However, four of the six patients with subpleural-predominant elastosis in their upper lobes were not diagnosed with PPFE as a predominant pattern of fibrosis because they had a more extensive non-PPFE pattern fibrosis in their lower lobes. That means that most patients with AID-ILD showed increase of elastic fibers, while the number of patients who showed a subpleural and upper lobe distribution of elastofibrosis was relatively low.

Meanwhile, in the patients with lower lobe-predominant elastosis, the main pattern of elastic fiber distribution in the lower lobes was diffuse, not subpleural, which was different from that in the upper lobes. Why did the pattern of elastosis distribution differ in the two lobes? In this study, nine cases of AID-ILD which showed a lower-lobe predominance and a diffuse distribution of elastic fibers were classified histologically as UIP ($n = 5$), NSIP ($n = 2$), and undetermined fibrosis ($n = 2$). Thus, diffuse elastosis in the lower lobes may reflect diffusely or randomly distributed nature of ILD such as NSIP, end-stage UIP, or unclassifiable fibrosis. We speculate that diffuse elastosis in the lower lobes as well as subpleural elastosis in the upper lobes might be histologic characteristics of AID-ILD.

In the present study, we came across a case complicated by microscopic polyangiitis and PPFE. The association between antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and pulmonary fibrosis has already been reported [33]. Although few studies have reported on an association between myeloperoxidase-ANCA and PPFE or between granulomatosis with polyangiitis and PPFE [4, 15, 16, 34], to the best of our knowledge, this represents the first case of microscopic polyangiitis–related PPFE. As we

described, vasculitis as well as CTD can be associated with PPFE. Further studies will be needed to investigate the correlation between vasculitis and PPFE.

The present study is associated with some limitations. First, this was a retrospective study performed in a single center, and the number of patients was relatively small because we only selected patients who had undergone autopsy or pneumonectomy to examine the whole lung. Therefore, a larger study is necessary to confirm the results. Second, the fibrosis score could be influenced not only by the elastosis or fibrosis in interstitial pneumonia but also by the amount of innate extracellular matrix in the lung. However, the fibrosis scores in the normal lung were much smaller than those in patients with AID-ILD or IPF; thus, the influence of innate extracellular matrix was considered to be negligible. Likewise, the collapse of the lung tissue will exaggerate the relative presence of innate extracellular matrix including elastic fibers or collagen fibers. However, as we described in Table 2 and the "Results" section, the elastic fiber scores in the AID-ILD group were significantly higher than those in the IPF group, but the collagen fiber scores of the AID-ILD group were not significantly different from those of the IPF group. These results may not be fully explained by the collapse of the lung only. Third, the fibrosis scores in this study might not represent whole-lung fibroelastosis exactly because the sampling sites of the autopsied lungs were decided by each pathologist who performed the autopsy.

In conclusion, we demonstrated that half of the patients with AID-ILD had PPFE pattern, and 8% of patients had PPFE as a predominant histological pattern of fibrosis. Thus, PPFE can be a manifestation of AID-ILD.

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Author contribution YK contributed to the design and concept of the study, data analysis, and writing of the manuscript. KW contributed to the design and concept of the study, data analysis, and development of the manuscript. KN contributed to the data analysis and gave advice on the design and concept of the study. HI, HK, MH, and MF contributed to the collection of the data and final approval of the manuscript.

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Compliance with ethical standards

This study was approved by The Fukuoka University Hospital Institutional Review Board, and it approved the study protocol and waived the requirement for informed consent.

Conflict of interest The authors declare that they have no conflicts of interest.

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