Original article

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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2.4. Respiratory function parameters

Forced vital capacity (FVC) was measured using spirometry. The results of this analysis are expressed as absolute values (mL) and as percentages of predicted values (%pred), which were calculated using the formulas of the Japanese Respiratory Society (JRS) adjusted for sex, height, and age [18].

Total lung capacity (TLC), functional reserve capacity (FRC), and residual volume (RV) were measured using the helium gas dilution method, and the diffusing capacity of carbon monoxide (DLco) was measured using the single-breath-holding method [19]. Predicted values for each lung volume parameter were estimated using Grimby's formula [20], and predicted values for DLco were estimated using Burrows's formula [21].

2.5. Baseline and follow-up data on respiratory function

Baseline respiratory function was estimated from the first measurement, which was conducted at our hospitals in 21 patients and at another hospital in one patient.

To estimate the annual change (∆) in FVC, TLC, RV/TLC, and DLco, we used respiratory function data collected over the period of at least 1 year. The annual change for each patient was estimated using simple linear regression, assuming time-dependency and linearity [17]. It was expressed as an absolute value and as a percentage of change from the baseline value. The annual change in RV/TLC (%) was defined as the slope on a linear equation obtained by linear regression.

Because the number of measurements of FVC and the years of follow-up differed among patients, a mixed-effect linear regression analysis was performed to estimate the annual decline of FVC for the whole cohort of patients ($n=21$), using FVC as a dependent variable, and years and patients (random effect) as independent variables.

The institutional review board of the Fukuoka University Hospital approved this retrospective study (#15-5-13, approved on May 27, 2015).

2.6. Statistical analysis

Numerical data are shown as mean±SD. $P<.05$ indicated statistical significance. The correlation between FVC and RV/TLC was assessed using Pearson's correlation. An extended kappa for the multi-interpreter agreement [22] for analysis of CT images and mixed-effect linear regression analysis was performed using SAS statistical software, version 9.4 (SAS Institute, USA); other analyses were performed using Prism 5 (GraphPad Software, USA).

3. Results

3.1. Clinical characteristics

The enrolled patients consisted of 13 females and nine males (Table 1). Fourteen patients have been reported previously [17,23,24]. We also previously reported nine patients with IPUF [17]. As the histology of IPUF is the same as that of PPFE, we included those nine patients in this analysis.

Age at onset was ranged from 41 to 81 years (56.6±11.0 years). Sixteen patients had never smoked. Steroids were administered to nine patients, but had no beneficial effect. Nontuberculous mycobacteria (NTM) were isolated from sputum twice or more in three patients (*Mycobacterium avium* in two of these patients). Rheumatoid arthritis (in one patient) and ulcerative colitis (in one patient) were noted as comorbidities. These patients were treated with nonsteroidal anti-inflammatory drugs and mesalazine, respectively. Two patients had suffered from Hashimoto's disease or Basedow's disease previously. One patient had worked as a welder for 26 years. One patient had esophageal cancer that had been irradiated 4 years prior to his death.

Cough or exertional dyspnea was the main symptom in the patients. Chest pain appeared in four patients. Patients were slender, with a BMI of 17.1±2.1 kg/m². Crackles were audible in 11 of the 22 patients. Thirteen patients died 1.8–14.8 years after the onset of the first symptom. A Kaplan–Meier survival curve for the 22 patients showed that the median survival was 7.3 years.

3.2. Histological and imaging findings

Histological features that are essential for PPFE were found in all patients; these included intra-alveolar collagenosis and subpleural elastosis, with preserved alveolar structures, as reported previously [6,10]. Collagenous thickening of visceral

Table 1 – Clinical characteristics.	
Number of subjects	22
Age at onset: years	56.6±11.0[a]
Sex: males/females	9/13
Smoking status: never-smokers/current or former smokers	16/6
Treatment with steroids	9
Comorbidities	
Nontuberculous mycobacteriosis	3
Rheumatoid arthritis	1
Ulcerative colitis	1
Past history	
Pneumothorax	9
Hashimoto's disease	1
Basedow's disease	1
Irradiation for esophageal cancer	1
Bladder cancer	1
Occupational history	
Welder	1
Lung transplantation	2
First symptom	
Exertional dyspnea	8
Dry cough	6
Chest pain	4
Cough and sputum	3
Weight loss	1
Body mass index (kg/m²)	17.1±2.1[a]
Crackles: audible/not audible	11/11
Follow-up periods from the first symptom to the last follow-up (years)	5.58±3.46[a]
Prognosis: alive/dead	9/13

[a] Mean±SD.

Table 2 – Imaging characteristics: predominantly involved fields.

Patient no.	Interpreter 1	Interpreter 2	Interpreter 3	Interpreter 4	Interpreter 5	Interpreter 6	Interpreter 7	Interpreter 8	Interpreter 9	Interpreter 10	Interpreter 11	U/U≒L/L	Predominantly involved fields by a majority decision
1	U	U	U	U≒L	U	U	U≒L	U≒L	U≒L	U	U≒L	6/5/0	U
2	U≒L	U	U	U≒L	U	U	U	U≒L	U	U	U	8/3/0	U
3	U≒L	U	U	U	U	U	U	U	U≒L	U≒L	U≒L	7/4/0	U
4	U	U	U	U≒L	U	U	U≒L	U≒L	U	U≒L	U	7/4/0	U
5	U≒L	U	U	U≒L	U	U≒L	U	U≒L	U	U≒L	U≒L	5/6/0	U≒L
6	U	U	U	U	U	U	U	U	U	U	U	11/0/0	U
7													
8	U	U	U	U	U	U	U	U	U	U	U	11/0/0	U
9	U	U	U	U	U	U	U	U	U	U	U	11/0/0	U
10	U≒L	U≒L	U	U≒L	U≒L	U≒L	U≒L	U≒L	U≒L	L	U≒L	1/9/1	U≒L
11	U≒L	U	U	U≒L	U	U	U	U≒L	U≒L	U	U	7/4/0	U
12	U≒L	U≒L	U	U≒L	U≒L	U≒L	U≒L	U≒L	U≒L	U≒L	U≒L	1/10/0	U≒L
13	U≒L	U	U	U	U	U	U≒L	U≒L	U	U≒L	U	7/4/0	U
14	U	U	U	U	U	U	U	U	U	U	U	11/0/0	U
15	U	U	U	U	U≒L	U	U	U	U	U	U	10/1/0	U
16	U	U	U	U	U	U	U	U	U	U	U	11/0/0	U
17	U	U	U	U≒L	U	U	U	U≒L	U	U	U	9/2/0	U
18	U≒L	U≒L	U	U≒L	U≒L	U≒L	U≒L	U≒L	U≒L	L	L	1/8/2	U≒L
19	U	U≒L	U	U≒L	U≒L	U≒L	U	U≒L	U≒L	U	U	5/6/0	U≒L
20	U	U	U	U≒L	U	U	U≒L	U≒L	U	U	U	8/3/0	U
21	U≒L	U≒L	U	U≒L	U≒L	U≒L	U≒L	U≒L	U≒L	U	U≒L	2/9/0	U≒L
22	U	U	U	U	U	U	U	U	U	U	U	11/0/0	U
												150/78/3 (total)	15/6 (U/U≒L)

U: upper lung field predominant; U≒L: upper and lower lung fields equally involved; L: lower lung field predominant.
An extended kappa for the multi-interpreter agreement was 0.341 (CI: 0.166–0.503). Since the sample size was not sufficiently large to apply the asymptotic theory, the bootstrap resampling method with replacement was used to estimate the kappa and confidence interval. The number of resampling was 1000 times.
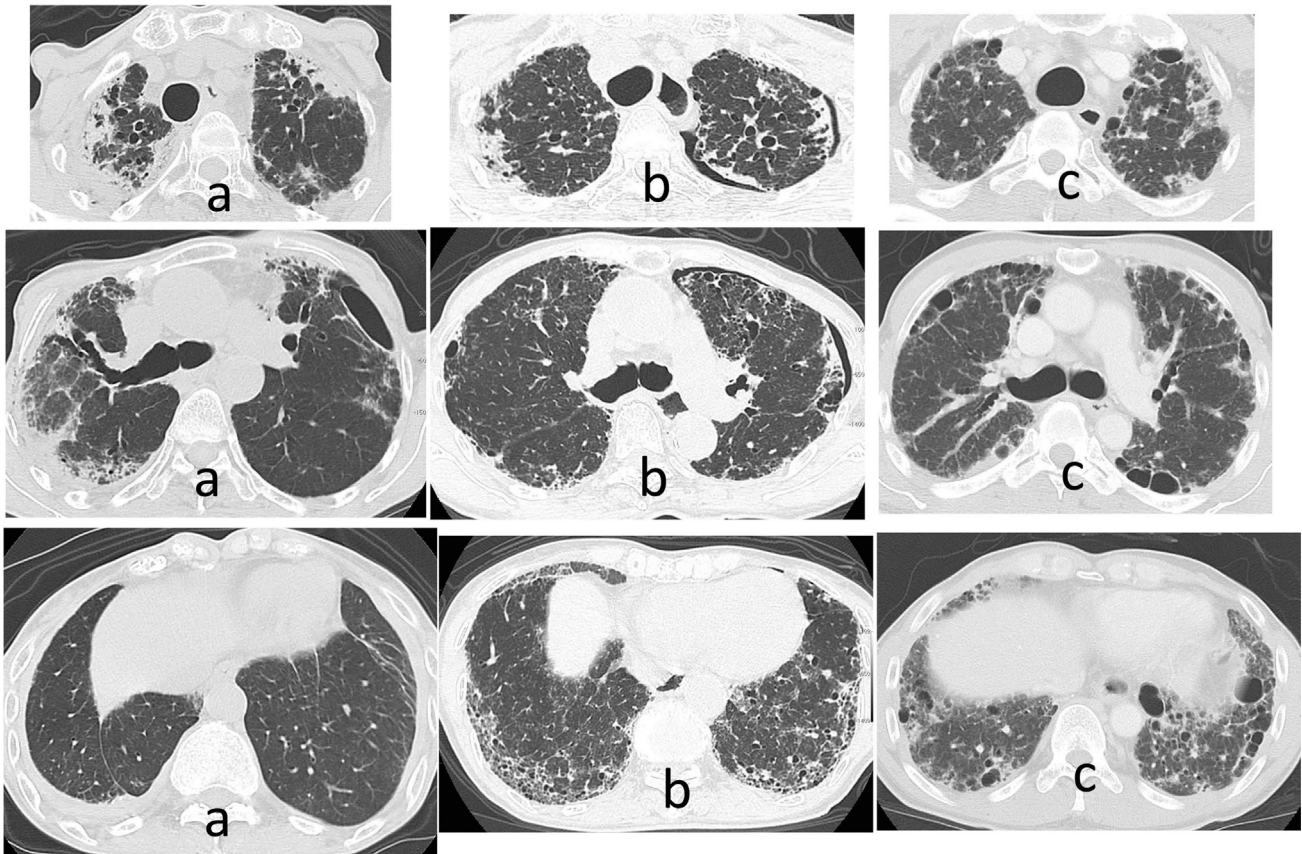
Fig. 1 – Chest computed tomography (CT) images presenting upper lung field predominance (A, patient #9) and equal involvement of upper and lower lung fields (B, #12; C, #18). Two of the 11 interpreters selected CT images of (C) for lower lung field predominance.

Table 3 – Baseline values of respiratory function parameters.	
FVC	
Number of subjects	22
FVC (mL)	2004±735
FVC (% pred)	66.0±20.1
Static lung volumes	
Number of subjects	19
TLC (mL)	3454±943
TLC (% pred)	72.1±20.5
RV/TLC (%)	46.4±12.9
RV/TLC (% pred)	144.0±±45.8
DLco	
Number of subjects	18
DLco (mL/min/mmHg)	11.4±3.9
DLco (% pred)	72.5±23.5
	(mean±SD)

FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; DLco: diffusing capacity of carbon monoxide.
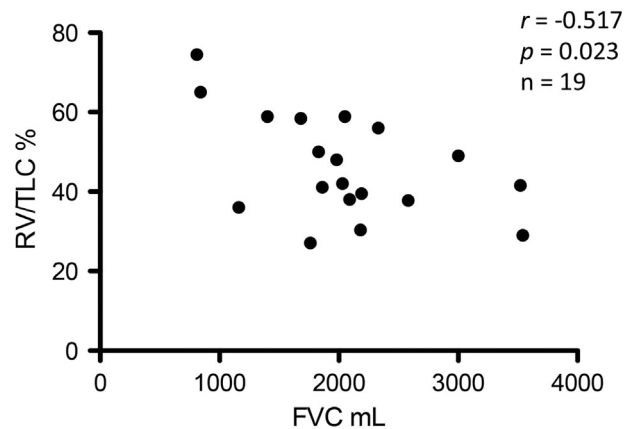

Fig. 2 – Relationship between residual volume/total lung capacity (RV/TLC) and forced vital capacity (FVC). The baseline values of RV/TLC (%) correlated negatively with those of FVC (mL).

pleura was found in 14 of the 22 patients. There was no disagreement regarding the histological diagnosis of PPFE among the three reviewers.

One-hundred-and-fifty series of CT images were interpreted as showing upper lung field predominance, 78 were interpreted as showing equal involvement of the upper and lower lung fields, and three were interpreted as showing lower lung field predominance (Table 2). Based on a majority decision reached

Table 4 – Changes per year of respiratory function parameters.

FVC	
Number of subjects	21
ΔFVC (mL)	−241±203
ΔFVC (% from baseline)	−11.2±9.3
Follow-up period (years)	4.54±3.45
Number of measurement per patient	11.1±7.2
Static Lung Volumes	
Number of subjects	14
ΔTLC (mL)	−443±355
ΔTLC (% from baseline)	−12.4±9.6
ΔRV/TLC (%)	2.23±5.86
Follow-up period (years)	2.71±2.37
Number of measurement per patient	7.5±3.7
DLco	
Number of subjects	11
ΔDLco (mL/min/mmHg)	−1.43±1.58
ΔDLco (% from baseline)	−13.5±14.1
Follow-up period (years)	1.96±0.79
Number of measurement per patient	5.5±2.3
	(mean±SD)

Δ: change per year; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; DLco: diffusing capacity of carbon monoxide. Change per year for each patient was calculated using a simple linear regression.
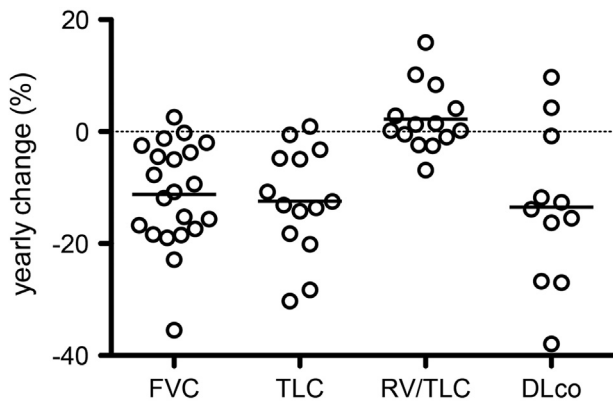

Fig. 3 – Annual change in forced vital capacity (FVC), total lung capacity (TLC), residual volume/total lung capacity (RV/TLC), and diffusing capacity of carbon monoxide (DLco). The values of FVC, TLC, and DLco declined annually; in contrast, RV/TLC increased. Annual changes were estimated using simple linear regression. Annual changes in FVC, TLC, and DLco were expressed as the percentage of change from the baseline, and the annual change in RV/TLC was defined as the slope of a linear equation obtained by linear regression.
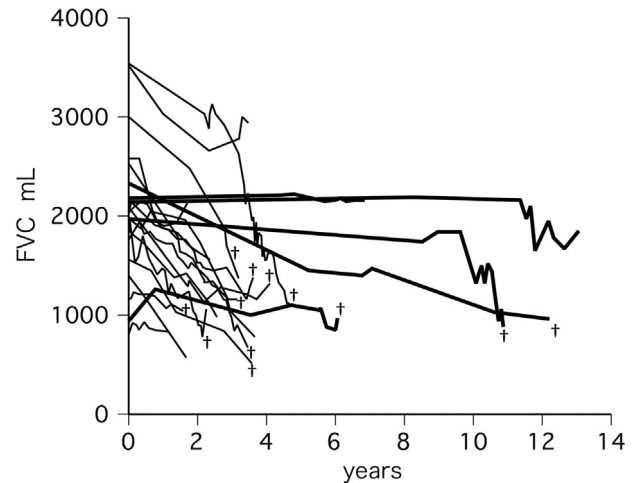

Fig. 4 – Time-course decline of forced vital capacity (FVC). The decline of FVC indicated by the thick-line graphs was gradual during more than 6 years of follow-up. However, the decline of FVC indicated by the thin-line graphs seemed more rapid, over a shorter follow-up period. Deceased patients are denoted by †.

3.3. Baseline values and yearly decline in respiratory function parameters

The baseline levels of FVC and DLco were lower than the predicted values: 2004±735 mL (66.0±20.1%pred) and 11.4±3.9 mL/min/mmHg (72.5±23.5%pred), respectively. The baseline levels of TLC (3454±943 mL; 72.1±20.5%pred) decreased as observed for FVC and DLco, but those of RV/TLC increased (144.0±45.8%pred; Table 3). Initial FVC (mL) correlated negatively with RV/TLC (%) ($r = -0.517$, $P = 0.023$; Fig. 2).

ΔFVC was −241±203 mL (−11.2±9.3%). TLC and DLco also declined annually: −443±355 mL (−12.4±9.6%) and −1.43±1.58 mL min^{-1} mmHg^{-1} (−13.5±14.1%), respectively. In contrast, ΔRV/TLC was increased (2.23±5.86%; Table 4 and Fig. 3).

Fig. 4 shows the time-course changes in FVC in the patients ($n = 21$). A mixed-effect regression analysis of the whole cohort of patients fit well with an FVC decline of −135 mL/year and an R^2 of 0.679. The patients seemed to be divided into two groups according to the different patterns of FVC decline: one showed a gradual decline in FVC over a follow-up period of more than 6 years in five patients, while the other showed a relatively rapid decline in FVC over a shorter follow-up period. When the two groups were analyzed separately, the annual decline and R^2 were −55 mL/year and 0.799, and −364 mL/year and 0.855, respectively.

4. Discussion

Currently, PPFE is known to have a well-established histological pattern; its histology is quite characteristic and is distinct from that of UIP and other IIPs. In contrast, its clinical features in relation to other chronic fibrosing IIPs, in particular idiopathic pulmonary fibrosis (IPF), have not been fully elucidated. This study aimed to identify the imaging and functional characteristics of patients with pulmonary fibrosis

by the 11 interpreters, 15 of the 21 patients were judged as having fibrotic lesions, with upper lung field predominance (Fig. 1A), and the remaining six patients were considered as having equal involvement of upper and lower lung fields (Fig. 1B and C). The extended kappa for the multi-interpreter agreement was 0.341 (95% confidence interval [CI]: 0.166–0.503).

presenting a PPFE histology, regardless of the presence or absence of associated diseases or underlying conditions.

Various underlying conditions or diseases have been reported in PPFE; however, it is not clear whether they are closely related to the occurrence and development of PPFE or whether they are simply comorbidities that incidentally complicate the condition. The reported number of patients with PPFE is limited. We investigated the significant features of PPFE in terms of pathogenesis and pathophysiology, by taking all clinical backgrounds and underlying conditions into consideration.

Four patients had a current or past autoimmune disease as a comorbidity; autoimmune predisposition may be partly responsible for the pathogenesis of PPFE [10]. NTM were repeatedly isolated from sputum in three patients. Rifampicin, ethambutol, and clarithromycin were administered to two patients, albeit without a favorable effect. However, NTM infection may be pathognomonic to PPFE, rather than simply being a comorbidity. In one patient, *Mycobacterium avium* was isolated from sputum during the early stages of PPFE, and the infection progressed along with the progression of PPFE. A mixed-effect linear regression analysis was performed after excluding two patients in whom PPFE was probably not idiopathic, but rather secondary (patient #6, who had active rheumatoid arthritis, and patient #21, who had been irradiated for esophageal cancer); the results of this analysis was virtually the same as those obtained for analysis of the 21 patients. The annual decline in the 19 patients was −132 mL/year, with an R^2 of 0.679. The annual decline in the subgroup of rapid decliners was −365 mL/year, with an R^2 of 0.858, and that in the subgroup of gradual decliners was the same as the previous result, because the two patients who had been excluded were both rapid decliners. The extended kappa for the level of agreement among the 11 interpreters after excluding the two patients was 0.302 (95% CI: 0.137–0.485).

Although the official statement by the ATS/ERS [1] emphasizes the predominant involvement of the upper lung lobes in PPFE, our results showed that, although in some cases, the upper lung field was predominantly involved, in other cases, the upper and lower lung fields were equally involved. Amitani disease, which exclusively involves fibroelastosis in the upper lobes [2], may be one end of a wide spectrum of pulmonary fibrosis showing PPFE histology. It is possible that PPFE is not as rare as was thought previously [25]. In addition, we showed that a considerable number of patients have pulmonary fibrosis with PPFE histology, without upper lung field predominance.

The concept of upper lung field predominance may be the result of biased biopsies. The chance of undergoing biopsy may be higher in patients who have upper lobe fibrosis on CT images, under a suspected diagnosis of PPFE or non-UIP lacking lower lobe-dominant fibrosis. However, 11 interpreters, 10 of whom had more than 10 years of experience in the field of pulmonology, concluded from the CT images that the upper and lower lung fields were equally involved in about one-third of the CT image series in our patients. The biopsied samples obtained from patients whose clinical diagnosis does not appear to be PPFE should be reviewed to examine whether fibroelastosis is truly rare among IIPs.

Increased RV/TLC, which is not typically observed in IPF, is quite characteristic of PPFE, and our results were similar to those reported by other investigators [11,26,27]. We further

demonstrated that RV/TLC was inversely correlated with FVC, i.e., an increase in RV/TLC may appear in the advanced stage of PPFE. This relationship between initial RV/TLC and FVC is consistent with the subsequent changes seen in these parameters in a time-course: FVC and TLC decreased over time, whereas RV/TLC increased, although marginally. Fibrotic collapse of the upper lobes may lead to compensatory overinflation of the lower lobes, probably resulting in increased RV/TLC [28]. Another possibility is that the flattened chest cage observed in the advanced stage of PPFE [24] may restrict the expansion of both lungs. Restricted mobility in relatively well-preserved lower lobes may be responsible for the increased RV/TLC observed; alternatively, a decrease in the strength of the respiratory muscles may be responsible for this phenomenon.

As reported previously, FVC declined over time in most patients; however, in the present study, the annual decline in FVC followed two patterns: a rapid decline in FVC over a short period, as has been demonstrated previously [17], and a slow decline in FVC over a longer period. These patterns suggest that the clinical course of PPFE is heterogeneous; or that the decline in FVC may not be linear. We postulate that FVC declines gradually to a point in time, after which it begins to decline rapidly. We may only have observed the gradually declining FVC phase in five patients, and the rapidly declining phase in the 16 patients who had already passed the endpoint of the gradually declining phase.

The present study had several limitations. Our study was a retrospective study. In most of the patients who had undergone lung biopsy, samples were obtained from the upper lobes. The biopsied specimens in patients with lower lung field-predominant fibrosis should be reviewed after staining for elastic fibers to detect fibroelastosis.

Not all of the CT images were interpreted without clinical information: YY and KW interpreted CT images after reviewing the clinical information of all patients, and each interpreter recognized his or her patients' CT images as the respective attending physician. Although the kappa value did not seem to be sufficiently large, disagreement was unavoidable when abnormal opacities were diffusely distributed. Therefore, we used a majority decision to determine the predominantly involved sites from among three alternatives.

Fibrosis of PPFE extends to the lower lung fields as the disease progresses. Our analysis of CT images may be biased due to inclusion of cases with advanced PPFE. However, the FVC %pred obtained in our study (66.0±20.1) was not markedly low as compared with the FVC or VC %pred values reported by other investigators: 59.2±26.5 [2], 60.7±16.6 [3], 50.0±15.8 [6], 73.9±12.2 [11], and 70.5 [25], 76.5 [26], and 56.9±15.6 [27].

We obtained a high R^2 in the mixed-effect linear regression analysis of the entire group of patients. However, the annual decline estimated by mixed-effect linear regression (−135 mL) was considerably different from that obtained by simple linear regression (−241±203 mL; Table 4). This may be partly because the absolute value of FVC was different in each patient and because the number of patients was small.

5. Conclusions

We have demonstrated that the mainly involved sites as determined by CT images were not limited to the upper lobes

in patients with pulmonary fibrosis and PPFE histology. In one-third of the CT image series of the patients in this study, the upper and lower lung fields were equally involved. There appears to be two patterns of FVC decline: a rapid decline over a short period and a slow decline over a longer period, suggesting that the disease follows a heterogeneous clinical course.

Conflict of interest

The authors have no conflicts of interest.

Acknowledgments

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