Respiration

Clinical Investigations

Respiration 2021;100:19–26
DOI: 10.1159/000511965

Received: July 4, 2020
Accepted: September 29, 2020
Published online: January 5, 2021

Pneumothorax in Patients with Idiopathic Pleuroparenchymal Fibroelastosis: Incidence, Clinical Features, and Risk Factors

Masato Kono[a, b] Yutaro Nakamura[a] Yasunori Enomoto[a] Hideki Yasui[a] Hironao Hozumi[a] Masato Karayama[a] Yuzo Suzuki[a] Kazuki Furuhashi[a] Yoshihiro Miki[b] Dai Hashimoto[b] Tomoyuki Fujisawa[a] Noriyuki Enomoto[a] Naoki Inui[a] Yusuke Kaida[c] Koshi Yokomura[d] Naoki Koshimizu[e] Mikio Toyoshima[f] Shiro Imokawa[g] Takashi Yamada[h] Toshihiro Shirai[i] Hiroshi Hayakawa[j] Hidenori Nakamura[b] Takafumi Suda[a]

[a]Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan; [b]Department of Pulmonary Medicine, Seirei Hamamatsu General Hospital, Hamamatsu, Japan; [c]Department of Respiratory Medicine, Enshu Hospital, Hamamatsu, Japan; [d]Department of Respiratory Medicine, Seirei Mikatahara General Hospital, Hamamatsu, Japan; [e]Department of Respiratory Medicine, Fujieda Municipal General Hospital, Fujieda, Japan; [f]Department of Respiratory Medicine, Hamamatsu Rosai Hospital, Hamamatsu, Japan; [g]Department of Respiratory Medicine, Iwata City Hospital, Iwata, Japan; [h]Department of Respiratory Medicine, Shizuoka City Shizuoka Hospital, Shizuoka, Japan; [i]Department of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan; [j]Department of Respiratory Medicine, Tenryu Hospital, National Hospital Organization, Hamamatsu, Japan

Keywords
Pleuroparenchymal fibroelastosis · Idiopathic interstitial pneumonia · Pneumothorax

Abstract
Background: Idiopathic pleuroparenchymal fibroelastosis (PPFE) is a rare form of idiopathic interstitial pneumonia that is characterized by predominantly upper lobe pleural and subpleural lung parenchymal fibrosis. Pneumothorax is one of the major respiratory complications in PPFE patients; however, its clinical features are poorly understood. ***Objective:*** We aimed to investigate the complication of pneumothorax in patients with idiopathic PPFE. ***Methods:*** A retrospective multicenter study involving 89 patients who had been diagnosed with idiopathic PPFE was conducted. We investigated the cumulative incidence, clinical features, and risk factors of pneumothorax after the diagnosis of idiopathic PPFE. ***Results:*** Pneumothorax developed in 53 patients (59.6%) with 120 events during the observation period (41.8 ± 35.0 months). The cumulative incidence of pneumothorax was 24.8, 44.9, and 53.9% at 1, 2, and 3 years, respectively. Most events of pneumothorax were asymptomatic (n = 85; 70.8%) and small in size (n = 92; 76.7%); 30 patients (56.6%) had recurrent pneumothorax. Chest drainage was required in 23 pneumothorax events (19.2%), and a persistent air leak was observed in 13 (56.5%). Patients with pneumothorax were predominantly male and frequently had pathological diagnoses of PPFE and prior history of pneumothorax and corticosteroid use; they also had significantly poorer survival than those without pneumothorax (log-rank test; p = 0.001). Multivariate analysis revealed that a higher residual volume/total lung capacity ratio was significantly associated with the development of pneumothorax after the

karger@karger.com
www.karger.com/res

Karger

Masato Kono
Pulmonary Medicine, Seirei Hamamatsu Hospital
2-12-12 Sumiyoshi
Hamamatsu 430-8558 (Japan)
masato.k@sis.seirei.or.jp

diagnosis. ***Conclusion:*** Pneumothorax is often asymptomatic and recurrent in patients with idiopathic PPFE, leading to poor outcomes in some cases.

Introduction

Idiopathic pleuroparenchymal fibroelastosis (PPFE) is a rare form of idiopathic interstitial pneumonia that is characterized by predominantly upper lobe pleural and subpleural lung parenchymal fibrosis [1–3]. Amitani et al. [1] first reported idiopathic pulmonary upper lobe fibrosis (IPUF) in Japanese literature. Frankel et al. [2] described 5 cases and named the condition "idiopathic pleuroparenchymal fibroelastosis." Idiopathic PPFE has been widely considered as rare and having a distinct clinicopathological entity in the international multidisciplinary classification of interstitial pneumonias [3].

Pneumothorax frequently develops during the clinical course of idiopathic PPFE [4–8]. In the original report of IPUF [1], bilateral and/or recurrent pneumothorax developed in 7 (53.8%) of 13 patients, suggesting it was one of the clinical features of IPUF. The subsequent case series of idiopathic PPFE showed that the incidence of pneumothorax after the diagnosis was 25–89% [9–21], which varied with the population studied. Since a postoperative iatrogenic pneumothorax commonly occurs in these patients and can cause a prolonged air leak [12, 16, 22], surgical lung biopsy (SLB) should be avoided [5–8]. Therefore, recent studies have proposed the clinical diagnostic criteria for PPFE without SLB [16, 23].

It has been reported that the cumulative incidence of pneumothorax in patients with idiopathic pulmonary fibrosis (IPF) was 8.5, 12.5, and 17.7% at 1, 2, and 3 years, respectively, and pneumothorax was associated with poor prognosis [24]. Although patients with idiopathic PPFE had a higher complication rate of pneumothorax or pneumomediastinum than those with IPF [11, 19, 25], the cumulative incidence, clinical features, and risk factors of pneumothorax are poorly understood in patients with idiopathic PPFE. Therefore, this study aimed to investigate the cumulative incidence, clinical features, and risk factors for pneumothorax in patients with idiopathic PPFE.

Materials and Methods

Patients and Diagnostic Criteria for Idiopathic PPFE

We conducted a retrospective multicenter study involving 116 patients diagnosed with PPFE or IPUF who were admitted to Hamamatsu University School of Medicine and its 9 associated hospitals from 2005 to 2016. Patients were recruited into the study consecutively. The diagnosis of idiopathic PPFE was based on the following criteria [16]: (1) a radiologic PPFE pattern on chest computed tomography (CT) characterized as bilateral subpleural dense consolidation with or without pleural thickening in the upper lobes and less marked or absent involvement of the lower lobes; (2) radiologic confirmation of disease progression, which was characterized as an increase in the upper lobe consolidation with or without pleural thickening and/or a decrease in upper lobe volume on serial radiologic assessment; and (3) exclusion of other lung diseases with identifiable etiologies, such as connective tissue disease (CTD), chronic hypersensitivity pneumonitis (CHP), pulmonary sarcoidosis, pneumoconiosis, and active pulmonary infection. Based on the criteria, 27 patients were excluded, 15 had other lung diseases (CTD; $n = 9$, active pulmonary infection; $n = 4$, chronic hypersensitivity pneumonitis [CHP]; $n = 1$, pneumoconiosis; $n = 1$), 8 had no confirmation of disease progression radiologically, and 4 had inadequate clinical information. Finally, 89 patients with confirmed idiopathic PPFE were enrolled in the study. Chest CT images were reviewed by radiologists, and 2 trained pulmonologists from our institution confirmed the diagnosis. Radiologic interstitial lung disease (ILD) patterns in cases with lower-lobe ILD were classified as usual interstitial pneumonia (UIP) or a non-UIP pattern according to the criteria described in previous studies [3, 26]. The histological criteria of PPFE [9] were applied to patients whose lung specimens were obtained.

Data Collection

Clinical data including age, sex, smoking status, BMI, symptoms at the time of idiopathic PPFE diagnosis, respiratory infections after the diagnosis of idiopathic PPFE (nontuberculous mycobacterial pulmonary disease and pulmonary aspergillosis), treatment for idiopathic PPFE, and the outcomes were obtained from patients' medical records. Laboratory data, including Krebs von den Lungen-6, surfactant protein-D, PaO_2 and $PaCO_2$, bronchoalveolar lavage findings, and pulmonary function tests, including forced vital capacity (FVC), forced expiratory volume in 1 S (FEV_1)/FVC, residual volume (RV)/total lung capacity (TLC), and diffusing capacity for carbon monoxide, at the time of idiopathic PPFE diagnosis were also obtained.

Chest X-ray and/or CT images were obtained during the observation period and reviewed by pulmonologists at each institution for the presence of pneumothorax. In patients with pneumothorax, time to first pneumothorax after idiopathic PPFE diagnosis, total pneumothorax, symptoms at the time of pneumothorax, pneumothorax size according to the guidelines [27, 28] (small; small rim of air around the lung, moderate; lung collapsed halfway toward the heart border, complete; airless lung), pneumothorax site (right, left, or both sides), and treatment for pneumothorax were recorded.

Statistical Methods

For 2-group comparisons, we used the χ^2 test or Mann-Whitney U test. The cumulative incidence of pneumothorax and survival after the diagnosis of idiopathic PPFE were estimated using the Kaplan-Meier method, and the log-rank test was performed. Pneumothorax at the time of initial diagnosis of idiopathic PPFE was excluded from the cumulative incidence. Cox proportional hazard analysis was used to identify significant variables that were

Table 1. Clinical characteristics of pneumothorax in patients with idiopathic PPFE

Patients with pneumothorax, *n*	53
Time to first pneumothorax after the diagnosis, months	20.4±18.8
Pneumothorax, *n* (%)	
1	23 (43.4)
2	13 (24.5)
3	7 (13.2)
>4	10 (18.9)
Recurrent pneumothorax, *n* (%)	30 (56.6)
Bilateral pneumothorax, *n* (%)	24 (45.3)
Entire events of pneumothorax, *n*	120
Symptoms at the time of pneumothorax, *n* (%)	
Asymptomatic	85 (70.8)
Chest pain	9 (7.5)
Dyspnea	30 (25.0)
Pneumothorax size, *n* (%)	
small/moderate/complete	92/21/7 (76.7/17.5/5.8)
Pneumothorax site, *n* (%)	
right/left/bilateral	57/44/19 (47.5/36.7/15.8)
Treatment for pneumothorax, *n* (%)	
Observation	97 (80.8)
Chest drainage	23 (19.2)
Pleurodesis	13[a] (10.8)
Bronchial occlusion	2 (1.7)
Surgical intervention	1 (0.8)

PPFE, pleuroparenchymal fibroelastosis. [a] Autologous blood patch (*n* = 7), OK-432 + minocycline (*n* = 2), autologous blood patch + minocycline (*n* = 1), talc (*n* = 1), autologous blood patch + minocycline +50% glucose (*n* = 1), autologous blood patch + OK-432 + minocycline + talc (*n* = 1).

predictive of the development of pneumothorax. Statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA). A *p* value of 0.05 was considered significant.

Results

Incidence and Clinical Features of Pneumothorax in Idiopathic PPFE

Of the 89 patients who were diagnosed with idiopathic PPFE, pneumothorax developed in 53 (59.6%) with entire 120 events during the observation period. The clinical characteristics of pneumothorax are shown in Table 1. The time to first pneumothorax after the diagnosis of idiopathic PPFE was 20.4 ± 18.8 months, and the cumulative incidence of pneumothorax was 24.8, 44.9, and 53.9% at 1, 2, and 3 years, respectively (shown in Fig. 1). At the time of initial diagnosis, 8 patients had already developed pneumothorax. Of 53 patients of pneumothorax, 30 (56.6%) were recurrent and 24 (45.3%) became bilateral during the observation period. Asymptomatic (*n* = 85; 70.8%), small size (*n* = 92; 76.7%), and right-sided (*n* = 57; 47.5%) events were predominant out of the 120, and 85 events (70.8%) improved spontaneously. Chest drainage was required in 23 events (19.2%) (16 patients [30.2%]), and a persistent air leak was observed in 13 (56.5%) (9 patients [56.3%]). These pneumothorax events required multiple additional treatments as follows (including duplication): pleurodesis (*n* = 13), bronchial occlusion with Endobronchial Watanabe Spigot (*n* = 2), or surgical intervention (*n* = 1). Of the methods of pleurodesis, an autologous blood patch was most common (*n* = 10).

Comparison of Patient Characteristics in Idiopathic PPFE by the Presence of Pneumothorax

The baseline patient characteristics at the initial diagnosis of idiopathic PPFE are shown in Table 2. The clinical diagnostic criteria for idiopathic PPFE were fulfilled in all 89 patients, and 14 (15.7%) were confirmed histologically: SLB (*n* = 6), autopsy (*n* = 6), and SLB and autopsy (*n* = 2). The mean age was 68.5 years, and males (*n* = 54; 60.7%) and nonsmokers (*n* = 57; 64.0%) were predominant. During the observation period (41.8 ± 35.0 months), approximately half of the patients (*n* = 44; 49.4%) died, including 7 patients who had pneumothorax at the time of death.

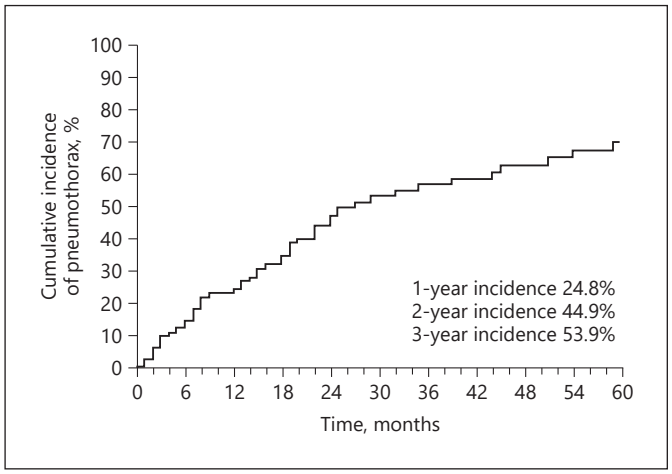

Fig. 1. Cumulative incidence of pneumothorax after the diagnosis of idiopathic PPFE. The cumulative incidence of pneumothorax after the diagnosis of idiopathic PPFE was 24.8, 44.9, and 53.9% at 1, 2, and 3 years, respectively. PPFE, pleuroparenchymal fibroelastosis.

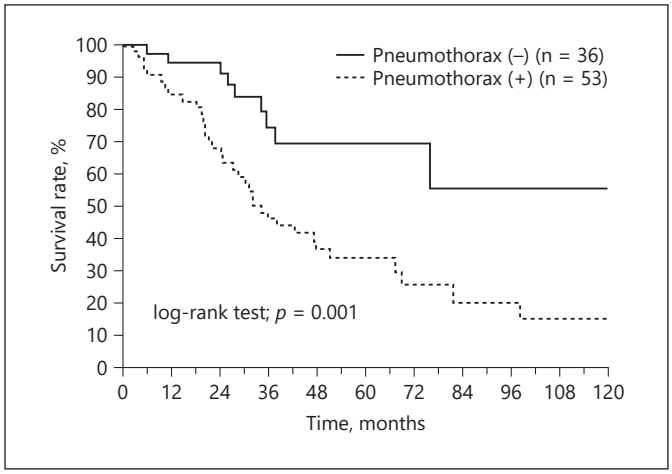

Fig. 2. Survival curves in patients with idiopathic PPFE based on the presence of pneumothorax. Patients with idiopathic PPFE who had pneumothorax (n = 53) showed significantly poorer survival than those who did not have pneumothorax (n = 36) (log-rank test; p = 0.001). PPFE, pleuroparenchymal fibroelastosis.

We compared patients with idiopathic PPFE who developed pneumothorax (n = 53) and those who did not develop pneumothorax (n = 36). Patients with pneumothorax were predominantly males, frequently pathologically diagnosed with PPFE, and had previous pneumothorax. There was no significant difference in baseline characteristics of symptoms at diagnosis, laboratory findings, bronchoalveolar lavage findings, pulmonary function tests, the presence of lower-lobe ILD on chest CT, or the respiratory infections after the diagnosis of idiopathic PPFE (nontuberculous mycobacterial pulmonary disease and pulmonary aspergillosis) between the 2 groups. Regarding treatment for idiopathic PPFE, there were more cases treated with prednisolone and/or immunosuppressive agents, pirfenidone, and long-term oxygen therapy in patients with pneumothorax than in those without pneumothorax. In addition, patients with idiopathic PPFE who had pneumothorax showed significantly poorer survival than those who did not have pneumothorax (log-rank test; p = 0.001) (shown in Fig. 2). In patients with idiopathic PPFE who developed pneumothorax, the median survival time from the initial diagnosis of idiopathic PPFE and from the first onset of pneumothorax was 34.0 and 18.0 months, respectively.

Risk Factors for Pneumothorax after the Diagnosis of Idiopathic PPFE

Finally, we investigated the risk factors for the development of pneumothorax in patients with idiopathic PPFE (Table 3). Univariate analysis showed that older age, higher FEV_1/FVC, and RV/TLC, and the presence of lower-lobe UIP pattern on chest CT were significantly associated with the occurrence of pneumothorax. Multivariate analysis revealed that only higher RV/TLC was significantly associated with developing pneumothorax after the diagnosis of idiopathic PPFE.

Discussion

This study investigated the cumulative incidence, clinical features, and risk factors of pneumothorax as an important respiratory complication in patients with idiopathic PPFE. We reviewed 89 patients diagnosed with idiopathic PPFE and found that pneumothorax developed in 53 patients (59.6%) during the observation period with a cumulative incidence of 24.8, 44.9, and 53.9% at 1, 2, and 3 years, respectively. Most cases of pneumothorax were asymptomatic and had a small size, and approximately, half of them became recurrent and bilateral. A persistent air leak was observed in half of the patients who required chest drainage, and patients with pneumothorax had a

Table 2. Patient characteristics in idiopathic PPFE by the presence of pneumothorax

	All cases, $n = 89$	Pneumothorax (+), $n = 53$	Pneumothorax (–), $n = 36$	p value
Age, years	68.5±10.8	68.7±8.4	68.1±12.2	0.89
Male sex, *n* (%)	54 (60.7)	37 (69.8)	17 (47.2)	0.03
Nonsmokers, *n* (%)	57 (64.0)	31 (58.5)	26 (72.2)	0.18
BMI, kg/m^2	17.0±2.7	17.1±3.0	16.9±2.3	0.82
Pathological diagnosis, *n* (%)	14 (15.7)	12 (22.6)	2 (5.6)	0.02
Previous pneumothorax, *n* (%)	13 (14.6)	11 (20.8)	2 (5.6)	0.03
Observation period, months	41.8±35.0	39.3±32.7	45.5±38.1	0.40
Symptoms at diagnosis, *n* (%)				
Cough	33 (37.1)	20 (37.7)	13 (36.4)	0.87
Dyspnea	43 (48.3)	29 (54.7)	14 (38.9)	0.14
Laboratory findings				
KL-6, U/mL	563±439	697±516	486±250	0.33
SP-D, ng/L	228±227	244±275	199±96	0.96
PaO_2, torr	79.8±11.3	79.3±9.8	80.8±13.8	0.48
$PaCO_2$, torr	46.7±9.0	46.2±6.3	47.5±12.6	0.81
BAL, %				
Macrophage	78.8±20.9	76.4±23.6	83.1±14.3	0.38
Lymphocytes	12.7±11.7	12.3±10.9	13.4±13.6	0.71
Neutrophils	7.0±17.6	9.7±21.5	2.1±1.7	0.15
Pulmonary function tests, %				
FVC	61.9±21.6	61.2±20.7	63.1±23.1	0.71
FEV_1/FVC	94.0±7.6	95.5±5.4	91.8±9.7	0.05
RV/TLC	48.9±12.4	49.8±13.2	47.3±11.0	0.28
DLco	84.9±34.5	85.8±33.8	83.4±36.6	0.99
Chest CT findings				
Lower-lobe ILD	62 (69.7)	40 (75.5)	22 (61.1)	0.15
Lower-lobe UIP	34 (38.2)	22 (41.5)	12 (33.3)	0.43
Respiratory infections after the diagnosis of idiopathic PPFE, *n* (%)				
NTM pulmonary disease	4 (4.5)	1 (1.9)	3 (8.3)	0.15
Pulmonary aspergillosis	3 (3.4)	3 (5.7)	0	0.07
Treatment for idiopathic PPFE				
PSL and/or ISA[a], *n* (%)	9 (10.1)	9 (17.0)	0	0.002
Pirfenidone	12 (13.5)	10 (18.9)	2 (5.6)	0.06
LTOT, *n* (%)	41 (46.1)	32 (60.3)	9 (25.0)	<0.001
Outcome, *n* (%)				
All-cause death[b]	44 (49.4)	35 (66.0)	9 (25.0)	<0.001

Data are shown as the mean ± SD, values. PPFE, pleuroparenchymal fibroelastosis; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity for carbon monoxide; CT, computed tomography; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; NTM, nontuberculous mycobacterial; PSL, prednisolone; ISA, immunosuppressive agents; LTOT, long-term oxygen therapy; SD, standard deviation. [a] PSL alone ($n = 5$), PSL + cyclosporine ($n = 2$), PSL + cyclophosphamide ($n = 2$). [b] Chronic respiratory failure ($n = 26$), bacterial pneumonia ($n = 6$), pneumothorax ($n = 4$), acute exacerbation + pneumothorax ($n = 3$), acute exacerbation ($n = 2$), hemoptysis ($n = 1$), unknown ($n = 2$).

significantly worse prognosis than those without pneumothorax. Multivariate analysis revealed that a higher RV/TLC ratio was an independent risk factor for pneumothorax in these patients.

Spontaneous secondary pneumothorax frequently occurs in patients with idiopathic PPFE and is considered to be one of their clinical features [1, 4–8]. The incidence of pneumothorax varied with the population studied and was reported within 25–89% [1, 9–21]. Pneumothorax was also reported in secondary PPFE, following bone marrow transplantation [29], chemotherapy agents [30], or CTD [31], among others. Radiologic PPFE pattern, re-

Table 3. Risk factors for pneumothorax after the diagnosis of idiopathic PPFE

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years	1.037	1.008–1.068	0.01	1.019	0.962–1.910	0.52
Male sex, *n*	1.720	0.960–3.224	0.07			
Smokers, *n*	1.410	0.804–2.431	0.22			
BMI, kg/m^2	0.971	0.881–1.068	0.54			
Previous pneumothorax, *n*	1.431	0.699–2.685	0.30			
KL-6, U/mL	1.001	1.000–1.001	0.06			
PaO_2, torr	0.758	0.233–2.495	0.64			
$PaCO_2$, torr	1.004	0.958–1.051	0.85			
Baseline FVC, %	0.990	0.978–1.003	0.12			
Baseline FEV_1/FVC, %	1.077	1.027–1.141	<0.001	1.050	0.976–1.137	0.19
Baseline RV/TLC, %	1.059	1.020–1.103	0.003	1.043	1.001–1.091	0.04
Baseline DLco, %	0.963	0.894–1.011	0.14			
Lower-lobe UIP on chest CT, *n*	2.274	1.285–3.967	0.005	1.194	0.541–2.510	0.64
PSL and/or ISA, *n*	1.566	0.713–3.690	0.24			

PPFE, pleuroparenchymal fibroelastosis; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity for carbon monoxide; UIP, usual interstitial pneumonia; CT, computed tomography; PSL, prednisolone; ISA, immunosuppressive agents, HR, hazard ratio, CI, confidence interval.

gardless of the underlying disease, was shown to be associated with a history of pneumothorax in patients with ILD registered for lung transplants [17]. Although several types of ILD, including IPF, have pneumothorax as a relatively frequent complication [24, 32], it was reported that patients with idiopathic PPFE showed a higher complication rate of pneumothorax or pneumomediastinum than those with IPF [11, 19, 25]. According to Nishimoto et al. [24], the cumulative incidence of pneumothorax in IPF was 8.5, 12.5, and 17.7% at 1, 2, and 3 years, respectively; our data revealed that it was 24.8, 44.9, and 53.9% at 1, 2, and 3 years, respectively. These suggest that pneumothorax develops more frequently in idiopathic PPFE than in IPF.

Regarding the clinical features of pneumothorax in patients with PPFE, previous studies have reported that it is frequently recurrent and intractable [4–8, 13, 16, 18–20]. In this study, approximately half of the patients who developed pneumothorax had a recurrence; however, most were asymptomatic and small in size and resolved spontaneously. Similar to our results, Amitani et al. [1] demonstrated that 7 (53.8%) of 13 patients with IPUF had recurrent and/or bilateral pneumothorax, and most of them were small in size and recovered spontaneously. From these results, we speculate that pneumothorax may recur incidentally in idiopathic PPFE. In addition, among patients with idiopathic PPFE in this study, more cases with pneumothorax were treated with the immunosuppressive and/or anti-fibrotic agents than those without pneumothorax, suggesting a relationship between disease progression and the occurrence of pneumothorax. In some cases of pneumothorax associated with idiopathic PPFE, persistent air leak and poor re-expansion of the underlying lung were observed [5–8], which may be related to a poor prognosis [16, 18–20]. In this study, we demonstrated that patients with idiopathic PPFE who had pneumothorax had a significantly poorer prognosis than those who did not have pneumothorax, and pneumothorax was the cause of death in some cases ($n = 7$).

The mechanism of pneumothorax in patients with PPFE is unclear, but large cysts and multiple bullae in the apical fibrotic area may be associated with the high occurrence of pneumothorax, along with an altered resistance of the pleura to mechanical stress [4–6, 25]. In addition, scarring of a visceral pleural defect following pneumothorax may lead to subpleural fibrosis [33]. In the present study, we demonstrated that a higher RV/TLC ratio was independently predictive of pneumothorax in patients with idiopathic PPFE. The increase in the RV/TLC ratio may result from the compensatory hyperinflation of the lower lobes due to the fibrotic collapse of the upper lobes and is a characteristic functional impairment of PPFE [4, 6, 23, 25]. Hence, it is suggested that pneumothorax can occur as a result of the disease progression of idiopathic PPFE.

There is no effective therapy for idiopathic PPFE; therefore, it is difficult to prevent pneumothorax in these patients. Lung or pleural biopsy should be avoided in patients suspected of PPFE [5–8] since a postoperative iatrogenic pneumothorax commonly complicates the procedure [12, 16, 22]. Among patients with pneumothorax associated with IPF, chest drainage is often ineffective due to the requirement of high negative pressure for lung re-expansion [24]. In the present study, a persistent air leak was observed in 13 (56.5%) of 23 pneumothorax events that required chest drainage, and the autologous blood patch was performed in most cases, as reported in a previous study [32].

This study had several limitations. First, it was a retrospective study. Second, a small number of patients are included due to the rarity of the disease. Third, the clinical diagnostic criteria have not been validated for the diagnosis of idiopathic PPFE, and only a few patients were definitively diagnosed histologically. Fourth, the incidence of pneumothorax is estimated to be lower since patients with asymptomatic pneumothorax may be overlooked. For instance, although chest X-ray was routinely and repeatedly examined, it was not regularly performed during the observation period; it depended on attending physicians. Finally, the results of the multivariate analysis of risk factors for pneumothorax development should be carefully interpreted because of the small sample size and outcome incidence. A prospective study on a larger scale is needed to confirm our results.

In conclusion, among patients with idiopathic PPFE, pneumothorax frequently occurs asymptomatically, recurs, and is intractable, leading to poor prognoses in some cases.

Statement of Ethics

This study protocol was approved by the Ethical Committee of the Hamamatsu University School of Medicine (approval number: 14-183). The requirement for informed consent was waived due to the retrospective review.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

The authors did not receive any funding.

Author Contributions

Conceptualization: M.K. and Y.N., methodology: M.K. and Y.N., formal analysis: M.K. and Y.N., investigation: M.K., Y.N., Y.E., H.Y., H.H., M.K., Y.S., K.F., Y.M., D.H., T.F., N.E., N.I., Y.K., K.Y., N.K., M.T., S.I., T.Y., T.S, and H.H., data curation: M.K., Y.N., and Y.E., writing original draft: M.K., writing review and editing: M.K., Y.N., H.N., and T.S., supervision: H.N. and T.S.

References

1 Amitani R, Niimi A, Kuse F. Idiopathic pulmonary upper lobe fibrosis (IPUF). Kokyu. 1992;11:693–9.
2 Frankel SK, Cool CD, Lynch DA, Brown KK. Idiopathic pleuroparenchymal fibroelastosis: description of a novel clinicopathologic entity. Chest. 2004;126(6):2007–13.
3 Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733–48.
4 Watanabe K. Pleuroparenchymal fibroelastosis: its clinical characteristics. Curr Respir Med Rev. 2013;9:299–37.
5 Camus P, von der Thüsen J, Hansell DM, Colby TV. Pleuroparenchymal fibroelastosis: one more walk on the wild side of drugs? Eur Respir J. 2014;44(2):289–96.
6 Bonifazi M, Montero MA, Renzoni EA. Idiopathic pleuroparenchymal fibroelastosis. Curr Pulmonol Rep. 2017;6(1):9–15.
7 Kokosi MA, Nicholson AG, Hansell DM, Wells AU. Rare idiopathic interstitial pneumonias: LIP and PPFE and rare histologic patterns of interstitial pneumonias: AFOP and BPIP. Respirology. 2016;21(4):600–14.
8 Chua F, Desai SR, Nicholson AG, Devaraj A, Renzoni E, Rice A, et al. Pleuroparenchymal fibroelastosis. a review of clinical, radiological, and pathological characteristics. Ann Am Thorac Soc. 2019;16(11):1351–9.
9 Reddy TL, Tominaga M, Hansell DM, von der Thusen J, Rassl D, Parfrey H, et al. Pleuroparenchymal fibroelastosis: a spectrum of histopathological and imaging phenotypes. Eur Respir J. 2012;40(2):377–85.
10 Watanabe K, Nagata N, Kitasato Y, Wakamatsu K, Nabeshima K, Harada T, et al. Rapid decrease in forced vital capacity in patients with idiopathic pulmonary upper lobe fibrosis. Respir Investig. 2012;50(3):88–97.
11 Oda T, Ogura T, Kitamura H, Hagiwara E, Baba T, Enomoto Y, et al. Distinct characteristics of pleuroparenchymal fibroelastosis with usual interstitial pneumonia compared with idiopathic pulmonary fibrosis. Chest. 2014;146(5):1248–55.
12 Watanabe S, Waseda Y, Takato H, Matsunuma R, Johkoh T, Egashira R, et al. Pleuroparenchymal fibroelastosis: distinct pulmonary physiological features in nine patients. Respir Investig. 2015;53(4):149–55.
13 Nakatani T, Arai T, Kitaichi M, Akira M, Tachibana K, Sugimoto C, et al. Pleuroparenchymal fibroelastosis from a consecutive database: a rare disease entity? Eur Respir J. 2015;45(4):1183–6.
14 Yoshida Y, Nagata N, Tsuruta N, Kitasato Y, Wakamatsu K, Yoshimi M, et al. Heterogeneous clinical features in patients with pulmonary fibrosis showing histology of pleuroparenchymal fibroelastosis. Respir Investig. 2016;54(3):162–9.
15 Nunes H, Jeny F, Bouvry D, Picard C, Bernaudin JF, Ménard C, et al. Pleuroparenchymal fibroelastosis associated with telomerase reverse transcriptase mutations. Eur Respir J. 2017;49(5):1602022.

16 Enomoto Y, Nakamura Y, Satake Y, Sumikawa H, Johkoh T, Colby TV, et al. Clinical diagnosis of idiopathic pleuroparenchymal fibroelastosis: a retrospective multicenter study. Respir Med. 2017;133:1–5.
17 Tanizawa K, Handa T, Kubo T, Chen-Yoshikawa TF, Aoyama A, Motoyama H, et al. Clinical significance of radiological pleuroparenchymal fibroelastosis pattern in interstitial lung disease patients registered for lung transplantation: a retrospective cohort study. Respir Res. 2018;19(1):162–72.
18 Ishii H, Watanabe K, Kushima H, Baba T, Watanabe S, Yamada Y, et al. Pleuroparenchymal fibroelastosis diagnosed by multidisciplinary discussions in Japan. Respir Med. 2018;141:190–7.
19 Shioya M, Otsuka M, Yamada G, Umeda Y, Ikeda K, Nishikiori H, et al. Poorer prognosis of idiopathic pleuroparenchymal fibroelastosis compared with idiopathic pulmonary fibrosis in advanced stage. Can Respir J. 2018;2018:6043053.
20 Kato M, Sasaki S, Kurokawa K, Nakamura T, Yamada T, Sasano H, et al. Usual interstitial pneumonia pattern in the lower lung lobes as a prognostic factor in idiopathic pleuroparenchymal fibroelastosis. Respiration. 2019;97(4):319–28.
21 Kono M, Fujita Y, Takeda K, Miyashita K, Tsutsumi A, Kobayashi T, et al. Clinical significance of lower-lobe interstitial lung disease on high-resolution computed tomography in patients with idiopathic pleuroparenchymal fibroelastosis. Respir Med. 2019 Jul–Aug;154:122–6.
22 Becker CD, Gil J, Padilla ML. Idiopathic pleuroparenchymal fibroelastosis: an unrecognized or misdiagnosed entity? Mod Pathol. 2008;21(6):784–7.
23 Watanabe K, Ishii H, Kiyomi F, Terasaki Y, Hebisawa A, Kawabata Y, et al. Criteria for the diagnosis of idiopathic pleuroparenchymal fibroelastosis: a proposal. Respir Investig. 2019;57(4):312–20.
24 Nishimoto K, Fujisawa T, Yoshimura K, Enomoto Y, Enomoto N, Nakamura Y, et al. The prognostic significance of pneumothorax in patients with idiopathic pulmonary fibrosis. Respirology. 2018;23(5):519–25.
25 Ishii H, Kinoshita Y, Kushima H, Nagata N, Watanabe K. The similarities and differences between pleuroparenchymal fibroelastosis and idiopathic pulmonary fibrosis. Chron Respir Dis. 2019 Jan–Dec;16:1479973119867945.
26 Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68.
27 Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. Chest. 2001;119(2):590–602.
28 Henry M, Arnold T, Harvey J; Pleural Diseases Group, Standards of Care Committee, British Thoracic Society. BTS guidelines for the management of spontaneous pneumothorax. Thorax. 2003;58(Suppl 2):ii39–52.
29 von der Thüsen JH, Hansell DM, Tominaga M, Veys PA, Ashworth MT, Owens CM, et al. Pleuroparenchymal fibroelastosis in patients with pulmonary disease secondary to bone marrow transplantation. Mod Pathol. 2011;24(12):1633–9.
30 Beynat-Mouterde C, Beltramo G, Lezmi G, Pernet D, Camus C, Fanton A, et al. Pleuroparenchymal fibroelastosis as a late complication of chemotherapy agents. Eur Respir J. 2014;44(2):523–7.
31 Enomoto Y, Nakamura Y, Colby TV, Johkoh T, Sumikawa H, Nishimoto K, et al. Radiologic pleuroparenchymal fibroelastosis-like lesion in connective tissue disease-related interstitial lung disease. PLoS One. 2017;12(6):e0180283.
32 Aihara K, Handa T, Nagai S, Tanizawa K, Watanabe K, Harada Y, et al. Efficacy of blood-patch pleurodesis for secondary spontaneous pneumothorax in interstitial lung disease. Intern Med. 2011;50(11):1157–62.
33 von der Thüsen . Pleuroparenchymal fibroelastosis: its pathological characteristics. Curr Respir Med Rev. 2013;9(4):238–47.