INTERNAL MEDICINE

□ CASE REPORT □

A Patient with Idiopathic Pleuroparenchymal Fibroelastosis Showing a Sustained Pulmonary Function due to Treatment with Pirfenidone

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Abstract

The patient was a 68-year-old man presenting with body weight loss and exertional dyspnea. High-resolution computed tomography of the chest showed dense subpleural consolidation with traction bronchiectasis and volume loss predominantly in bilateral apical lesions and upper lobes. A histopathological analysis of a specimen of the right upper lobe showed histological patterns which were consistent with idiopathic pleuroparenchymal fibroelastotis (IPPFE). Treatment with pirfenidone was introduced with the expectation of its potential benefit. The effect of pirfenidone was satisfactory, and a decline in forced vital capacity was inhibited during treatment. This is the first case report suggesting the efficacy of pirfenidone for patients with IPPFE.

Key words: idiopathic pleuroparenchymal fibroelastotis, idiopathic interstitial pneumonia, pirfenidone, pulmonary function

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Introduction

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a recently reported, rare disease entity among idiopathic interstitial pneumonias (IIPs) characterized by fibrotic thickening of the pleural and subpleural parenchyma, predominantly in the upper lobes (1). Several reports of idiopathic upper lobe fibrosis (IPUF) have been published in the Japanese literature since 1992 (2-4), and IPUF and IPPFE may belong to the same disease entity. While the clinical features of IPPFE are not entirely clear because of its extreme rarity, the condition may be divisible into subgroups with or without lesions of usual interstitial pneumonia (UIP) with fibroblastic foci in the lower lobes (5). The clinical course is considered progressive, and almost all patients clinically and functionally deteriorate even over a relatively short follow-up period (5, 6). The prognosis has been reported to be poor, and there are no established therapeutic options available for IPPFE except for supportive care and, ultimately, lung transplantation (7).

In the present study, we demonstrate a case of IPPFE that was successfully treated with pirfenidone. Pirfenidone treatment prevented a decline in the patient's forced vital capacity (FVC) during the treatment period. To the best of our knowledge, this is the first case report suggesting that pirfenidone can inhibit a decline of the pulmonary function in IPPFE patients.

Case Report

A 68-year-old man was referred to our hospital for further examination due to body weight loss and dyspnea on exertion. He formerly smoked 20 cigarettes per day for 40 years, but had no obvious history of exposure to any dust. A physical examination revealed bilateral middle-to-late inspi-

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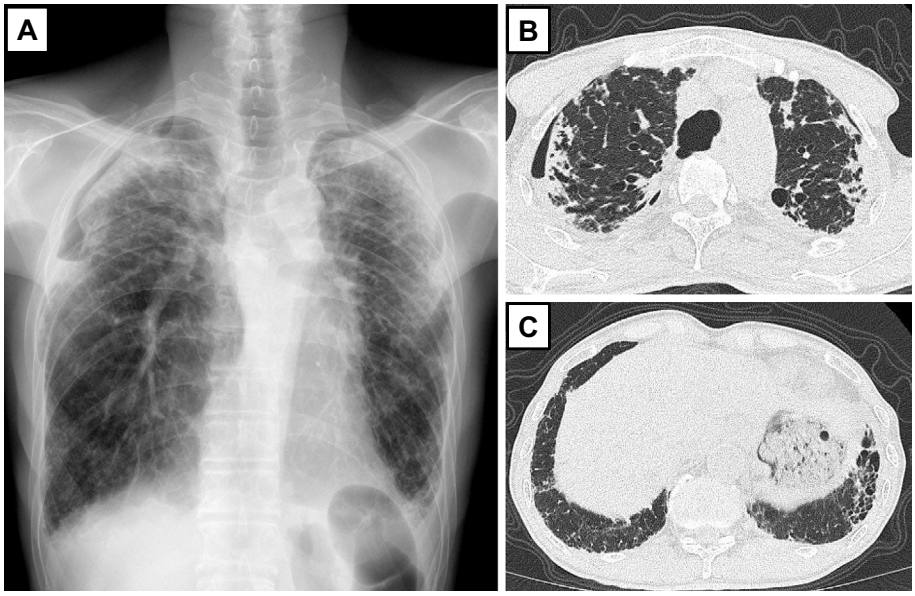

Figure 1. **Imaging findings. A: A chest radiograph showed marked apical pleural thickening associated with superior hilar retraction and bilateral pneumothoraces. B, C: HRCT revealed volume loss in the upper lobes, architectural distortion, traction bronchiectasis, and severe pleural and subpleural thickening with fibrotic changes in the marginal parenchyma.**

Table 1. **Laboratory Data on Admission.**

Hematology		Immunology	
WBC	5,200 /μL	CRP	<0.05 mg/dL
Neu	59.3 %	IgG	1,468 mg/dL
Lymph	30.8 %	IgG4	61.6 mg/dL
Mono	4.1 %	IgA	537 mg/dL
Eos	2.5 %	IgM	24 mg/dL
Baso	0.2 %	anti-nuclear antibody	×80
RBC	475×10^4 /μL	PR3-ANCA	<10 U/mL
Hb	14.6 g/dL	MPO-ANCA	<10 U/mL
Ht	46.2 %		
Plt	29.4×10^4 /μL	Blood gas analysis (room air)	
Biochemistry		pH	7.415
AST	22 U/L	PaO_2	100.1 mmHg
ALT	14 U/L	$PaCO_2$	40.1 mmHg
LDH	204 U/L	$HCO3^-$	25.1 mEq/L
T-bil	0.8 mg/dL	BE	0.6 mEq/L
γ-GTP	24 U/L		
CK	118 g/dL	Pulmonary function	
TP	7.9 g/dL	FVC	1.75 L
Alb	4.1 g/dL	VC	1.79 L
BUN	19 mg/dL	%VC	54.2 %
Cre	0.85 mg/dL	$FEV_{1.0}$	1.60 L
KL-6	468 U/mL	$FEV_{1.0}$%	91.4 %
SP-D	410 ng/mL	%$FEV_{1.0}$	65.8 %
SP-A	30.4 ng/mL	%DL_{CO}	71.7 %

ratory fine crackles in the lower lung field. While the percutaneous oxygen saturation in room air was 96%, he complained of dyspnea on exertion, with Modified British Medical Research Council (mMRC) grade one. Chest radiography revealed marked apical pleural thickening associated with superior hilar retraction and mild bilateral pneumothoraces. High-resolution computed tomography (HRCT) showed intense pleural thickening associated with evidence of fibrosis. The architectural distortion with volume loss, air space consolidation, and traction bronchiectasis were prominent with primary presentation in the upper lobes (Fig. 1). The pulmonary function test results were as follows: FVC: 1.75 L; VC: 1.79 L (54.2% predicted); $FEV_{1.0}$: 1.60 L (65.8% predicted); D_{LCO}: 9.59 mL/min/mmHg (71.7% predicted), showing severe, restrictive ventilatory impairment and a mild gas transfer defect (Table 1). A serological examination revealed the liver and renal functions, electrolytes, and CRP to all be within the normal limits. The serum level of SP-D was elevated, whereas those of KL-6 and SP-A were not. Antinuclear antibody was very weakly positive (x80 speckled pattern), but MPO-ANCA and PR3-ANCA were negative (Table 1). Taken together with these observations, the patient did not meet the criteria for the diagnoses of any collagen diseases.

As the radiological findings did not agree with the definite pattern of idiopathic pulmonary fibrosis (IPF)/UIP according to the criteria of the American Thoracic Society/European Respiratory Society, we performed video-assisted thoracoscopic surgery (VATS) of the right upper and lower lobes to obtain a definitive diagnosis. Histopathological analyses of the right upper lobe revealed a markedly thickened visceral pleura and prominent subpleural fibrosis characterized by elastic tissue. The border between the fibroelastosis and underlying normal lung parenchyma was clear and distinct, and the parenchyma distant from the pleura was spared. Fibroblastic foci were rarely noted at the leading edge of the fibrosis. Small and patchy lymphocyte infiltration was seen (Fig. 2). Since these findings completely fulfilled the previously described criteria (1), a diagnosis of

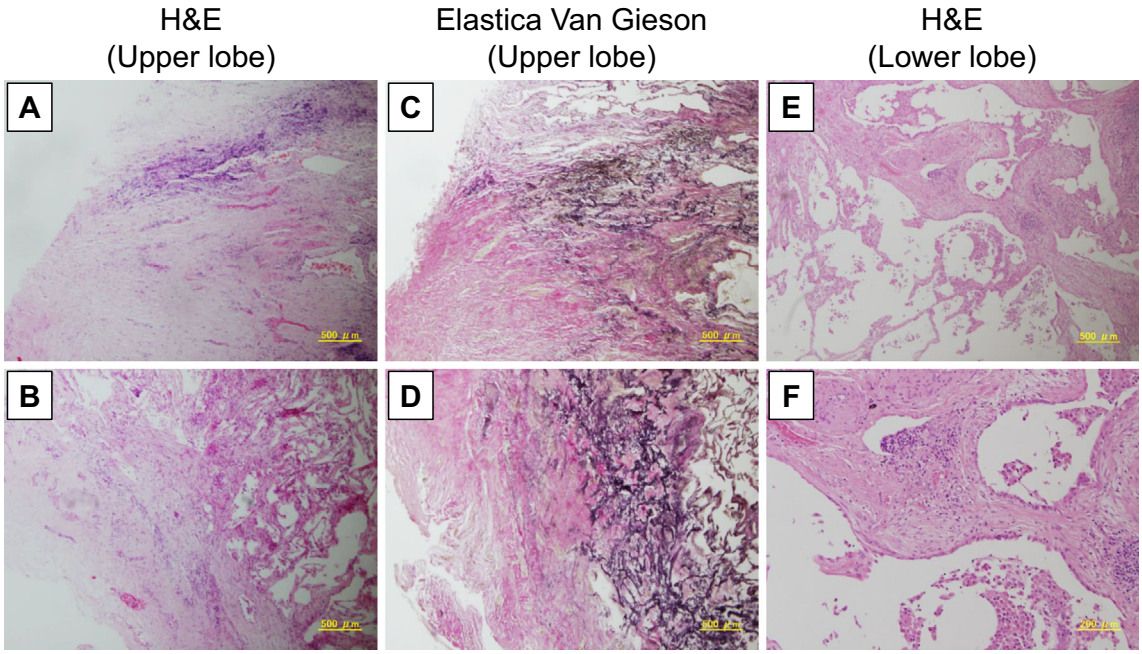

Figure 2. **Histopathological findings. A-D: Pathological specimens obtained from the right upper lobe showed a markedly thickened visceral pleura and prominent subpleural fibrosis characterized by elastic tissue. E, F: Pathological specimens obtained from the right lower lobe showed moderate honeycomb changes, and significant diffuse interstitial and pleural fibrosis with fibroblastic foci.**

IPPFE was made. In contrast, the histopathological findings of the right lower lobe showed moderate honeycomb changes, and significant diffuse interstitial and pleural fibrosis with fibroblastic foci. These features were consistent with the histological patterns of UIP. Taken together, the present patient was histologically considered to have the components of not only IPPFE, but also IPF. Since pirfenidone, which is an antifibrotic drug and currently approved for IPF/UIP, was considered to be potentially beneficial for this patient, we started its administration after obtaining informed consent. Pirfenidone was initially administered at 600 mg/day, and then it was increased to 1,200 mg/day. Its therapeutic efficacy was satisfactory, and a decline in FVC was thus prevented during the treatment course. Pneumothorax also improved gradually, and was completely cured by 11 months after the initiation of pirfenidone. However unfortunately, at that time, drug-induced liver disorder emerged, so we had to discontinue the treatment. Although the liver disorder improved two months after pirfenidone cessation, FVC decreased rapidly. Therefore, we restarted pirfenidone. The FVC decline was inhibited again, and pneumothorax did not recur as of the final observation at our hospital (Fig. 3).

Discussion

IPPFE is a new disease concept that was first described by Frankel et al. in 2004 (1), and was recently added to the new classification of IIPs as a rare form (8). IPPFE comprises dense established intra-alveolar fibrosis, with the alveolar walls in these areas showing prominent elastosis, and dense fibrous thickening of the visceral subpleura; these changes have a striking upper-zone predominance (9). Marked apical pleural thickening associated with superior hilar retraction is present on chest X-ray, and HRCT shows pleural thickening, fibrosis, architectural distortion, traction bronchiectasis, and honeycomb lung (7). The annual decline in the respiratory function is marked, and is similar to or more rapid than that observed for chronic fibrosing interstitial pneumonias such as UIP and fibrotic nonspecific interstitial pneumonia (6). The clinical course of this disease is progressive and almost all patients clinically and functionally deteriorate even over a relatively short follow-up period. Moreover, the prognosis of IPPFE patients has been reported to be poor (5).

There are no established therapeutic options available for IPPFE except for supportive care and, ultimately, lung transplantation (7). Treatment administered to patients in this series was highly variable and largely empirical, reflecting the lack of evidence on treating patients with IPPFE. Reddy et al. reviewed their experience of twelve IPPFE cases. The clinical course was progressive in many of the patients, despite aggressive treatment in some cases, including high-dose corticosteroids in the form of pulsed intravenous methyl-prednisolone, immunosuppressants, and N-acetylcysteine (9).

Watanabe et al. reported that the annual decline of FVC in the seven cases of IPUF was remarkable (6). In this report, five of seven patients received steroid treatment, and they conclude that steroid treatment did not appear to slow the decline in FVC. Kobayashi et al. also reported the rapid decrease of FVC in a case of IPUF despite the steroid treat-

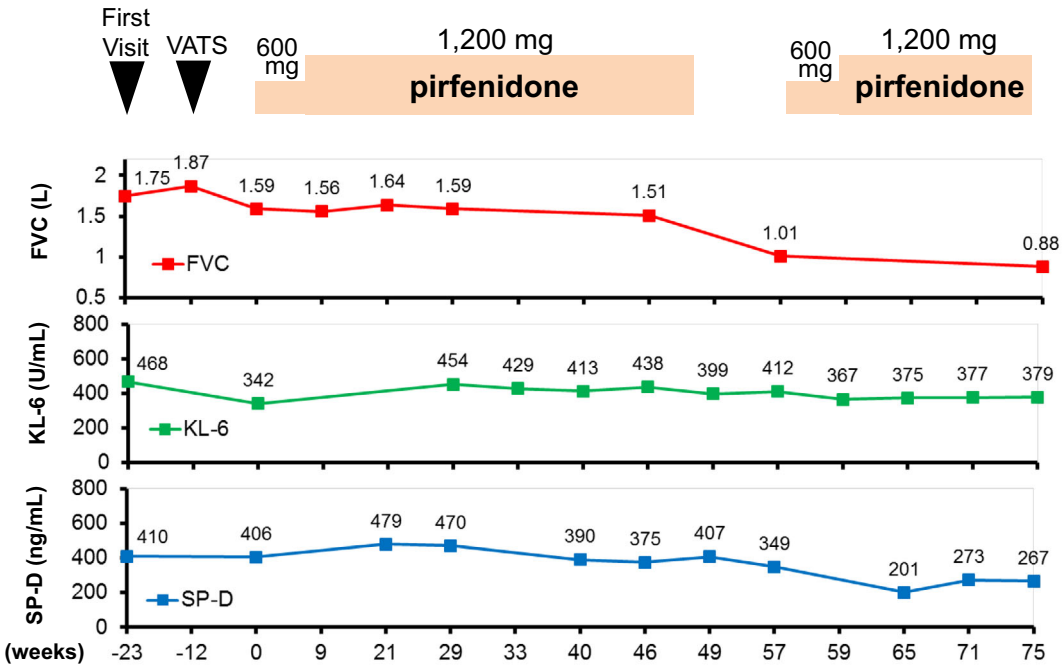

Figure 3. **Clinical treatment course. The serial changes of FVC, KL-6, and SP-D are shown.**

Table 2. **Changes of the Forced Vital Capacity (FVC) in Patients with PPFE and IPUF.**

Age (years)	Sex	Diagnosis	Diagnostic method	FVC (mL)		Interval between measurement (years)	ΔFVC (mL)	Treatment	Reference
				1st measurement	2nd measurement				
49	M	IPUF	SLB	2,000 (53.5%)[1]	1,600 (45.0%)	2.58	155	Symptomatic treatment	3
55	M	IPUF	SLB	3,030 (77.0%)	2,380 (55.0%)	4.67	650	Steroid	6
59	M	IPUF	SLB	1,160 (28.0%)	1,066 (20.3%)	1.58	94	Steroid	6
60	M	IPUF	SLB	2,580 (75.0%)	2,086 (56.1%)	2.95	494	Steroid	6
43	F	IPUF	SLB	1,680 (56.0%)	1,357 (35.7%)	3.58	323	Steroid	6
48	F	IPUF	SLB	2,030 (68.0%)	1,746 (55.0%)	3.42	284	N/D	6
81	F	IPUF	Autopsy	1,830 (80.0%)	1,414 (57.1%)	2.25	416	Steroid	6
69	M	IPUF	Autopsy	2,530 (80.0%)	1,942 (53.5%)	3.15	588	N/D	6
27	M	IPUF	SLB	3,780 (85.0%)	2,740 (60.5%)	4.00	260	Steroid	10
55	M	IPPFE	SLB	3,540 (87%)	1,120 (29%)	4.67	518.2	N/D	11
60	M	IPPFE	SLB	2,580 (78%)	1,040 (32%)	2.64	583.3	N/D	11
78	M	PPFE[2]	Autopsy	2,480 (69%)	1,370 (39%)	1.42	781.7	N/D	11
32	F	PPFE[3]	SLB	2,050 (69%)	640 (20%)	2.47	570.8	N/D	11
48	F	IPPFE	SLB	2,030 (67%)	1,380 (49%)	3.61	180	N/D	11
81	F	IPPFE	Autopsy	1,800 (83%)	1,060 (51%)	1.84	402.2	N/D	11
73	M	IPPFE	Autopsy	1,400 (46.5%)	1,190 (39.7%)	1.03	203.9	Symptomatic treatment	12
69	M	IPPFE	Clinical diagnosis	1,610 (46.8%)	1,360 (40.1%)	0.88	284.1	Steroid	12
68	M	IPPFE	SLB	1,590 (48.5%)	1,510 (46.5%)	0.82	97.5	Pirfenidone	The present case

M: male, F: female, SLB: surgical lung biopsy, FVC: forced vital capacity, ΔFVC: decline of FVC per year from 1st measurement, N/D: not described

[1]Numbers in parentheses indicate % predicted FVC

[2]Secondary to radiation therapy for oesophageal cancer

[3]Secondary to lung transplantation

ment (10). Additionally, Morimoto et al. and Harada et al. demonstrated a worsening FVC in a case of IPUF (3), and a remarkable decrease of FVC in six cases of PPFE (11), respectively, and those cases did not receive treatment with pirfenidone. Kusagaya et al. reported five cases of IPPFE with no treatment, and all cases had disease progression according to clinical perspectives and lung function tests, especially in terms of FVC (5). Although the use of FVC to assess the progression of IPPFE has not been validated with a large cohort or in clinical trials, we summarized the annual decline of FVC in patients with IPPFE in previous reports (3, 6, 10-12) in Table 2. The data showed that the decline of FVC in the present case during treatment with pirfenidone could be small as compared to those in other cases (Table 2). These data suggest that pirfenidone is effective for some of patients with IPPFE.

Pirfenidone is currently approved and used for IPF/UIP not only in Japan, but also in the USA (13, 14). Pirfenidone demonstrates pleiotropic pharmacological effects such as anti-fibrotic, anti-inflammatory, and anti-oxidative effects. Pirfenidone inhibits fibrotic factors, most notably transforming growth factor-β. Consequently, the downstream synthesis of extracellular matrix proteins, such as fibronectin, elastin, and collagen, is reduced (15). There is no evidence that pirfenidone is effective in treating typical IPPFE lesions. However, as pirfenidone was demonstrated to reduce the progression of IPF/UIP and the present patient also had a lesion of UIP, pirfenidone is potentially beneficial. In fact, we noted the preventive effects of pirfenidone on the decline of FVC, being much higher than expected, in the present patient. The fact that FVC decreased rapidly after the cessation of pirfenidone further emphasizes the potential significance of pirfenidone for IPPFE. To the best of our knowledge, this is the first case report demonstrating that pirfenidone can inhibit a decline of the pulmonary function in IPPFE.

Oda et al. conducted a retrospective review of the medical records of 110 consecutive patients with IPF with a histologic UIP pattern, and reported that 11 of these patients met the radiologic criteria for PPFE, while nine patients fulfilled the histologic criteria of PPFE (16). Similarly, Piciucchi et al. reported the case of IPPFE showing traction bronchiectasis and honeycombing by CT scan (7). The pathological pattern shown in these reports is similar to the present case. Hence, it is considered that subgroup of IPPFE cases with UIP pattern exists in no small part, and pirfenidone may be potentially beneficial in these cases.

We recently reported the characteristics of serum biomarkers in IPPFE patients, including the present case, which were different from those in IPF or NSIP patients (8). Recently, Enomoto et al. reported a pathological difference between IPPFE and IPF, and that the amount of elastic fibers in patients with IPPFE was more than twice that in those with IPF (17). They also demonstrated that the amount of elastic fibers was larger in patients with IPPFE than in those with IPF, even in the lower lobes, although the distribution of elastic fibers in lungs was heterogeneous in IPPFE specimens. These findings suggest a different pathogenesis in IPPFE from that in IPF, and may indicate the importance of identifying subgroups which are sensitive to pirfenidone therapy.

In summary, we encountered a rare case of IPPFE patient in whom a decline in the pulmonary function was successfully prevented by pirfenidone. Pirfenidone may therefore be a promising treatment option for IPPFE. Larger-scale studies will be required to verify our findings and establish an appropriate therapeutic strategy for this rare disorder.

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

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