Gender and Age

There is no gender preponderance in the incidence described in previous reports. Gender preponderance differed in each report [1, 3, 5-7, 10-33, 35-37] (Table 3).

Table 3. Clinical Characteristics of Pleuroparenchymal Fibroelastosis

No gender preponderance
Age at onset
Wide-ranging, younger than in idiopathic pulmonary fibrosis (IPF)
Smoking history
Unrelated to the incidence of PPFE
Clinical symptoms
Exertional dyspnea and dry cough with insidious onset
Chest pain due to pneumothorax
Loss of body weight
Physical findings
Slender stature and flattened thoracic cage
Crackles sometimes audible
Serum biomarkers
KL-6 within the normal or around the upper normal limit
Elevated Surfactant protein D (SP-D)
Autoantibodies such as rheumatoid factor and antinuclear antibody sometimes elevated
Prognosis
Wide-ranging in each case studies from slowly progressive with 10 - 20 years of presentation to rapidly progressive course
Poorer prognosis of secondary PPFE such as transplantation-associated PPFE

Age at onset is wide-ranging, from young to old age, and is therefore dissimilar to IPF, which affects older individuals. The fact that there are a substantial number of patients with PPFE aged in their third and fourth decade [1, 3-5, 7-13, 18, 26, 29, 30] is quite characteristic, even when transplantation-associated PPFE [24, 27, 28, 32, 33] is excluded. Underlying diseases or hereditary disposition could be responsible for age at onset in some patients with PPFE.

Smoking History

Smoking does not appear to have any effect on the occurrence of PPFE. Previous studies [1, 3, 11-14, 16, 18, 19, 21-24, 26, 27, 29-31, 35, 37] indicate that the smoking rate by current and former smokers was 29% of the total numbers of patients, which is a contrasting difference between PPFE and IPF [38].

Past History and Underlying Diseases or Conditions

There are many patients with PPFE who experienced recurrent pneumothorax. Multiple bullae in upper lung fields that appear in the course of the disease may be torn and be responsible for the recurrence of pneumothorax.

Some patients with PPFE have a past history of radiation therapy and/or anticancer chemotherapy for treating ankylosing spondylitis [4] or malignancy [1, 27]. Postradiation pulmonary fibrosis is usually confined to the irradiated area of the lung. PPFE might be a special form of radiation injury, extending to nonirradiated areas to form irreversible pulmonary fibrosis. Hamada *et al.* reported a patient with cyclophosphamide-induced pulmonary fibrosis and elastosis with pleural thickening after treatment for breast cancer [39]. The clinical and pathological features appear similar to those of current PPFE.

Bone marrow or stem cell transplantation [24, 27, 28] and lung transplantation [32, 33] are now known to cause PPFE, as a lung manifestation of chronic graft versus host disease (GVHD) and as a phenotype of chronic rejection of transplanted lungs. The fibrosis of the upper lobes described by Konen *et al.* [40] and the upper lobe fibrosis reported by Pakhale *et al.* [41] probably have the same histology as that of PPFE after lung transplantation. Transplantation-associated PPFE highlights the key roles of immune-mediated cells in the development of PPFE.

Occupational exposure to dust [3, 20, 26, 27, 29, 35] such as asbestos [27, 29] or aluminum [26, 35] is another important factor that induces PPFE. In general, pneumoconiosis such as asbestosis, silicosis, and berylliosis may present as upper-lobe fibrosis, although the PPFE pattern has not been histologically demonstrated in all of these pneumoconioses. As the interstitial connective tissue response in asbestosis is fibroelastotic rather than fibrotic [42], with pleural thickening, it is possible that asbestos exposure directly induces the pathology of PPFE.

Pulmonary mycobacterial disease due to the *Mycobacterium avium-intracellulare* complex (MAC) [23] and aspergillus infection [13, 16, 29, 30] have been reported in patients with PPFE. These infectious diseases may coexist, but it is not known currently whether the pathology of PPFE is induced by these infections or whether PPFE provides the circumstances for these infectious agents to grow, as does IPF [43]. Reddy *et al.* speculated that repeated inflammatory damage in a predisposed individual may lead to the pathology of PPFE [30].

Genetic or autoimmune mechanisms may be involved in the pathogenesis of PPFE. Some investigators reported PPFE in siblings [1, 10, 13] and a pair of parents and child [13], and PPFE with a family history of other pulmonary fibrosis [11, 30]. Ankylosing spondylitis [4], ulcerative colitis [36], and psoriasis [37] have also been previously reported as underlying diseases. Pulmonary upper-lobe fibrosis and cavitation in patients with rheumatoid diseases have also been reported [44]. Pleuroparenchymal disease in collagen vascular disease might share common histological features with PPFE.

The fibrotic stage of hypersensitivity pneumonitis, Langerhans cell histiocytosis, and sarcoidosis may also present as upper-lobe fibrosis clinically [45]. Reddy *et al.* [30] reported that two of 12 PPFE patients were exposed to environmental allergens in the form of mold and birds, and there was one patient whose biopsy specimens showed both a PPFE pattern and bronchocentric chronic inflammation and focal organizing pneumonia with poorly formed nonnecrotizing granulomas, which are histological features that are consistent with hypersensitivity pneumonitis.

Clinical Symptoms

The main symptoms are nonproductive cough and exertional dyspnea, which are also observed in IPF. Such symptoms appear insidiously. Chest pain due to pneumothorax may be the first symptom in some patients. Many patients complain of weight loss.

Although Amitani *et al.* pointed out that upper-lobe fibrosis was slowly progressive and fatal, with 10–20 years of presentation [10], some subsequent papers have suggested a poorer prognosis of the disease [23, 30]. There might be a long silent period in PPFE during which patients have no symptoms and the only abnormal finding is a pleural thickening-like appearance in bilateral apical areas of chest radiographs. However, the clinical course may be accelerated once symptoms appear [23].

Physical Findings

Patients with PPFE are often associated with slender stature [10-13, 15–25, 31]. "Flattened thoracic cage" is another characteristic physical finding in patients with PPFE. Japanese investigators have paid attention to a flattened thoracic cage in idiopathic PPFE [10-12, 14, 18, 21]. In flattened thoracic cages or abnormally narrowed anterior-posterior thoracic dimension, the ratio of the anterior-posterior diameter of the thorax to the transverse diameter of the thorax (APDT/TDT) is lower than that observed in the normal population, which gives an impression of weakness and is shown in the lateral view of chest radiographs (Fig. **1b**). A flattened thoracic cage is a similar physical finding to pectus excavatum, but a flattened thoracic cage is not associated with excavation of the sternum.

A flattened thoracic cage, which may result from a congenital disposition or may be a secondary change of the thorax as a consequence of the shrinkage of the upper lung lobes through the long-lasting process of fibrosing, may inhibit the distensibility of the lungs and inhibit the constant blood flow in the upper lobes, leading to a ventilation–perfusion imbalance. These pathophysiological conditions may further enhance the progress of the disease. A flattened thoracic cage is observed in patients with not only idiopathic PPFE but also secondary PPFE. Amitani *et al.* [10] and others [18, 21] have speculated on the importance of a hereditary disposition for the formation of a flattened thoracic cage in the development of idiopathic PPFE. However, Nakasone *et al.* reported two PPFE patients with a flattened thoracic cage who had undergone bone marrow transplantation [24]. We observed patients with PPFE whose thoracic cage became flattened during the progression of the disease (Fig. **2**) [46]. Therefore, a flattened thoracic cage might exist before the onset of overt PPFE, but it is more conspicuous in the course of the disease. Long-term follow-up from an initial stage of PPFE will elucidate the significance of a flattened thoracic cage.

Clubbed finger, which is often seen in patients with IPF, has been rarely reported in patients with PPFE. In the literature concerning PPFE, only two patients with clubbed fingers were found: a 36-year-old woman with PPFE after autologous stem cell transplantation [24] and a 70-year-old man with aluminum-induced pulmonary upper-lobe fibrosis [35].

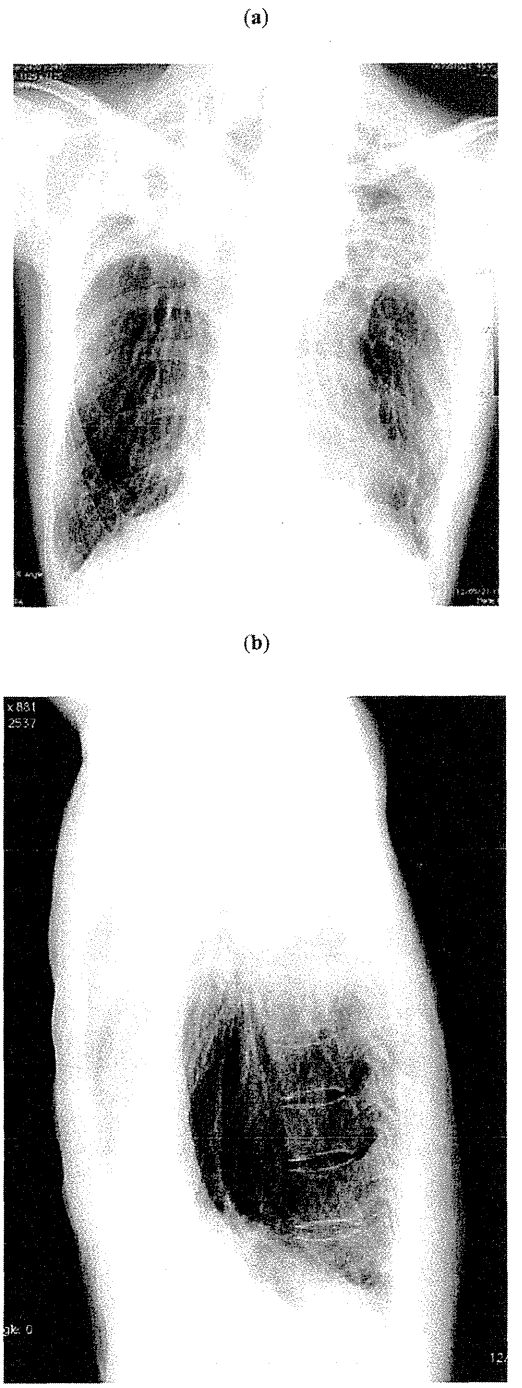


Fig. (1). Chest radiographs of a PPFE patient (44-year-old man) showing a thin thoracic cage.

A number of case studies have reported that crackles are audible in about half or less than half of patients [1, 3, 6, 11, 12, 15, 16, 19-21, 23, 26, 28, 29, 31, 35], which means that crackles are audible less frequently in PPFE than in IPF. Late-inspiratory crackles are considered to arise from the explosive opening of closed peripheral airways at a time when a critical transmural pressure develops as radial

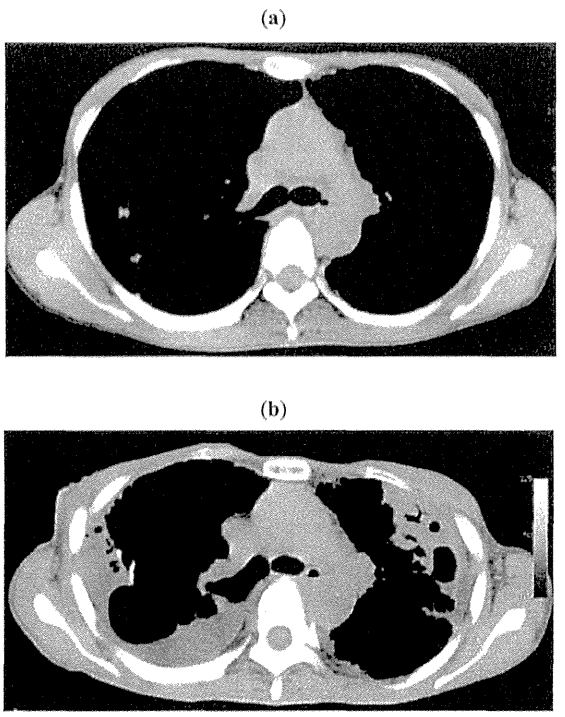


Fig. (2). (**a**) Chest CT in a 48-year-old woman with PPFE. (**b**) Chest CT taken after 4 years. Both CT scans were sliced at the level of the 6th thoracic vertebra. The ratio of the anterior–posterior diameter of the thorax to the transverse diameter of the thorax became lower after 4 years of disease progression.

traction increases during lung inflation [47]. As subpleural atelectasis consisting of closely packed elastic fibers and alveoli filled with mature collagen, which no longer open, is an essential histological feature in the lung parenchyma of PPFE, there might be little chance to hear late-inspiratory crackles from such areas. However, fibrotic NSIP-like or UIP-like lesions in the adjacent lobes or lower lobes, which often appear in the advanced stage, may be the source of the crackles.

Laboratory Data

KL-6, a mucin-like glycoprotein, is a reliable serum marker that is used for the diagnosis of interstitial lung diseases [48, 49]. Serum KL-6 is usually within the normal or around the upper normal limit in patients with PPFE [18-21, 23, 26, 30, 31]. However, as the disease progresses, the level tends to become higher [23]. Surfactant protein D (SP-D) may be elevated [23, 24, 31]. Histologically, PPFE is a fibrotic lung disease, but it is not an interstitial pneumonia such as UIP and NSIP, in which KL-6 is highly expressed in the regenerated type II pneumocytes, migrating into the bloodstream through the inflammatory and fibrosing process in the lung parenchyma [49]. Such histological difference could explain the fact that serum levels of KL-6 are normal or around the upper normal limit in the early stage of PPFE. However, in the advanced stage, UIP-like lesions could contribute to the increase in the serum levels of KL-6.

Reddy *et al.* [30] reported that five of 12 patients with PPFE demonstrated serum auto-antibodies, such as rheumatoid factor (RF), double-stranded DNA, and antinuclear factor, suggesting the role of autoimmune mechanisms in the pathogenesis of the disease in some patients. Frankel *et al.* [1] and Kusagaya *et al.* [31] also reported positivity for RF and antinuclear antibody in patients with PPFE (Table **3**).

Imaging Findings

Although surgical lung biopsy or autopsy is essential for the definite diagnosis of PPFE, imaging findings are also essential as the first step to the final diagnosis, as in other IIPs.

At the early stage of idiopathic PPFE, bilateral apical pleura appear irregularly thickened on the frontal view of chest radiographs; otherwise, appearance is almost normal, without any subjective symptoms. Such a finding may be incidentally observed in a medical checkup (Fig. **3a**). Later, chest radiograph shows the elevation of bilateral hilar opacities. However, a lateral view demonstrates an abnormally narrowed anterior–posterior thoracic dimension. Subsequently, reticular and nodular opacities appear in the bilateral upper lung fields, and hilar opacities are further elevated (Fig. **3b**). Chest CT shows subpleural nodular or reticular opacities in the lung parenchyma at the apex. Interlobular septal thickening is associated (Fig. **4a**). In contrast to such changes in the upper lobes, changes in the middle and lower lobes are minimal, if any. As the disease progresses, the opacities described above extend to the adjacent lobes.

At the advanced stage, fibrotic shadows extend to lower lung fields, and the diaphragm is elevated with the loss of bilateral lung volume. Multiple bullae and large cysts often appear in the upper lung fields (Figs. **3c**, **4b**), which allow aspergillus infection. Multiple fibrocystic changes also appear in the lower lobes (Fig. **4c**).

Pneumothorax may complicate the course of the disease and recur. Multiple bullae may be responsible for pneumothorax.

Isolated reticular opacities or honeycombing sometimes appear in the subpleural areas of bilateral lower lobes, which raises the possibility of the combination of PPFE with UIP or NSIP (Table **4**) [23, 30].

Respiratory Function

PPFE is histologically characterized by alveolar collapse with subpleural elastosis and intra-alveolar fibrosis, in addition to the thickening of the pleura mainly in upper lobes. It is easy to imagine that such histological changes induce restrictive ventilatory impairment as the main functional abnormality. Forced vital capacity (FVC) and total lung capacity (TLC) are decreased, but the ratio of forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) is rather increased. These physiological changes are the same as those of IPF. Fibrotic collapse of upper lobes leads to the compensatory overinflation of lower lobes, resulting in the increase of the ratio of residual volume/TLC (RV/TLC) [31], which is a peculiar functional impairment that is not usually seen in IPF.

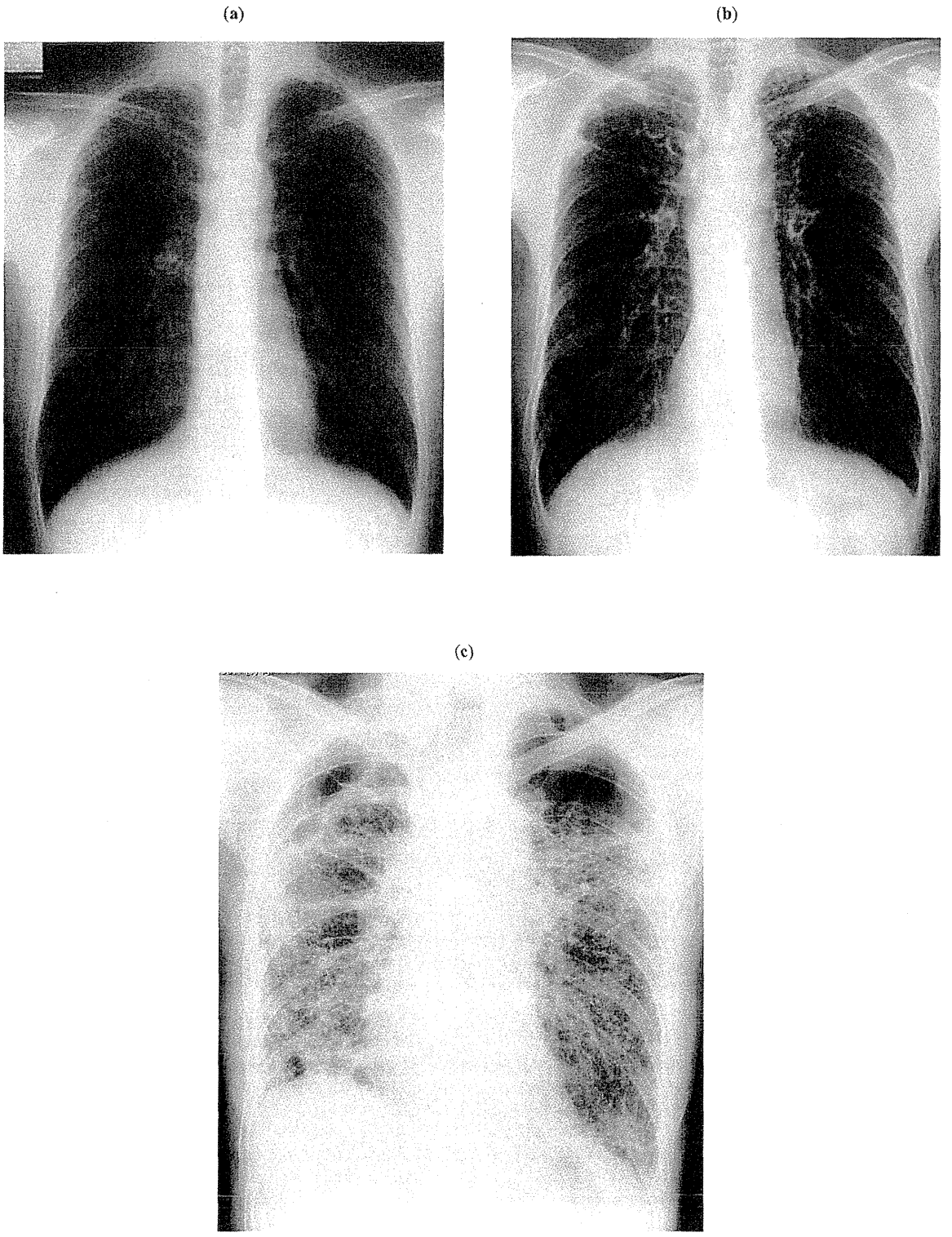
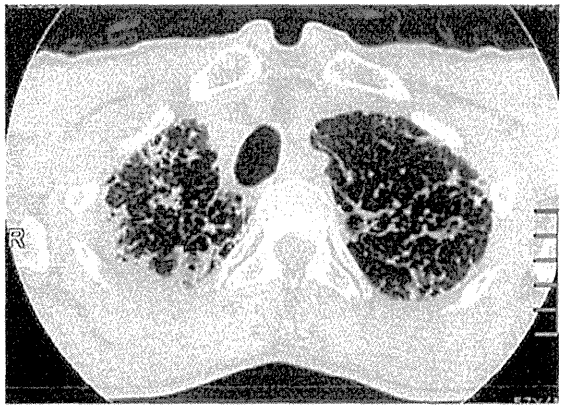
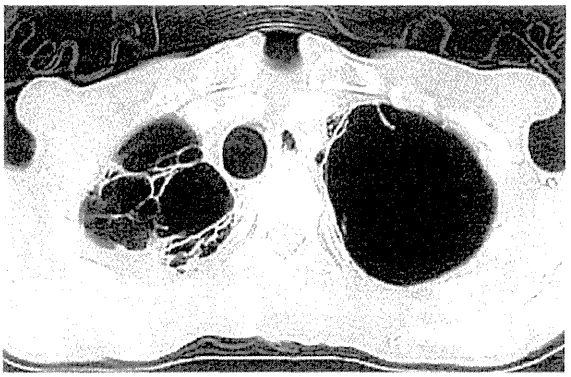


Fig. (3). (**a**) Chest radiograph of a 50-year-old man with PPFE. At the early stage, the bilateral apical pleura appeared irregularly thickened; otherwise, they were almost normal. (**b**) Chest radiograph taken 4.7 years after the image shown in 3a. Reticular and nodular opacities appeared in the bilateral upper lung fields, and hilar opacities were further elevated. (**c**) Chest radiograph taken 9.7 years after the image shown in 3a. Fibrotic shadows extended to lower lung fields, and the diaphragm was elevated, with the loss of bilateral lung volume. Multiple bullae and large cysts appeared in the upper lung fields.

(a)



(b)



(c)

Fig. (4). (Same patient as in Fig. **3**) (**a**) Chest CT showing subpleural nodular or reticular opacities in the lung parenchyma at the apex. Interlobular septal thickening was associated (taken 7 years after the image shown in Fig. **3a**). (**b**) Chest CT taken 2.8 years after the image shown in 4a. Multiple bullae and large cysts appeared in the upper lung fields. (**c**) Chest CT taken 2.8 years after the image shown in 4a. Multiple fibrocystic changes appear in the lower lobes.

Gas exchange impairment also appears as a restrictive impairment. The diffusing capacity of carbon monoxide (DLco) is decreased. However, in many instances, the diffusing capacity is normal or minimally reduced when DLco is divided by alveolar volume (DLco/VA) (Table **5**).

Table 4. Imaging Characteristics of Pleuroparenchymal Fibroelastosis

Chest Radiograph
Abnormally narrowed anterior-posterior thoracic dimension (flattened thoracic cage)
Elevated hilar opacities
Reticular and nodular opacities in the bilateral upper lung fields
Fibrocystic opacities in the upper lung fields and occasional reticular opacities in the lower lung fields in the advanced stage
Chest CT
Initial stage:
Subpleural nodular and reticular opacities in the apex, but minimal changes in the middle and lower lobes
Advanced stage:
Fibrotic opacities with traction bronchiectasis extending to adjacent lobes with multiple bulla and large cysts at the upper lung fields
Occasional subpleural reticular opacities in the bilateral lower lobes resembling usual interstitial pneumonia (UIP)

Table 5. Respiratory Function Characteristics in Pleuroparenchymal Fibroelastosis

Ventilatory Impairment
Decreased FVC
Increased FEV_1/FVC (%)
Decreased TLC
Increased RV/TLC (%)
Gas Exchange Impairment
Decreased DLco
Normal or minimally decreased DLco/VA

We examined the annual decline of FVC in seven patients with idiopathic PULF and found that the yearly decline of FVC was 20.3% [23], which seems larger than that observed in IPF, although the number of patients included in the study was small. Although rapid decline of FVC is related to the prognosis of pulmonary fibrosis [50], the degree of annual decline may depend on the stage of the disease at the start of the examination of the annual change. Further studies are needed.

Treatment

Idiopathic PPFE is usually slowly progressive and refractory to steroids or immunosuppressive agents. Only one paper has reported a beneficial effect of prednisolone, which increased PaO_2, although transiently [12]. Therapeutic options for chronic fibrosing interstitial pneumonia, such as IPF and fibrotic NSIP, seem useless. In the advanced stage, home oxygen therapy is necessary if the patient is hypoxemic, and infection control is important, as in IPF. *Aspergillus* infection will be superimposed, especially in the fibrocystic lesions of the disease [13, 16, 29, 30], as in the advanced stage of IPF [43].

The categorization of the fibrotic process in pulmonary fibrosis into two aspects, collagenosis and elastosis, showed that the predominant process is elastosis in PPFE, whereas collagenosis is predominant in IPF; however, both processes are found in PPFE as well as in IPF [51]. Targeting the

inhibition of elastosis instead of collagenosis might represent a novel therapeutic avenue in PPFE.

Prognosis

Amitani *et al.* demonstrated that idiopathic PPFE is slowly progressive with 10-20 years of presentation. A Kaplan–Meier survival curve drawn using 85 patients from studies that included both idiopathic and secondary PPFE [1, 3-6, 10-16, 19-24, 26-31, 33, 35, 37], but not including the patients with lung-transplantation-associated PPFE reported by Ofek *et al.* [32] (Fig. **5**), showed that the median survival of the disease was 11 years. Although the censoring of 49 of the 85 patients was a limitation of the analysis, the survival time of the patients with PPFE was longer than that of IPF patients, which supports the observation of Amitani *et al.* [10]. However, the prognosis of transplantation-associated PPFE appears to be poorer, as reported by von der Thusen *et al.* [28] and Ofek *et al.* [32].

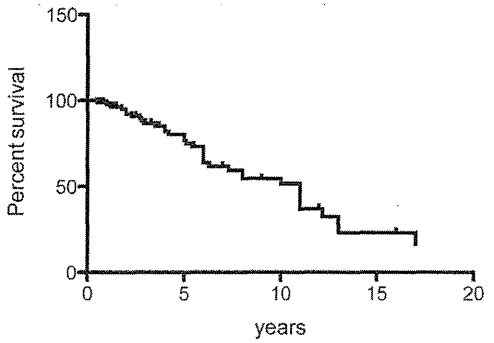


Fig. (5). A Kaplan-Meier survival curve using 85 patients from previous studies.

We showed poor prognosis in nine patients with idiopathic PPFE [23]. Our result may have been partly derived from the fact that the majority of the patients were in the advanced stage of the disease. The prognosis of PPFE was wide-ranging in each case study.

The definition of the onset time of PPFE is an important determinant for the prognosis of the disease, because idiopathic PPFE may have a long subclinical stage in which lesions are confined at the apex of the lungs, without symptoms. Another important point, which is more essential than the onset of the disease, is the definition of the disease. As stated above, there is a group of patients with PPFE involving the bilateral upper lobes only for a long time, without invasion of adjacent lobes or lower lobes. The majority of these patients may fall under the diagnosis "Amitani disease". The prognosis of such patients is better than that of patients with multiple lobe involvement, especially lower lobe involvement with UIP-like lesions. Currently, PPFE appears to include patients with heterogeneous etiologies.

Dilemma Between Idiopathic PPFE and Amitani Disease

I started this review article under the assumption that PPFE is the same as PULF, to avoid confusion between the two concepts. However, as described above, Japanese investigators are still debating whether idiopathic PPFE is really the same entity as idiopathic pulmonary upper-lobe-localized fibrosis (Amitani disease) and idiopathic pulmonary upper-lobe-predominant fibrosis. Amitani et al. originally proposed the concept of this disorder, and although they described the clinical characteristics of the disease in detail, its histological description was insufficient [10]. Later, Frankel et al. clearly stated the histological characteristics of PPFE, which were, they thought, considered to be the same as or similar to those of Amitani disease [1], but the description for clinical features was insufficient. Compared with the Japanese literature, the various articles on PPFE from Western countries published to date have not mentioned detailed physical findings, such as slender stature and flattened thoracic cage [27-30].

Although both imaging and histological findings are quite similar, the clinical features of Amitani disease might be different from those of idiopathic PPFE from Western countries.

CONCLUSION

PPFE is a rare pulmonary fibrosis. The number of patients published in case reports or original articles is currently around 100 worldwide. However, the knowledge gathered to date regarding PPFE is totally dependent on case reports or small case series, and not on large-scale studies.

PPFE is tentatively categorized as idiopathic PPFE and secondary PPFE. Idiopathic PPFE is now considered as one of the rare IIPs (2). Because of the rarity of the fibrosis, its clinical characteristics have not been fully elucidated. However, upper-lobe-predominant lesions and pleuroparen-chymal histopathology are quite characteristic of idiopathic PPFE. Subpleural reticular opacities may not be rarely found in the lower lobes of patients with PPFE, which raises the possibility that another IIP coexists with PPFE.

Large-scale international studies are needed to elucidate the natural history and prognosis of this disease, as well as the relationship between idiopathic and secondary PPFE. In addition, such global studies might tell us whether Amitani disease is a different disorder from, or one phenotype of, idiopathic PPFE.

CONFLICT OF INTEREST

The author confirms that this article content has no conflicts of interest.

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ORIGINAL ARTICLE

Prognostic significance of fibroblastic foci in usual interstitial pneumonia and non-specific interstitial pneumonia

TAISHI HARADA,[1,2] KENTARO WATANABE,[2] KAZUKI NABESHIMA,[1] MAKOTO HAMASAKI[1] AND HIROSHI IWASAKI[1]

Departments of [1]Pathology and [2]Respiratory Medicine, Fukuoka University School of Medicine, Fukuoka, Japan

ABSTRACT

Background and objective: **Fibroblastic foci (FF) composed of an accumulation of fibroblasts or myofibroblasts may be related to the progression of pulmonary fibrosis leading to respiratory insufficiency. Several studies have shown that the number of FF is a significant prognostic factor in usual interstitial pneumonia (UIP). The purpose of the present study was to examine whether the extent of FF is related to impairment of respiratory function and prognosis in patients with biopsy-proven fibrosing interstitial pneumonia, including UIP and fibrotic non-specific interstitial pneumonia (fNSIP).**

Methods: **Fifty patients with histologically confirmed interstitial pneumonia including UIP or fNSIP were investigated, and correlations between FF and pulmonary function were evaluated. FF area was calculated as the proportion of total area (%FF) and the number of FF (FF/cm^2) in the whole histological specimen from each patient.**

Results: **The UIP group showed significantly higher %FF and FF/cm^2 than the fNSIP group. When UIP and fNSIP patients were analysed together, the group of patients who had died (death group) revealed significantly higher %FF and FF/cm^2 compared with the group of survivors, and the impairment of vital capacity and diffusing capacity of carbon monoxide was correlated with %FF and FF/cm^2.**

Conclusions: **FF correlated with impaired pulmonary function and may be a useful parameter to predict prognosis in patients with UIP and fNSIP.**

Key words: fibroblastic focus, non-specific interstitial pneumonia, pulmonary function, usual interstitial pneumonia.

Abbreviations: DL_{CO}, diffusing capacity of carbon monoxide; FF, fibroblastic foci; fNSIP, fibrotic non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; VC, vital capacity.

Correspondence: Taishi Harada, Department of Respiratory Medicine, Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. Email: haradata@adm.fukuoka-u.ac.jp

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SUMMARY AT A GLANCE

A significant correlation was demonstrated between histological findings and respiratory function in fibrosing interstitial pneumonia. Our findings indicate that fibroblastic foci are a reliable predictor of prognosis in usual interstitial pneumonia and fibrotic non-specific interstitial pneumonia.

INTRODUCTION

Fibroblastic foci (FF) are characteristic features of usual interstitial pneumonia (UIP) and are associated with progression of disease and a poor prognosis.[1–3] They are composed of aggregates of mesenchymal cells including fibroblasts and myofibroblasts and may play a critical role in the progression of pulmonary fibrosis.

There has been an interest in the prognostic significance of FF in UIP. Several studies have demonstrated the clinical importance of FF as a prognostic parameter, establishing that poor prognosis is related to a greater number of FF.[1–3] However, some studies have failed to demonstrate the correlation between FF and survival in patients with idiopathic pulmonary fibrosis, indicating that quantitative assessment of FF in surgical lung biopsy specimens is of limited prognostic value.[4–6] These conflicting results are probably a result of the different methods used to select samples from patients. In the previous studies, FF was examined only in UIP, not in non-specific interstitial pneumonia. Furthermore, previous studies analysed FF in selected areas of lung specimens using a score grading system, not in the whole specimen.[7] In addition, a recent guideline indicates that surgical lung biopsy is not essential in the subjects showing UIP pattern on high-resolution computed tomography. As a result, biopsy would be performed only in patients with the difficulty in computed tomography diagnosis. This could cause a difficulty to distinguish histologically between UIP and fibrotic non-specific interstitial pneumonia (fNSIP). The purpose of the

present study was to examine whether the extent of FF is related to impairment of respiratory function and prognosis in patients with biopsy-proven fibrosing interstitial pneumonia, including UIP and fNSIP.

METHODS

Patients

We reviewed patients with interstitial pneumonia who had open or a video-assisted thoracoscopic lung biopsy in Fukuoka University Hospital, National Hospital Organization Kyushu Medical Center, and Fukuoka National Hospital between 1995 and 2008. Fifty patients with histologically confirmed UIP or fNSIP were selected. Patients with concomitant lung neoplasms were excluded. Histological diagnosis of UIP and fNSIP was based on a previously published report[8] and the criteria in the American Thoracic Society/European Respiratory Society consensus classification.[9] The study protocol was approved by the ethics committee of our institute.

Pathological evaluation

The specimens were routinely fixed in 10% formalin and were processed into paraffin blocks for histopathological examination. Tissue sections were cut 4 μm thick and stained with HE, Alcian blue-periodic acid Schiff and elastica van Gieson.

FF, newly formed connective tissue bundles, were defined as subepithelial, interstitial areas in which fibroblasts and myofibroblasts were arranged in a linear manner within a pale staining matrix and which were stained blue by Alcian blue-periodic acid Schiff (Fig. 1).

The area of FF and the whole lung tissue area were measured using image analysis software (WinROOF version 5.5, Mitani Corporation, Fukui, Japan). The total number of FF was obtained by counting all FF in all specimens from each patient, and FF/cm^2 was calculated by dividing the total number of FF by the whole lung tissue area (cm^2). %FF was calculated by dividing the total area of FF by the whole lung tissue area.

Respiratory function data

All respiratory function data, including vital capacity (VC) and diffusing capacity (diffusing capacity of carbon monoxide (DL_{CO})) during the entire follow-up period, were obtained from the medical records. Annual changes in respiratory function were estimated from linear regressions, assuming time dependency and linearity. Percentage decrease from the baseline per year (%ΔVC, %ΔDL_{CO}) was obtained from the linear equation, and the correlation between the respiratory function impairment and FF was evaluated.

Statistical analysis

Numerical data are presented as the mean ± standard error of the mean. For analysis, the unpaired Student's *t*-test was used for pairwise comparisons. Categorical data were compared between UIP and fNSIP using the chi-square test for independence. Prognostic data were analysed using the Kaplan–Meier curve with log–rank test. Correlations involving FF and respiratory function data were evaluated using the Spearman rank coefficient. Statistical analysis was performed with StatView software for Windows version 5.0 (SAS Institute Inc., Cary, NC, USA). *P*-values less than 0.05 were considered significant.

RESULTS

Clinical characteristics, laboratory and physiological findings

The patient population consisted of 28 males and 22 females; mean age was 61.2 years. Of the 50 patients, 24 (48.0%) were diagnosed with UIP and 26 (51.0%)

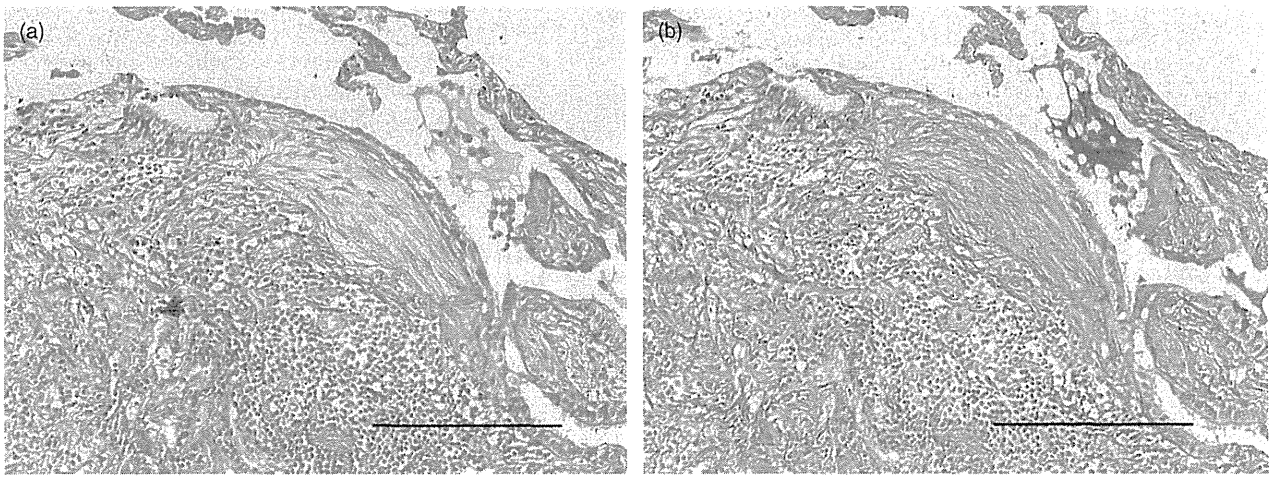

Figure 1 A histopathological example of fibroblastic foci. (a) HE section. Fibroblastic foci are composed of aggregates of fibroblasts or myofibroblasts arranged in a linear manner within a pale staining matrix. Scale bars = 200μm. Original magnification × 200. (b) Alcian blue-periodic acid Schiff (AB-PAS) section. Matrix of fibroblastic foci is stained blue. Scale bars = 200μm. Original magnification × 200.

Table 1 Clinical characteristics, and laboratory and physiological findings of the study population

Variables	UIP	NSIP	*P*-value
Clinical characteristics			
Male/female gender, No.	15/9	13/13	0.3737
Age at biopsy, year	65.3 ± 9.8	57.4 ± 11.5	0.0120*
Pack years of smoking	18.4 ± 28.9	19.0 ± 30.0	0.9476
Month since onset of symptoms	24.3 ± 37.8	12.3 ± 16.0	0.2064
Laboratory findings			
Serum KL-6, U/mL	1075 ± 615	2190 ± 2263	0.0423*
Serum LDH, IU	298 ± 191	286 ± 121	0.7930
Physiological findings			
VC, %predicted	72.5 ± 18.8	85.5 ± 16.2	0.0387*
DL_{CO}, %predicted	70.6 ± 23.4	82.9 ± 20.3	0.1261
PaO_2 at room air, torr	81.5 ± 14.1	83.5 ± 11.1	0.6181

* $P < 0.05$.

DL_{CO}, diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; NSIP, non-specific interstitial pneumonia; PaO_2, partial pressure of oxygen (arterial); UIP, usual interstitial pneumonia; VC, vital capacity.

with fNSIP. The clinical characteristics and laboratory findings of the patients are summarized in Table 1.

Of the clinical characteristics, age at lung biopsy was significantly different between UIP and fNSIP. Of 50 cases, 9 were current smokers, 13 were ex-smokers and 28 were never smokers. Serum Krebs von den Lungen-6 levels differed significantly between UIP and fNSIP groups (UIP < fNSIP).

Collagen vascular disease was found in five cases from the UIP group and four cases from the fNSIP group during the follow-up period.

Quantitative analysis of FF: Comparison between UIP and fNSIP, and between death and survival groups

Of 50 cases in our study, 9 cases had one biopsy sample and 41 patients had multiple biopsy samples. We divided all the samples into four groups based on biopsied sites (i.e. upper lobe, middle lobe, lingula and lower lobe). Nineteen per cent were obtained from upper lobe, 21% from middle lobe, 12% from lingula and 48% from lower lobe.

In UIP patients, %FF (0.266 ± 0.233) and FF/cm^2 (7.07 ± 45.12) were significantly higher than in fNSIP patients: %FF (0.045 ± 0.054) ($P < 0.0001$, Fig. 2a) and FF/cm^2 (1.69 ± 2.07) ($P < 0.0001$, Fig. 2b).

We investigated the area of normal lung, fibrosis and honeycomb lung by reviewing the available samples of 30 patients. In fNSIP, the area of normal lung to fibrosis was 40.7 ± 29.4% and 59.3 ± 29.4%, respectively, and in UIP, 36.5 ± 34.3% and 63.5 ± 34.3%, respectively (not significant). Among fibrosis, the honeycombing area was 4.8 ± 10.3% in fNSIP and 24.6 ± 24.7% in UIP, a significant difference ($P = 0.0284$).

Since follow up was done in all patients, we divided these into those who died (death group, $n = 13$) and those who survived (survival group, $n = 37$) and compared %FF and FF/cm^2 between the groups. The mean follow-up period for the survival group and the mean survival period for the death group were 55.2 months and 33.6 months, respectively. %FF in the death group (0.292 ± 0.259) was significantly higher than in the survival group (0.101 ± 0.106) ($P = 0.0020$, Fig. 3a). FF/cm^2 in the death group (7.45 ± 6.17) was also higher than in the survival group (3.16 ± 3.49) ($P = 0.0034$, Fig. 3b). Significant differences in %FF and FF/cm^2 between the two groups were also demonstrated when only UIP patients were analysed, but results for fNSIP patients only showed no significance (data not shown).

We reviewed the prognosis and clinical course for all patients enrolled in this study to draw the Kaplan–Meier curve. Significant prognostic difference between UIP and fNSIP was demonstrated by log–rank test ($P = 0.0233$, Fig. 4).

Correlation between FF and respiratory function parameters

The initial value of %VC has an inverse correlation with FF/cm^2 when UIP and fNSIP patients were analysed together ($rs = 0.211$, Fig. 5a). Also, as shown in Figure 5b,c, %ΔVC was correlated with both %FF and FF/cm^2 ($rs = 0.333$ and 0.294). %ΔDL_{CO} was correlated only with %FF ($rs = 0.268$, Fig. 5d). However, the initial value of %DL_{CO} did not have any obvious correlation with FF. When the UIP and fNSIP patients were analysed separately, no significant correlations were observed (data not shown).

DISCUSSION

This is the first study to examine the area and the number of FF in both UIP and fNSIP samples obtained from surgical lung biopsy. Based on the assumption that FF is a common histological finding in both UIP and fNSIP that reflects disease progression, we examined the relationship between the extent of FF and the respiratory function in a combined group of patients with UIP or fNSIP. A correlation between FF and both respiratory function and

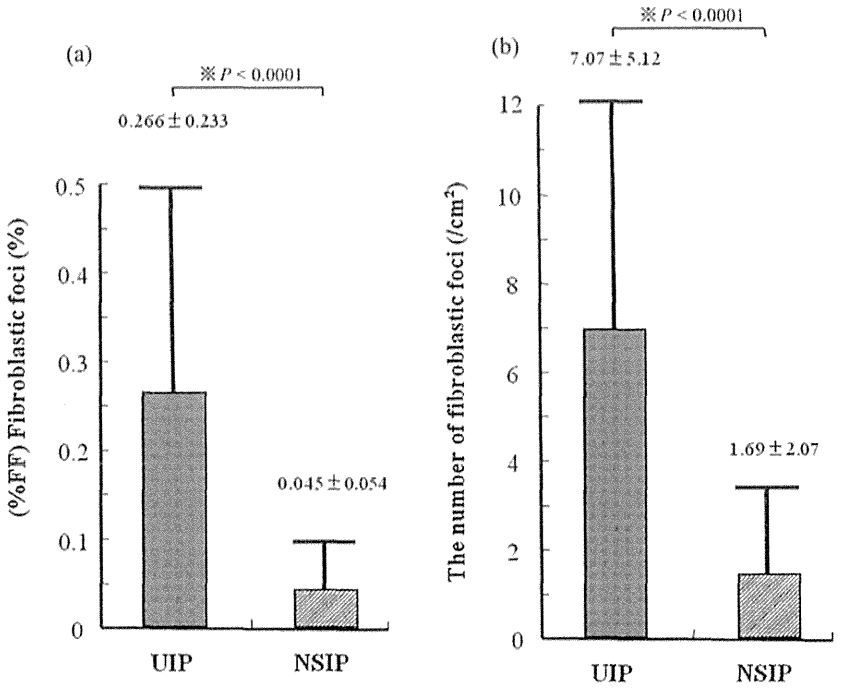

Figure 2 Quantitative analysis of fibroblastic foci in the whole specimen. (a) The areal percentage of fibroblastic foci was significantly higher in usual interstitial pneumonia (UIP) group than in non-specific interstitial pneumonia (NSIP) group. (b) The number of fibroblastic foci was significantly higher in UIP group than in NSIP group. Data are mean ± standard deviation.

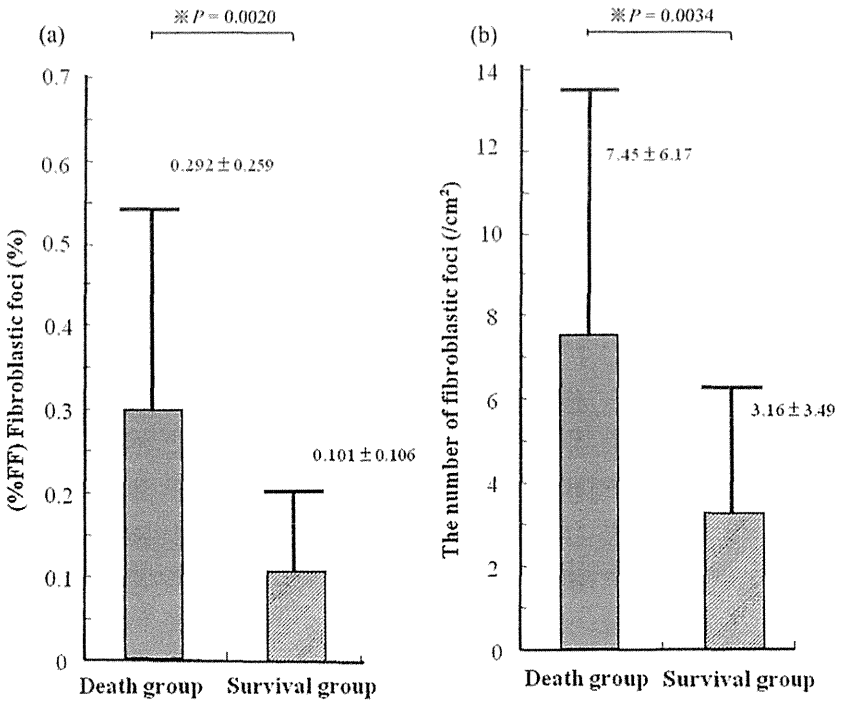

Figure 3 Quantitative analysis of fibroblastic foci of all cases comparing death group and survival group. (a) The areal percentage of fibroblastic foci was significantly higher in death group than in survival group. (b) The number of fibroblastic foci was significantly higher in death group than in survival group. Data are mean ± standard deviation.

prognosis was demonstrated. Our result revealed that the decline in VC and DL_{CO} was significantly correlated with the increasing area and/or number of FF. Furthermore, the group of patients who died had a higher degree of FF compared with the survival group.

There have been various attempts to relate disease progression to the extent of FF.[1–7] Most of these studies were performed using UIP samples. However, fNSIP accepts some temporal range in lung injury, allowing the presence of some FF coexistent with old fibrosis (e.g. honeycombing).[9–11] These ambiguous criteria might be confusing when making a differentiation between UIP and fNSIP. Furthermore, to what extent FF are considered to exist in the case of an fNSIP pattern remains unclear.

Practically, lung biopsy tends to be performed in patients whose computed tomography patterns are non-UIP-like, and patients with computed tomogra-

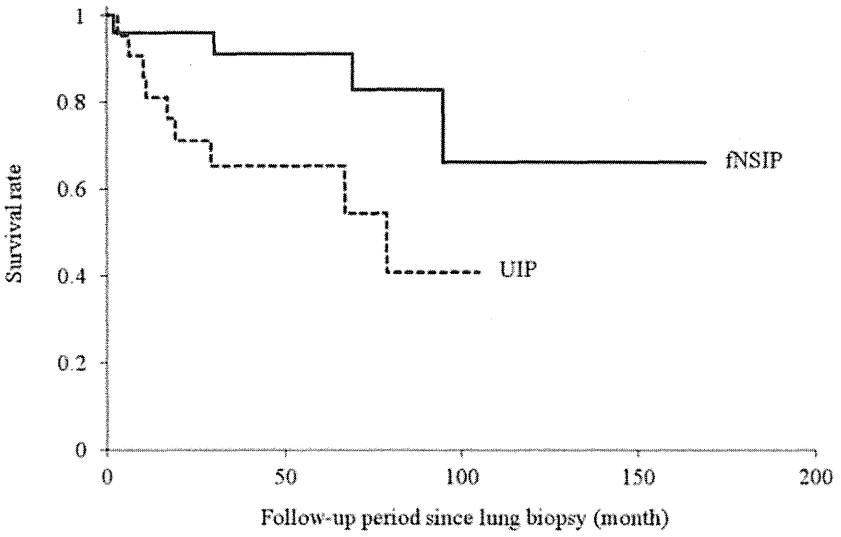

Figure 4 Kaplan–Meier curve of patients enrolled in the study. Patients with fibrotic non-specific interstitial pneumonia (fNSIP) survived significantly longer than those with usual interstitial pneumonia (UIP) by log–rank test ($P = 0.0233$).

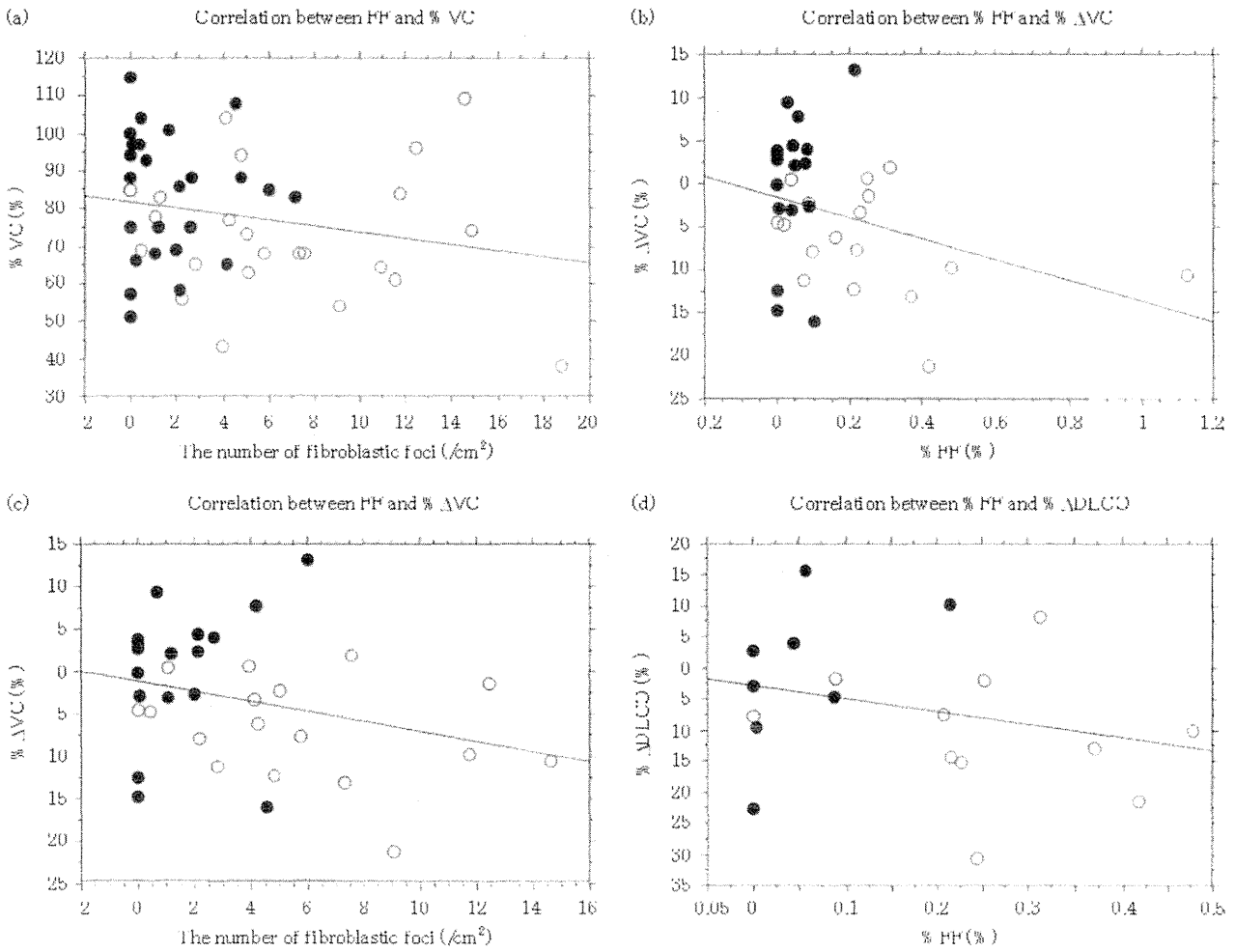

Figure 5 Correlation between pulmonary function and fibroblastic foci (FF). %FF and the number of FF correlated inversely with (a) % vital capacity (VC) and (b,c) %ΔVC (a: $rs = 0.211$; b: $rs = 0.333$; c: $rs = 0.294$); (d) %Δ diffusing capacity of carbon monoxide correlated only with %FF ($rs = 0.268$). (·) fNSIP, fibrotic non-specific interstitial pneumonia; (·) UIP, usual interstitial pneumonia.

phy patterns typical of UIP rarely have the opportunity to receive a lung biopsy. This may cause difficulty in histologically categorizing interstitial pneumonia. Furthermore, in our fNSIP patients, the time between onset of symptoms and the visit to the hospital was longer than previously reported.[12] It is therefore possible that some cases classified as fNSIP in our study could be diagnosed as idiopathic pulmonary fibrosis after consensus clinical, radiological and pathological review. According to the report of an American Thoracic Society project,[13] a high-resolution computed tomography showing a pattern typical of UIP, such as honeycombing in the subpleural areas of the bilateral lower lobes, could lead to a diagnosis of idiopathic pulmonary fibrosis even when a surgical lung biopsy shows the histological pattern of fNSIP.

Latsi and co-workers[14] analysed the prognosis of idiopathic fibrosing interstitial pneumonia, demonstrating that the distinction between UIP and fNSIP provides no additional prognostic information once serial pulmonary function trends have been taken into account at 12-month follow up. Furthermore, when the initial DL_{CO} was less than 35% predicted, there was no significant difference in outcome between UIP and fNSIP, suggesting that the pathological pattern is less important for prognosis in the setting of relatively severe impairment of lung function. Similarly, patients who exhibit more than 10% decrease in forced VC have a poor outcome, whether they are classified as UIP or fNSIP.[15] These data show the role of respiratory function in addition to histological classification as a prognostic indicator. Our results indicate the significance of FF related to deteriorating pulmonary function in fibrosing interstitial pneumonia consisting of UIP and fNSIP.

It is also known that FF represent a measure of UIP activity, being associated with a poor prognosis, and several studies demonstrate the clinical importance of FF as a prognostic factor.[1–3] Nicholson and co-workers[3] demonstrated that an increasing semiquantitative FF score was independently associated with greater declines in forced VC and DL_{CO} at both 6 months and 12 months. King and co-workers[2] demonstrated an association between increasing FF, including the results of semiquantitative grading of the number of FF, and decreased survival in UIP. These data suggest that quantifying the number of these lesions in a biopsy specimen provides additional prognostic information. Moreover, Enomoto and co-workers[7] reported quantitative analysis of FF in UIP, showing that the quantitative fibroblast score was a highly significant predictor of outcome in combined analysis of patients with idiopathic pulmonary fibrosis and those with collagen vascular disease. Our results are almost entirely in agreement with these previous investigations. However, the %FF in this study is definitely lower, even in UIP samples, than that reported by Enomoto *et al.* Their analysis differed from ours in that 10 randomly selected fields were chosen for analysis. These differences in methods for selecting microscopic fields for study may cause the difference in the %FF data.

We have provided evidence of a correlation between FF and pulmonary function in both UIP and fNSIP patients. This result indicates that FF may be another factor predicting the prognosis of fibrosing interstitial pneumonias including both UIP and fNSIP. Increasing degrees of FF and the decline of forced VC or DL_{CO} might be important prognostic predictors for fNSIP as well as for UIP. Given the poor benefit achieved with immunosuppressive or anti-inflammatory agents, these data suggest that future therapies should be aimed at preventing or inhibiting the fibroproliferative response.

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INTERNAL MEDICINE

□ CASE REPORT □

Combined Unclassifiable Interstitial Pneumonia and Emphysema: A Report of Two Cases

Nobuhiko Nagata[1], Kentaro Watanabe[2], Michihiro Yoshimi[3], Hiroshi Okabayashi[4], Katsuo Sueishi[5], Kentaro Wakamatsu[6], Hiroyuki Kumazoe[7] and Yoshinori Nagamatsu[8]

Abstract

We herein report two cases of combined pulmonary fibrosis and emphysema (CPFE), whose histological patterns of lung pathology could not be categorized into any subset of idiopathic interstitial pneumonias (IIPs). Case 1 was a 62-year-old man, who presented with dyspnea on exertion and cough. Case 2 was a 51-year-old man with a dry cough. The CT findings of both cases fit the definition of CPFE. Surgical lung biopsies of both patients revealed alveolar septal widening due to collagen deposition, with emphysema and respiratory bronchiolitis mainly in the subpleural parenchyma. These cases suggest that the fibrosis of CPFE includes smoking-related interstitial fibrosis other than the known histological patterns of IIPs.

Key words: interstitial pneumonia, pulmonary fibrosis, pulmonary emphysema, smoking

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Introduction

The term 'unclassifiable interstitial pneumonia' is assigned if the histology of fibrosis does not fit any subset of the existing classification of idiopathic interstitial pneumonias [IIPs (1)]. Combined pulmonary fibrosis and emphysema (CPFE), originally described by Cottin et al. (2), is defined by imaging findings. There is a well-established relationship between smoking and CPFE, but the histological patterns of its fibrosis have not been fully examined. We herein report two patients with CPFE whose fibrotic lungs were biopsied, but the histological patterns could not be categorized into any existing IIPs subset.

Case Reports

Case 1

In January, 2008, a 62-year-old man visited our hospital presenting with gradually increasing dyspnea on exertion and a cough that had lasted for five years. He had smoked two packs of cigarettes a day for 42 years and was obese (height, 162 cm; weight, 91.1 kg). Chest auscultation revealed fine crackles in both lung bases. Neither cyanosis nor clubbing was noted. Blood tests showed mild increases in the WBC count (11.4×10^9 cells/L) and the CRP (0.68 mg/dL), KL-6 (865 IU/mL), SP-D (176 ng/mL) and SP-A (264 ng/mL) levels. The results of an arterial blood gas analysis were normal, with a PaO_2 of 90.4 torr, a $PaCO_2$ of 40.6 torr and a pH of 7.433. Pulmonary function tests showed a decreased diffusing capacity for carbon monoxide (DL_{CO} and $DL_{CO/VA}$ of 78.1% and 79.5% of the predicted values, respec-

[1]Department of Respiratory Medicine, Fukuoka University Chikushi Hospital, Japan, [2]Department of Respiratory Medicine, Fukuoka University School of Medicine, Japan, [3]Department of Respiratory Medicine, National Hospital Organization Fukuoka-Higashi Medical Centre, Japan, [4]Department of Surgery, National Hospital Organization Fukuoka-Higashi Medical Centre, Japan, [5]Department of Pathology, National Hospital Organization Fukuoka-Higashi Medical Centre, Japan, [6]Department of Respiratory Medicine, National Hospital Organization Omuta Hospital, Japan, [7]Department of Radiology, National Hospital Organization Omuta Hospital, Japan and [8]Department of Surgery, National Hospital Organization Omuta Hospital, Japan
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Correspondence to Dr. Nobuhiko Nagata, nbnagata@fukuoka-u.ac.jp

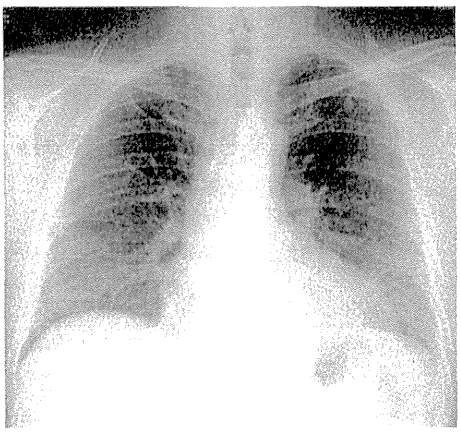

Figure 1. A chest X-ray of Case 1 showing hyperlucency in both upper lung fields and reticular shadows in both lower lung fields.

tively) with a normal vital capacity (VC, 106.2% of the predicted value) and a normal forced expiratory volume in one second (FEV1). Chest X-rays showed hyperlucency in both upper lung fields and reticular shadows in both lower lung fields (Fig. 1). High-resolution computed tomography (HRCT) confirmed low-attenuation areas primarily in the outer zones of both upper lung fields, and diffuse reticular and ground-glass opacities in the subpleural areas of both lung bases (Fig. 2, left column). The percentage of emphysema of the whole lung field on CT measured by a 3D visualization system (AZE Virtual Place, Fujin AZE Ltd., Tokyo, Japan) was 3.7%. Surgical lung biopsy of the left S2 and S8 was performed by video thoracoscopy. The histological findings revealed alveolar septal widening due to collagen deposition with emphysema and respiratory bronchiolitis. Fibrosis was present in the subpleural parenchyma, and surrounded not only the enlarged airspaces, but also the non-emphysematous parenchyma (Fig. 2, right panel). Four years after the initial visit to our hospital, his chest X-ray and pulmonary function test revealed no deterioration.

Case 2

In March 2012, a 51-year-old man visited our hospital presenting with a four-month history of a persistent dry cough. He had smoked two packs of cigarettes a day for 31 years. Fine crackles were audible in both lung bases. Neither cyanosis nor clubbing was noted. Blood tests were unremarkable, with a normal KL-6 (407 IU/mL) level and a normal SpO_2 (97%). Pulmonary function tests showed a normal VC (106.2% of predicted value) and FEV1. Chest X-rays showed hyperlucency in both upper lung fields and reticular shadows in both lower lung fields (Fig. 3). HRCT revealed low-attenuation areas primarily in the outer zones of both upper lung fields, and diffuse reticular and ground-glass opacities with traction bronchiectasis in the subpleural areas of both lung bases (Fig. 4, left column). The percentage of emphysema of whole lung field on CT measured by the 3D visualization system (AZE Virtual Place, Fujin) was 8.1%.

The patient was suspected to have smoking-related interstitial lung disease. A follow-up CT showed a gradually increasing focal density in the right lower lobe, while the other findings revealed no changes. A positron emission tomography (PET) scan demonstrated high FDG uptake in the nodular density noted in the CT image. He was diagnosed with a nodular lesion in the right lower lobe and interstitial lung disease. A right lower lobectomy was performed in November 2012. The pathological examination of the nodular lesion confirmed granulomatous inflammation with multinucleated giant cells. Although no acid-fast bacilli were identified in the lesion, incidental infection with non-tuberculous mycobacteria, such as *Mycobacterium avium-intracellulare*, was suspected. The pathology of the interstitial lung disease was similar to that of Case 1 (Fig. 4, right panel).

Discussion

Although diseases consistent with CPFE had been reported in case reports and series in the past (3-5), it began to attract attention when Cottin et al. described CPFE in 61 patients with both emphysema in the upper zones and diffuse parenchymal lung disease with fibrosis in the lower zones of the lungs on chest CT (2). The nature of the fibrosis was not determined, in those cases, because the pathological features were examined in only eight patients, five of whom had been reported to have usual interstitial pneumonia (2). Based on the pathological analyses of resected lungs from smokers with lung cancer who showed no signs or symptoms related to fibrosis, pathologists have found that interstitial fibrosis in smokers is histologically distinct from that of IIPs. These findings were classified as airspace enlargement with fibrosis (6), smoking-related interstitial fibrosis (SRIF) (7) or respiratory bronchiolitis-associated interstitial lung disease with fibrosis (8) by different pathologists. Most importantly, these lesions show a stable clinical course, rather than deteriorating, as does idiopathic pulmonary fibrosis. The relationship of these lesions with CPFE is unknown.

The CT findings of our two cases fit the definition of CPFE; however, the histological patterns of fibrosis did not fit any IIP subset. They differed from the usual interstitial pneumonia (UIP) histological patterns because there was no patchwork pattern, temporal heterogeneity of fibrosis or remodelling of the lung architecture, such as honeycombing and scarring. They also differed from nonspecific interstitial pneumonia (NSIP), because the fibrosis was localized in the subpleural lung parenchyma, rather than the more diffuse fibrosis in NSIP, and because the fibrosis surrounded the enlarged airspaces, and little inflammatory infiltration was seen in the fibrously thickened alveolar septa. The pathological features of the two cases reported here are similar to the smokers' fibrosis described above, but are more likely to fit the definition of SRIF, as reported by Katzenstein et al. (6). Although desquamative interstitial pneumonia and respira-

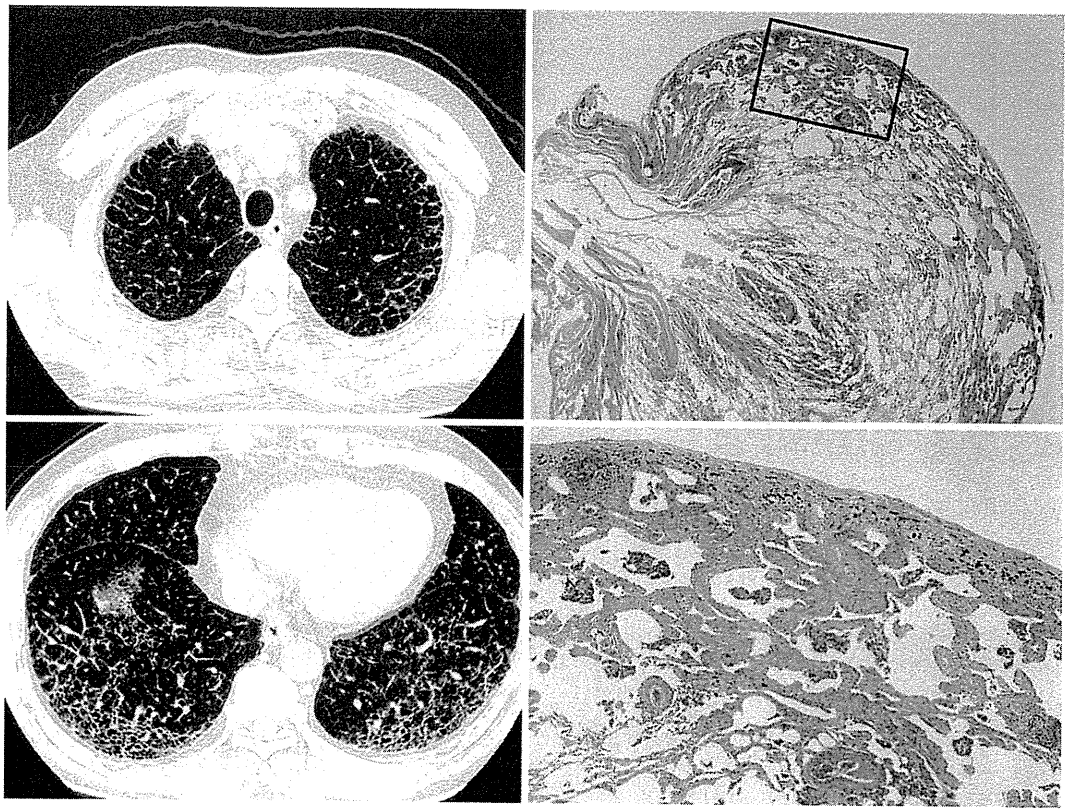

Figure 2. A chest high-resolution computed tomography image (left column) and photomicrograph of the biopsied lung tissue (right column) from Case 1. The upper lung fields showed low-attenuation areas primarily in the subpleural area (upper left), while diffuse reticular and ground-glass opacities were noted in the subpleural area of both lung bases (lower left). The photomicrograph revealed alveolar septal widening due to collagen deposition, with emphysema and respiratory bronchiolitis. The fibrosis is seen in the subpleural parenchyma, and surrounds not only the enlarged airspaces, but also the non-emphysematous parenchyma. The right lower photomicrograph shows a higher magnification of the boxed area of the right upper one photograph (Hematoxylin and Eosin staining, original magnification: right upper, 14×; right lower, 56×).

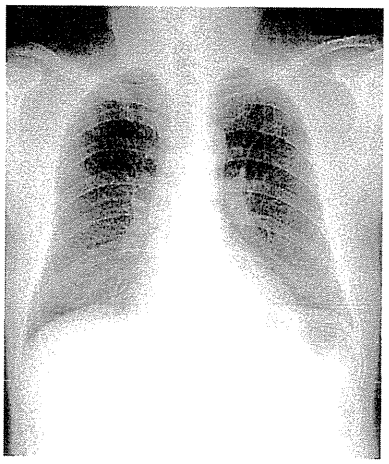

Figure 3. A chest X-ray from Case 2 showing hyperlucency in both upper lung fields and reticular shadows in both lower lung fields.

tory bronchiolitis-associated interstitial lung disease are subsets of IIPs (1) with characteristic clinical symptoms and signs, SRIF has not yet been recognized as a clinically-established interstitial pneumonia with symptoms or impaired respiratory function.

SRIF was proposed based on a pathological study of lobectomy specimens excised for neoplasm from cigarette smokers with no clinical evidence of interstitial lung disease (7), and its clinical significance is unknown at present. Both patients in this report visited the hospitals because of subjective symptoms such as dyspnoea on exertion and cough (Case 1) or dry cough (Case 2). Moreover, Case 1 had impairment of the diffusing capacity and elevation of the levels of KL-6, SP-A and SP-D. The possibility that the patients' symptoms and impaired diffusing capacity were solely caused by emphysema and the fibrous pathology that we reported to only represent trivial fibrotic lesions in smokers cannot be completely ruled out. However, the attending physicians in our cases diagnosed the patient's illness as interstitial lung disease as the primary diagnosis, and performed surgical lung biopsy or lobectomy for the diagnosis of interstitial lung disease. Therefore, we think that the fibrotic lesion noted in our patients contributed at least

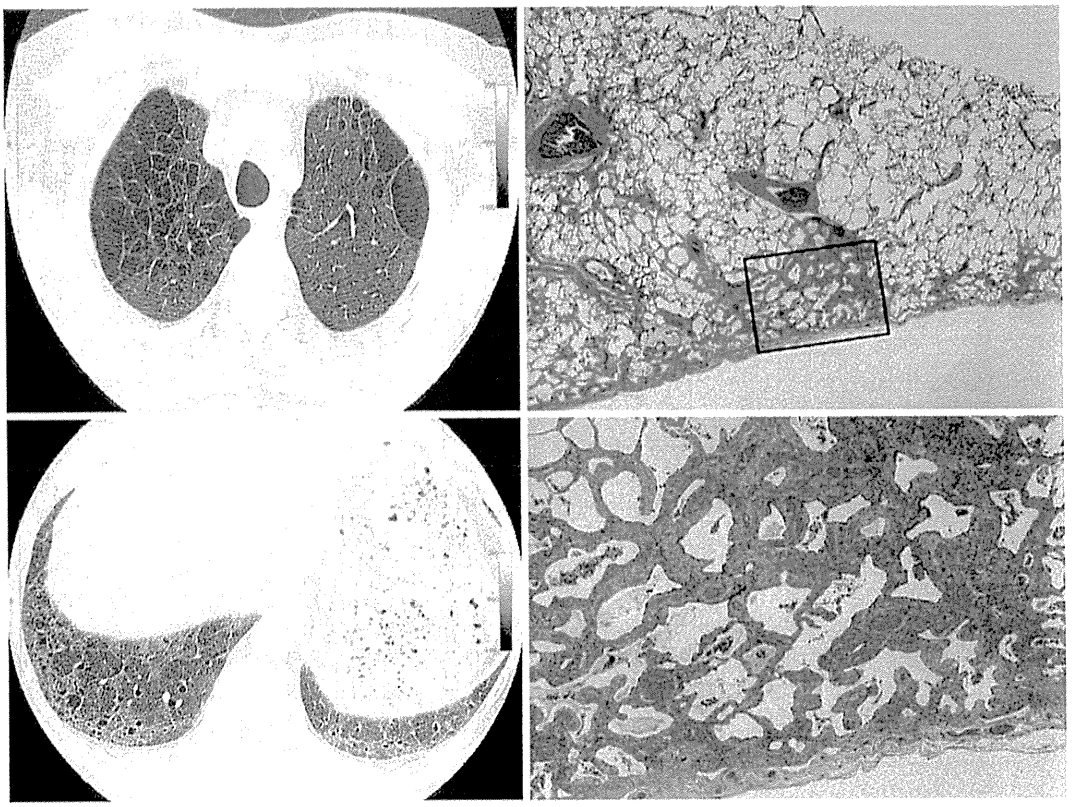

Figure 4. A chest high-resolution computed tomography image (left column) and photomicrograph of the biopsied lung tissue (right column) from Case 2. The upper lung fields showed low attenuation areas mainly in the subpleural area (upper left), while diffuse reticular and ground-glass opacity with traction bronchiectasis were noted in the subpleural areas of both lung bases (lower left). The photomicrograph revealed alveolar septal widening due to collagen deposition, with emphysema and respiratory bronchiolitis. The fibrosis occurred in the subpleural parenchyma, and surrounded not only the enlarged airspaces of emphysema but also non-emphysematous parenchyma. The right lower photomicrograph shows a higher magnification of the boxed area of the right upper photograph (Hematoxylin and Eosin staining, original magnification right upper 14×; right lower 56×).

partly to the patients' clinical features. Yousem reported similar pathology in terms of respiratory bronchiolitis-associated interstitial lung disease with fibrosis from the study of nine cases with clinical and radiological chronic interstitial lung disease (8).

The chest X-rays and pulmonary function tests in Case 1 revealed no deterioration during the four years after lung biopsy, and the chest CT of Case 2 did not show worsening of the interstitial opacities during the 1.5 year follow-up period before lung biopsy. These clinical features are inconsistent with idiopathic pulmonary fibrosis and fibrosing NSIP.

In this report, we showed that SRIF is a pathological counterpart of pulmonary fibrosis in CPFE. In addition to the CT findings, the histological patterns in the lower lobes associated with CPFE are various and complicated, especially in patients with concomitant emphysema. Further studies are needed to clarify the histological nature of the fibrosis in CPFE and the clinical significance of SRIF. There may be other features, in addition to SRIF, in the lungs with CPFE, which cannot be classified as known histological patterns of IIPs. We therefore believe that the histology of the reported cases is one of the variety of smoking-related interstitial lung diseases.

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

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ORIGINAL ARTICLE

Elevation of serum C-reactive protein predicts failure of the initial antimicrobial treatment for febrile neutropenia with lung cancer

Takemasa Matsumoto · Masaki Fujita · Takako Hirota · Satoshi Takeda · Ryousuke Hirano · Junji Uchino · Taishi Harada · Kentaro Watanabe

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Abstract Febrile neutropenia frequently develops after chemotherapy, and the prompt administration of antimicrobial agents is required for treatment. In the present study, we searched for predictive factors for the failure of the initial antimicrobial agents used for febrile neutropenia (FN) in patients with lung cancer. Sixty FN patients treated in our ward from June 2005 to May 2011 were retrospectively analyzed. The definition of FN and the response to antimicrobial agents were determined by the Japanese guidelines. We divided the FN patients into two groups by their response to the initial antimicrobial agents. Next, the characteristics of the two groups were compared. The Multinational Association of Supportive Care in Cancer (MASCC) score did not differ between the two groups. The non-responder group demonstrated significant elevation of serum C-reactive protein (CRP) level. A multivariate analysis demonstrated that a CRP level higher than 10 mg/dl is an independent risk factor for the failure of initial antimicrobial agents for FN with lung cancer (OR 11.0, 95 % CI 1.635–74.5). When the CRP score was added to the MASCC score, the scoring system could more precisely predict the failure of initial antimicrobial agents in patients with lung cancer who developed febrile neutropenia.

Keywords Risk factor · Febrile neutropenia · Lung cancer · CRP

T. Matsumoto · M. Fujita (✉) · T. Hirota · S. Takeda · R. Hirano · J. Uchino · T. Harada · K. Watanabe
Department of Respiratory Medicine, Fukuoka University Hospital, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
e-mail: mfujita@fukuoka-u.ac.jp

Introduction

Febrile episodes in cancer patients with chemotherapy-induced neutropenia can be life threatening and thus require the prompt administration of empiric, broad-spectrum antimicrobial agents. This events have been defined as febrile neutropenia (FN). FN in cancer patients is associated with considerable morbidity, mortality, and cost [1]. An excellent guideline for FN has been published and updated by the Infectious Diseases Society of America (IDSA) [2–5]. FN is characterized by (i) a polymorphonuclear neutrophil count <500/μl, or neutrophils <1,000/μl with an expected drop to <500/μl, and (ii) a temperature >38.3 °C at one point or ≥38.0 °C for 1 h. In Japan, the definition of FN was modified in terms of the second item as (ii) a temperature of ≥37.5 °C at the axillary fossa according to routine measuring method in Japan [6, 7].

According to the guidelines, FN patients are divided into two groups, a low-risk group and a high-risk group, depending on the severity of their FN, for selection of the initial antimicrobial agents. The Multinational Association of Supportive Care in Cancer (MASCC) proposed a scoring system that could be used as a method to select low-risk patients. This scoring system (MASCC score) consists of the severity of disease, the presence of hypotension, chronic obstructive pulmonary disease (COPD), dehydration, solid organ malignancy or history of fungal infection, outpatient care, and age younger than 60 years old. A MASCC score ≥21 was identified to be associated with low risk, with a positive predictive value of 91 %, specificity of 68 %, and sensitivity of 71 % [8]. High-risk patients require hospitalization with empirical antimicrobial agent therapy: monotherapy with an anti-pseudomonal β-lactam agent, such as cefepime, a carbapenem, or piperacillin-tazobactam. If antimicrobial resistance is

suspected or proven, aminoglycosides, fluoroquinolones, and/or vancomycin may be added to the initial regimen. On the other hand, low-risk patients are treated with oral antimicrobial agents in an outpatient setting. Ciprofloxacin in combination with amoxicillin-clavulanate is recommended for oral empirical treatment. Alternatively, monotherapy with an antipseudomonal beta-lactam antibiotic, such as cefepime, a carbapenem, or piperacillin-tazobactam, could be selected in a hospital setting.

The FN guidelines are intended to cover both patients with solid tumors and those with hematological malignancies, although there are some differences in the characteristics of the risk factors between the two groups, including the duration of neutropenia, use of a central venous line, and the incidence of complications of COPD. In particular, the mortality rate of FN patients with lung cancer is clearly lower compared to that of patients with hematological malignancies in a previous report [9]. Therefore, the goal for treating FN with lung cancer should be prevention of failure of the initial antimicrobial agents, because failure of the initial antimicrobial agents leads to a longer hospitalization and higher cost. Thus, we focused this study on a search for predictive factors for failure of the initial antimicrobial agents used for FN with lung cancer.

Patients and methods

Patients and data collection

This study was retrospective, and the data were collected from medical records. Patients with lung cancer who developed FN after receiving anticancer chemotherapy in our ward between June 1, 2005 and May 31, 2011 were enrolled. The definition of FN, and the response to antimicrobial agents, were determined by Japanese guidelines [7]. Briefly, FN was defined as follows: (1) a granulocyte count <1,000/μl, including polymorphonuclear leukocytes and band forms, and (2) a fever higher than 37.5 °C as a result of the treatment. The response to therapy was defined as fever resolution for 5 consecutive days without a serious medical complication. Changes in antimicrobial agents and the persistence of the fever were regarded as evidence that the infection was refractory to the empiric choice of antimicrobial agent(s).

The relationships among such factors as patient background, patient condition at the time of onset, chemotherapy regimen, response to antimicrobial agents, and the prognosis of FN were analyzed. We classified the FN patients into two groups: responders and non-responders to the initial antimicrobial agents. We compared the data from the two groups to identify the factors that could predict response to the initial antimicrobial agents.

This study was approved by the institutional review board of Fukuoka University Hospital.

Statistical analyses

The differences between responders and non-responders were screened by Student's t test or Fisher's exact test for classified variations. A logistic regression analysis was applied to the derivation set to determine the association between the covariates and outcomes to the odds ratios (ORs) with 95 % confidence intervals (95 % CIs). Univariate analyses were performed to select the first set of covariates to be tested for inclusion in a multivariate model, in which all covariates with a P value less than 0.2 by a simple logistic regression analysis were included. $P < 0.05$ was considered to be statistically significant. These statistical analyses were performed using the Stata Mate version 6 software package.

Results

Sixty of the 765 patients treated with chemotherapy for lung cancer experienced a neutropenic fever episode, and 2 of these patients died. The characteristics of the patients are described in Table 1. Their median age was 68 years, and 45 (75 %) patients were male: 44 (48 %) patients had small cell lung cancer, 25 (36.7 %) patients had COPD, 28 (46.7 %) of the 60 patients developed FN during their first round of chemotherapy, and 56 (63 %) patients were treated with a platinum-based doublet regimen. Docetaxel was administered most frequently as a single agent. With regard to the MASCC score, 40 patients were considered to be in the low-risk group and 20 patients in the high-risk group. There were no cases of pneumonia, urinary tract infection, or other organ infection.

We classified the FN patients into two groups, responders and non-responders, by their response to the initial antimicrobial agents used for treatment of their FN. Forty-seven patients (78.3 %) showed a response to the initial antimicrobial agents (responders) and 13 patients (21.7 %) were resistant (non-responders). Although 36 patients were examined for sputa culture or blood culture, no causative organisms could be identified. The patient characteristics separated by the treatment response are shown in Table 1. To identify the risk factor(s) for failure of the initial antimicrobial agents in lung cancer patients with FN, we compared the data of responders with those of non-responders. The results of a single logistic regression analysis at the time of FN onset are shown in Table 2. There were significant differences in the serum C-reactive protein (CRP) level between responders and non-responders.