the BLM challenge, resulted in a significant but borderline difference with a *P*-value of 0.0495 (Fig. 3). An increase in the study size may produce a result with clearer statistical significance.

The main adverse effects of TJ-41 in humans are diarrhoea, appetite loss and/or hypokalaemia. Although a dose of 1 g/kg of TJ-41 was used, which was roughly equivalent to a dose six to seven times greater than the daily human dose, mice on the TJ-41-containing diet gained weight to the same degree as control mice (data not shown). Furthermore, no difference was seen in serum potassium concentrations between the TJ-41-treated and untreated mice (data not shown).

The results of the present study indicate that treatment with TJ-41 partially prevents experimental lung fibrosis through correction of the Th1/Th2 imbalance skewed to Th2. However, the precise mechanism by which TJ-41 modulates Th1/Th2 cytokine production remains unclear. Further studies to elucidate this issue are needed.

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Comparative Clinicopathology of Obliterative Bronchiolitis and Diffuse Panbronchiolitis

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Key Words
Diffuse panbronchiolitis · Obliterative bronchiolitis · Pathology · Prognosis

Abstract
Background: The progressive airway obliteration caused by obliterative bronchiolitis (OB) has been widely noted in the world. In contrast, the obstructive respiratory disorder caused by diffuse panbronchiolitis (DPB) has been reported mainly from Japan. Therefore, there might be a considerable overlap between OB and DPB in Japan. ***Objectives and Methods:*** To clarify the clinicopathological similarities as well as the differences between OB and DPB, 15 patients with OB and 6 patients with DPB were evaluated clinicopathologically. ***Results:*** The underlying disorders in OB were graft-versus-host disease (GVHD) in 7, rheumatoid arthritis in 3, Kartagener's syndrome in 2, and polymyositis/dermatomyositis, non-tuberculous mycobacterial disease and mycoplasmal pneumonia in one each. The lung pathology demonstrated that the primary obstructive lesions were in the membranous bronchioli in OB. In contrast, they were confined to the respiratory bronchioli in DPB. In addition, OB was classified into two major morphologic types, namely, constrictive and cellular. Clinical manifestations included cough and/or dyspnea in 13 with OB and in 6 with DPB, chronic parasinusitis in 3 with cellular OB and in 6 with DPB. The pulmonary function tests revealed obstructive impairments in all patients with OB and DPB. The chest CT images showed small centrilobular nodules in 64% of those with OB and in all with DPB. The prognosis of constrictive OB was worse than that of cellular OB and DPB. ***Conclusions:*** This study demonstrated that histopathologically marked differences existed between OB and DPB, although striking similarities in clinical manifestations were also noted in both diseases.

Introduction

The association of progressive airway obliteration with obliterative bronchiolitis (OB) has been noted in patients with various clinical settings worldwide [1–5]. In contrast, the incidence of diffuse panbronchiolitis (DPB), a disorder principally affecting the respiratory bronchioli and causing a severe obstructive respiratory impairment, has been reported mainly in Oriental countries such as Japan and Korea [6–8]. Therefore, there might be a considerable overlap between OB and DPB in Japan. The aim of this study was to clarify the clinicopathological similarities as well as the differences between OB and DPB.

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Subjects and Methods

From 1983 through 2004, 15 patients (6 males and 9 females with a mean age of 47 years) were diagnosed as having OB, and 6 patients (5 males and 1 female with a mean age of 48 years) were diagnosed as having DPB. All patients underwent chest radiographs, pulmonary function tests (PFTs) and video-assisted thoracoscopic surgery or postmortem examination as diagnostic procedures.

DPB was diagnosed using the clinical diagnostic criteria established with the aid of the Ministry of Health and Welfare of Japan [9]: (1) cough, sputum and shortness of breath on exertion, (2) presence of chronic parasinusitis, (3) chest X-ray or computed tomography (CT) scan findings of diffuse scattered granular shadows or small centrilobular nodules in both lung fields and hyperinflation, and (4a) coarse crackles with wheeze and/or rhonchi on the chest, (4b) impaired pulmonary function with decreased forced expiratory volume in 1 s ($FEV_{1.0}$%, below 70%) and hypoxemia (below 80 mm Hg), and (4c) elevation of cold hemagglutinin titer. To establish the diagnosis, at least one to three of these criteria must be met. In making the diagnosis of DPB, histological studies have been applied as much as possible. Chronic bronchitis, bronchiectasis, primary ciliary dyskinesia, cystic fibrosis and OB have been carefully excluded.

OB was mainly diagnosed based on the clinical diagnostic criteria established by the International Society for Heart and Lung Transplantation [10], and the histopathological findings of the lung: (1) cough, sputum and shortness of breath, (2) radiographic findings of hyperinflation or mosaic perfusion by chest X-ray or high-resolution computed tomography (HRCT), and (3a) wheeze and/or rhonchi on the chest, or (3b) impaired pulmonary function with decreased $FEV_{1.0}$%. To establish the diagnosis of OB, histological studies of the lung have been applied in all cases.

Morphological Analysis

Out of these 21 patients, 4 underwent postmortem examination, 16 received biopsy under video-assisted thoracoscopic surgery and 1 had both video-assisted thoracoscopic surgery and autopsy. The lung specimens were fixed with 10% formaldehyde and embedded in paraffin from which 3-μm-thick sections were cut and stained with hematoxylin-eosin and Elastica van Gieson. Those sections were mounted in aqueous mounting medium and observed by light microscopy to determine the characteristics of the bronchiolitis.

Pulmonary Function Tests

Lung volume, $FEV_{1.0}$, maximal midexpiratory flow and blood gas were measured according to the standard methods with a Chestac-55V (Chest, Tokyo, Japan) and ABL510 (Radiometer, Copenhagen, Denmark).

X-Ray Images

Chest radiographs and chest CT images before treatment were evaluated.

Criteria for Assessment of the Responses to Therapy

The responses to treatment and prognoses for OB and DPB were defined as follows. Improved response to therapy was defined as two or more of the following criteria: (1) an improvement in symptoms, specifically an increase in the capability of exertion without becoming intolerant due to breathlessness, or a decrease in the frequency and severity of cough and sputum; (2) improvement in parenchymal abnormalities on chest HRCT scan, and (3) physiological recovery defined by one or more of the following criteria: (a) an increase in $FEV_{1.0} \geq 200$ ml and (b) an increase in PaO_2 of ≥ 10 mm Hg from the previous level at rest.

Unchanged response to therapy was defined as (1) persistence of parenchymal abnormalities on chest HRCT scan, and (2) physiological stability defined by (a) a change in $FEV_{1.0}$ not greater than 200 ml and/or (b) an increase in PaO_2 of ≤ 10 mm Hg from the previous level at rest.

A failure in response to therapy was defined as two or more of the following criteria: (1) worsening of symptoms, especially dyspnea, or cough and sputum; (2) progression in parenchymal abnormalities on chest HRCT scan, and (3) physiological deterioration defined by (a) a decrease in $FEV_{1.0} \geq 200$ ml, and/or (b) a decrease in PaO_2 of ≥ 10 mm Hg from the previous level at rest.

The responses to treatment were assessed according to the above-described criteria, and prognoses were evaluated.

Statistical Analysis

Clinical findings, results of PFTs, X-ray images, pathological findings and prognoses were summarized and compared between OB and DPB. Statistical differences of the data between OB and DPB were assessed by Student's t test. The level of significance was set to a p value of less than 0.05.

Results

Demography of the Subjects

Among 15 patients with OB, the documented underlying disorders were post-transplant graft-versus-host disease (GVHD) in 7, rheumatoid arthritis (RA) in 3, Kartagener's syndrome (KS) in 2, and polymyositis/dermatomyositis, non-tuberculous mycobacterial disease associated with RA and mycoplasmal pneumonia in 1 patient each. Among the 6 patients with DPB, 1 had RA, but the remaining 5 had no associated diseases.

Pathological Findings

The comparative lung pathology showed obliteration of the membranous bronchioli, whereas the distal respiratory bronchioli were spared in most cases of OB (fig. 1). In DPB, obstructive thickening of the respiratory bronchioli with infiltration of lymphocytes and histiocytes associated with ectasis of the proximal membranous bronchioli were observed in all 6 (fig. 2). Thus, the primary obstructive lesions were in the membranous bronchioli in OB and respiratory bronchioli in DPB, respectively. In addition, OB was classified into two major morphologic subtypes: constrictive OB and cellular OB. Constrictive OB is a disorder characterized by concentric narrowing or complete obliteration of the airway lumen due to submucosal fibroblastic proliferation. This subtype of OB is not associated with complete destruction of the bronchiolar walls (fig. 1a–c). In contrast, cellular OB is a disorder characterized by con-

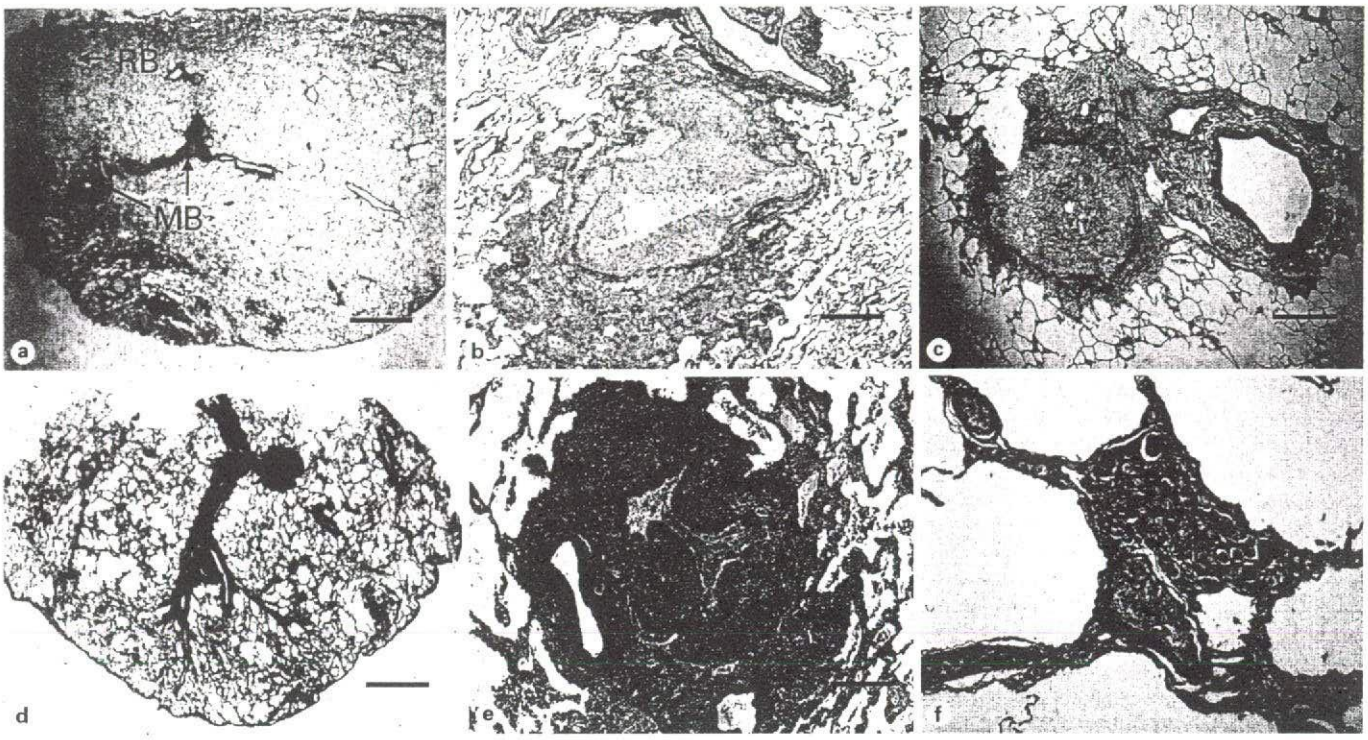

Fig. 1. Microscopic appearances of OB. **a** Low-magnification view in a case of constrictive OB associated with GVHD. Note that the lesions are exclusively limited to the area of the membranous bronchioli (MB), but that the distal respiratory bronchiole (RB) is spared (HE). Bar = 2 mm. **b** The primary lesion of the case shown in **a**. The lumen of a membranous bronchiole is obliterated by submucosal granulation tissues, but is not associated with complete destruction of the bronchiolar wall (Elastica van Gieson stain). Bar = 220 μm. **c** The primary lesion in a case of constrictive OB associated with GVHD. Note that the lumen of a membranous bronchiole is completely obliterated by granulation tissue, but is not associated with complete destruction of the bronchiolar wall (Elastica van Gieson stain). Bar = 400 μm. **d** Low-magnification view of a case of cellular OB associated with polymyositis/dermatomyositis. The lesions are exclusively limited to the area of the membranous bronchioli (HE). Bar = 2 mm. **e** The primary lesion in a case of cellular OB associated with RA. The lumen of a membranous bronchiole is obliterated by intraluminal, mural and peribronchiolar infiltration of inflammatory cells (HE). Bar = 200 μm. **f** The primary lesion in a case of cellular OB associated with KS. Note that the lumen of a membranous bronchiole is completely obliterated by fibrous scarring associated with complete destruction of the bronchiolar wall (Elastica van Gieson stain). Bar = 125 μm.

centric narrowing of the airway lumen due to intraluminal, mural and peribronchiolar infiltration of inflammatory cells. In addition, this subtype of OB was frequently accompanied by complete destruction of bronchiolar walls with obliteration of the airway lumen (fig. 1d–f). Lymphoid hyperplasia and follicular bronchiolitis were observed in a few patients with both cellular OB and DPB, but not with constrictive OB. The characteristic accumulation of foamy cells (fig. 2b) was observed in all DPB patients, but only in 27% of those with OB (table 1).

Underlying Disorders and Histological Subtypes of OB

A comparison of the documented underlying disorders in constrictive OB and cellular OB was shown in table 2. Interestingly, in all 5 patients with constrictive OB, the underlying disorder was GVHD. In contrast, there were several underlying disorders in patients with cellular OB.

Clinical Findings

The comparative clinical features of OB and DPB were summarized in table 3. Chronic parasinusitis was present in all DPB patients compared to only 20% of those with OB. Initial respiratory symptoms of OB and DPB were cough, sputum and dyspnea on exertion. The increased sputum production was observed in all DPB patients, but only in 33% of those with OB. High levels of serum cold hemagglutinin (>64-fold) were observed in all DPB patients, but only in 27% of those with OB. Interestingly, chronic parasinusitis, increased sputum volume and elevated serum cold hemagglutinin were observed exclu-

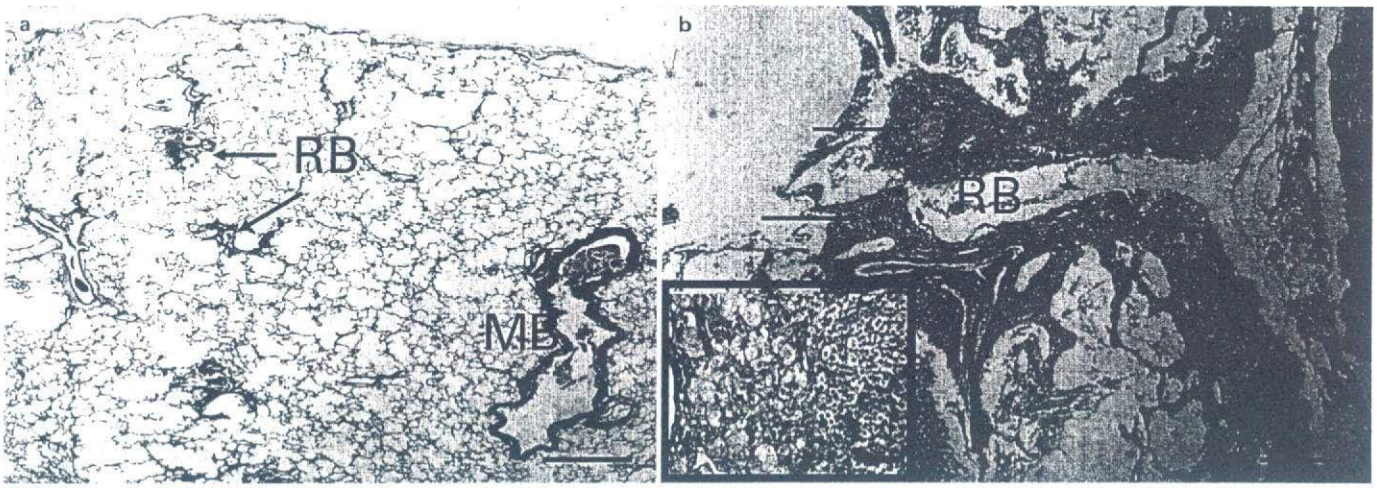

Fig. 2. Microscopic appearances of DPB. **a** Low-magnification view of a case of DPB. Note that the lesions are exclusively limited to the areas of the respiratory bronchioli (RB), associated with ectasis of the proximal membranous bronchiole (MB) (HE). Bar = 2.0 mm. **b** Appearance of the primary lesion in DPB. The wall of a respiratory bronchiole (RB) and the neighboring area are thickened by infiltration of lymphocytes and plasma cells accompanied by accumulation of foamy cells (arrows) (HE). Bar = 200 μm. An inset demonstrates a higher magnification of foamy cells. Bar = 50 μm.

Table 1. Pathological findings

	Primary obstructive lesions				LH		FB		Foamy cells		Complete destruction of the bronchiolar walls	
	RB		MB									
	n	%	n	%	n	%	n	%	n	%	n	%
OB (n = 15)	0	0	15	100	3	20	3	20	4	27	3	20
Constrictive (n = 5)	0	0	5	100	0	0	0	0	2	40	0	0
Cellular (n = 10)	0	0	10	100	3	30	3	30	2	20	3	30
DPB (n = 6)	6	100	0	0	2	33	1	17	6	100	0	0

RB = Respiratory bronchiolus; MB = membranous bronchiolus; LH = lymphoid hyperplasia; FB = follicular bronchiolitis.

Table 2. Underlying disorders and histological subtypes of OB

	Constrictive OB (n = 5)		Cellular OB (n = 10)	
	n	%	n	%
GVHD (n = 7)	5	71	2	29
RA (n = 3)	0	0	3	100
KS (n = 2)	0	0	2	100
PM/DM (n = 1)	0	0	1	100
NTM/RA (n = 1)	0	0	1	100
Mycoplasmal pneumonia (n = 1)	0	0	1	100

PM/DM = Polymyositis/dermatomyositis; NTM/RA = nontuberculous mycobacterial disease associated with RA.

sively in cellular OB but not in constrictive OB. There was no close relationship with smoking history or inhalation of toxic dust in either OB or DPB.

Pulmonary Function Tests

The results of PFTs at the time of the first visit were shown in table 4. In both OB and DPB, marked obstructive impairment and slight hypoxemia were noted. Although there was no statistical difference between OB and DPB in terms of pulmonary function, $FEV_{1.0}$% in constrictive OB was significantly worse than that in cellular OB.

X-Ray Images

The chest CT findings of OB and DPB were compared in table 5. The incidence of small centrilobular nodules

Table 3. Clinical features

	Chronic parasinusitis		Respiratory symptoms						Cold hemagglutinin (≥ ×64)		Smoking history		Inhalation of toxic dust	
			cough		sputum		dyspnea							
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
OB (n = 15)	3	20	9	60	5	33	7	47	4	27	4	27	0	0
Constrictive (n = 5)	0	0	3	60	0	0	3	60	0	0	1	20	0	0
Cellular (n = 10)	3	30	6	60	5	50	4	40	4	40	3	30	0	0
DPB (n = 6)	6	100	4	67	6	100	3	50	6	100	3	50	0	0

Table 4. Pulmonary function test

	VC, %	$FEV_{1.0}$, %	RV/TLC, %	MMF, l/s	$PaO_2/PaCO_2$, mm Hg
OB (n = 15)	2.61 ± 0.77 (82.6 ± 13.6)	1.52 ± 0.64 (58.6 ± 17.4)	44.4 ± 5.5	1.07 ± 1.02	71.1 ± 10.9/38.9 ± 5.5
Constrictive (n = 5)	2.75 ± 1.18 (74.4 ± 17.1)	1.34 ± 0.85 (48.0 ± 15.1) *	45.0 ± 4.2	0.61 ± 0.36	66.8 ± 7.3/39.6 ± 3.8
Cellular (n = 10)	2.34 ± 0.53 (80.8 ± 11.6)	1.55 ± 0.60 (65.7 ± 14.4) *	43.2 ± 5.8	1.31 ± 1.24	73.3 ± 12.1/38.6 ± 6.4
DPB (n = 6)	3.21 ± 1.15 (91.2 ± 26.1)	2.16 ± 0.97 (64.7 ± 14.3)	37.8 ± 12.1	1.7 ± 1.5	74.8 ± 8.2/39.5 ± 4.8

* $p < 0.05$ (mean ± SD). VC = Vital capacity; RV/TLC = residual volume/total lung capacity; MMF = maximal midexpiratory flow.

Table 5. Chest CT findings

	Centrilobular small nodules		Bronchiolectasis		Hyperinflation		Mosaic perfusion	
	n	%	n	%	n	%	n	%
OB (n = 14)	9	64	7	50	10	71	5	36
Constrictive (n = 5)	2	40	2	40	4	80	2	40
Cellular (n = 9)	7	78	5	56	6	67	3	33
DPB (n = 5)	5	100	5	100	3	60	0	0

up to 5 mm in diameter associated with bronchiolectasis throughout both lungs was higher in DPB than in OB. In addition, small nodules were present more frequently in cellular OB (78%) than in constrictive OB (40%). The incidence of hyperinflation was more than 60% in both groups. Mosaic perfusion as a characteristic image of air trapping was observed only in OB, but not in DPB.

Prognoses

Table 6 summarized the comparative prognoses and underlying disorders in constrictive OB, cellular OB and DPB. Corticosteroids and/or cyclosporin A, methotrexate, macrolide or new quinolone were given for OB, and macrolide alone for DPB. The prognosis of constrictive OB was the worst compared to that of cellular OB and DPB. Importantly, the prognosis of DPB has been markedly improved after the introduction of macrolide therapy.

Discussion

In the present study, chest CT images revealed small centrilobular nodules and bronchiolectasis throughout both lungs in patients with OB and DPB. With regard to pulmonary function, obstructive impairment was prominent in both OB and DPB. Thus, striking similarities exist between OB and DPB in the radiological findings and the functional impairments of the lung, in addition to the

Table 6. Prognosis in histological subtypes of OB and DPB

	Improved	Unchanged	Deteriorated	Treatment
Constrictive OB (n = 5)	1/5 (20%) (GVHD: 1)	2/5 (40%) (GVHD: 2)	2/5 (40%) (GVHD: 2)	prednisolone: 11 cyclosporin: 4 methotrexate: 1
Cellular OB (n = 10)	4/10 (40%) (GVHD: 1, RA: 1, PM/DM: 1, MPN: 1)	5/10 (50%) (GVHD: 1, RA: 1, KS: 2, NTM/RA: 1)	1/10 (10%) (RA: 1)	macrolide: 6 new quinolone: 3
DPB (n = 6)	5/6 (83%)	0/6 (0%)	1/6 (17%) (RA: 1)	macrolide: 5

PM/DM = Polymyositis/dermatomyositis; MPN = mycoplasmal pneumonia; NTM/RA = non-tuberculous mycobacterial disease associated with RA.

common clinical features such as increased sputum, cough and dyspnea on exertion. However, histopathological characteristics obtained by reconstructing the lung specimens differed considerably between these two diseases. Primary obstructive lesions occurred in the membranous bronchioli in OB and in the respiratory bronchioli in DPB. Likewise, we have demonstrated the histopathological distinctions between DPB and cellular OB associated with RA and KS in the recently published papers [11, 12].

Colby and Myers [13] described that cellular bronchiolitis is a useful morphologic descriptor for the surgical pathologist even though it is a common pattern seen in a variety of clinicopathologic settings such as inflammatory bowel diseases, post-transplant OB or idiopathic OB. The inflammation might be acute or chronic (or both), and OB could be associated with intraluminal polyps or constrictive bronchiolitis. Neither proliferative OB nor constrictive bronchiolitis are entirely satisfactory terms, but they do tend to emphasize that the histologic lesions of OB vary considerably and fall into two general categories that are recognizable and separable [13]. In addition, Abernathy et al. [14] reported that there were two histological forms of OB in heart-lung transplant recipients. OB from patients who had received their transplants more than 6 months previously was characterized by a diffuse, relatively acellular concentric fibrosing process, which concentrically narrowed the lumina of the terminal bronchioles. In contrast, OB from patients who had received their transplants less than 6 months previously was more cellular. These two forms of OB may represent different stages of the same process: the former may represent an inactive form, while the latter may represent an active form of OB.

The histopathological features of the cases of OB presented in our current study fitted the above description. According to their study, small airway diseases were divided into two groups: (1) acute and chronic cellular bronchiolitis with less conspicuous scarring (corresponding to cellular OB in the present study), and (2) constrictive bronchiolitis, varying from fibrotic and inflammatory airway lesions to complete airway obliteration (corresponding to constrictive OB in the present study).

In addition to these features, we have found that cellular OB frequently includes a component of complete destruction of bronchiolar walls with obliteration of the airway lumen (so-called destructive OB) [15], whereas constrictive OB is not associated with complete destruction of the bronchiolar walls. Furthermore, the present study demonstrated that OB occurs in a number of clinical settings in addition to RA and KS. These conditions could include GVHD, infectious diseases, or collagen vascular diseases. Interestingly, however, in all the patients with constrictive OB in the present study, the underlying disorder was GVHD. In contrast, there were several underlying disorders in patients with cellular OB.

The 5-year survival from the onset of respiratory symptoms in patients with DPB has been markedly improved from 62.8 to 91.4% after the introduction of macrolide therapy for DPB in the past 20 years in Japan [16, 17]. The mechanisms by which macrolide therapy may render marked and sufficient effects on DPB would not be antibacterial, but rather anti-inflammatory in nature [18–20].

In the present study, macrolide was not applied to 1 of the 6 DPB patients, because he had deceased before the introduction of macrolide therapy for DPB. In contrast,

corticosteroids or immunosuppressants, rather than macrolide, may be beneficial to patients with OB [21–24]. However, Gerhardt et al. [25] have recently reported the efficacy of oral maintenance therapy with azithromycin for OB. It may be important to institute the treatment in the early course of the illness, before irreversible structural changes could develop. However, if a patient with OB does not respond to these treatments, lung transplantation may be the most reasonable therapeutic modality for such end-stage patients thus far.

Conclusions

The present study has demonstrated that histological characteristics of OB are obliteration of the membranous bronchioli, whereas the distal respiratory bronchioli were spared. In DPB, in contrast, obstructive thickening of the respiratory bronchioli with infiltration of lymphocytes and histiocytes associated with ectasis of the proximal membranous bronchioli was commonly observed. Thus marked differences were present in histopathology between OB and DPB, although striking similarities were also noted in both diseases. In addition, OB was classified into two major morphologic types: constrictive and cellular OB. The prognosis of constrictive OB was worse than that of cellular OB.

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High-Resolution Computed Tomography Findings of Lung Cancer Associated With Idiopathic Pulmonary Fibrosis

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Objective: The purpose of this study was to evaluate high-resolution computed tomography (HRCT) findings of lung cancer associated with idiopathic pulmonary fibrosis (IPF).

Methods: Thirty patients with lung cancer who had preceding IPF and were receiving regular follow-up between 1993 and 2002 were examined. Medical records, radiographs (including HRCT scans), and histologic slides were reviewed.

Results: In 28 of the 30 patients, the most common HRCT pattern of lung cancer was a nodular lesion with soft tissue attenuation. Nodule margins were well defined in 23 lesions (82.1%), associated with lobulation in 24 (85.7%), or characterized by spiculation in 14 (50%). Air bronchogram was observed in 16 lesions (57.1%). All nodules were located in the peripheral area of fibrotic lesions. Squamous cell carcinoma and adenocarcinoma were the most frequent histologic types.

Conclusions: The typical HRCT findings of lung cancer were well-defined nodular lesions with lobulation in peripheral areas of the lung.

Key Words: lung cancer, interstitial lung diseases, high-resolution computed tomography

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Idiopathic pulmonary fibrosis (IPF) is known to be associated with an increased risk of developing lung cancer.[1–5] The individuals with lung cancer associated with IPF are predominantly male smokers, and their cancer is usually located in the peripheral lung areas.[2–6] Chest radiographic features of lung cancer developing with IPF have been described as nodular or linear densities that are sometimes accompanied by honeycomb formation.[7] There are only a limited number of studies focusing on computed tomography (CT) findings of lung cancer associated with IPF, however. Lee et al[8] reported that typical CT findings of lung cancer were ill-defined consolidation-like masses at the peripheral portion, which were located mainly in the lower lobe. Conversely, Sakai et al[9] showed that most lung cancer associated with diffuse pulmonary fibrosis consisted mainly of IPF, was round or lobulated in shape with sharp margins, and was located in the peripheral area of honeycombing.

We reviewed the clinical, radiologic, and pathologic findings of patients with lung cancer who had preceding IPF and further clarified the high-resolution computed tomography (HRCT) characteristics of lung cancer associated with IPF.

MATERIAL AND METHODS

We retrospectively studied 30 patients with histologically confirmed lung cancer of 64 patients having IPF during the period from March 1993 through August 2002. Idiopathic pulmonary fibrosis was diagnosed by clinical and HRCT findings according to the American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias.[10] In these 30 patients, the diagnosis of lung cancer was based on transbronchial lung biopsy in 11 patients, on surgery in 6, on sputum cytology in 6, on percutaneous needle biopsy in 6, and on autopsy in 1, respectively.

Medical records were reviewed for age, sex, smoking history, time of diagnosis of IPF, symptoms of IPF, time of diagnosis of primary lung cancer, cancer-related symptoms, visibility of lung cancer on chest radiographs, and treatment.

A CT scan was performed on a CT 9800 scanner or High Speed Advantage scanner (General Electric Medical Systems, Milwaukee, WI). Routine scanning of the entire lung was carried out with a 10-mm section thickness. Additional HRCT images with a 1- to 3-mm section thickness were acquired through the tumor with a bone algorithm using fixed window settings (lung center, −500 Hounsfield units [HU]; width, 1800 HU) for all patients.

A consensus reading of the HRCT images was conducted by 2 observers (AK, KK). The shape of the lung cancer was divided into 2 categories of a nodular lesion with soft tissue attenuation or an undetermined pattern. According to the description of Zwirewich et al,[11] the HRCT findings of the nodular lesion were analyzed on the basis of marginal

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characteristics (well defined, poorly defined, smooth, irregular, spiculation, lobulation, convergence of peripheral vessels and bronchi, and pleural retraction) and internal characteristics (air bronchogram, calcification, and cavitation).

The locations of lung cancer were categorized into the central or peripheral type by an imaginary line located 3 cm away from the pleura, and the lobar distribution was evaluated.[8]

Lung cancer was subtyped according to the World Health Organization histologic classification of lung tumors.[12] The association of carcinomas with areas of fibrotic change was evaluated histologically using 9 surgically resected and 4 autopsied samples.

RESULTS

Clinical Findings

The clinical findings in 30 patients with IPF and lung cancer are summarized in Table 1. Twenty-seven patients were male, and 3 were female. The mean age of the patients was 69 years, ranging from 54 to 84 years.

TABLE 1. Clinical Findings in 30 Patients With IPF and Lung Cancer

Characteristics	Number (%)
Sex	
Male	27 (90)
Female	3 (10)
Mean age (y)	69
Smoking status	
Current	18 (60)
Past	12 (40)
Mean pack-years	56.9
Carcinoma-related symptoms	
Incidental	21 (70)
New complaints	9 (30)
Hoarseness	4
Pain	3
Sputum	2
Clinical stages	
IA/IB	5/4
IIA/IIB	0/1
IIIA/IIIB	3/7
IV	10
Histologic types	
Squamous cell carcinoma	12 (40)
Adenocarcinoma	12 (40)
Small cell carcinoma	5 (17)
Large cell neuroendocrine carcinoma	1 (3)
Treatment	
Chemotherapy	15 (50)
Surgery	10 (33)
Radiotherapy	1 (3)
No treatment	4 (13)

All the patients had a smoking history. Eighteen were current smokers, and 12 were past smokers, with a mean exposure of 56.9 pack-years (range: 16.5–120 pack-years).

In 22 patients (73.3%), the clinical diagnosis of IPF preceded the detection of lung cancer by an average of 4.9 years (range: 0.6–11.0 years). Eight patients (26.7%) had IPF and lung cancer diagnosed at the same time.

Seventeen patients had symptoms of IPF, including dyspnea on exertion, nonproductive cough, and sputum. Lung cancer was incidentally discovered in the follow-up of IPF or in mass screening by chest radiography in 15 patients and by CT in 6. Nine patients presented with new complaints associated with lung cancer, with the most frequent being hoarseness.

Twenty-five lung cancers were visible on chest radiographs. The remaining 5 cancers were invisible on chest radiographs and only detectable on CT (Fig. 1). The size of 3 of these 5 cancers was less than 2 cm in diameter. Two cancers were concealed by the mediastinum on chest radiographs.

The clinical stage was IA in 5 patients, IB in 4, IIB in 1, IIIA in 3, IIIB in 7, and IV in 10, respectively. Ten patients with non-small cell lung carcinoma and 5 patients with small cell lung carcinoma received chemotherapy. Ten patients underwent surgery, including lobectomy in 7 and wedge resection under video-assisted thoracoscopic surgery in 3. Four patients received best supportive care, and 1 patient underwent radiotherapy.

High-Resolution Computed Tomography Findings

The shape of the lung cancer was a nodular lesion in 93.3% (28 of 30) of patients and an undetermined pattern in 6.7% (2 of 30) of patients (see Fig. 1). The mean maximum diameter of nodular lesions was 36 mm, ranging from 10 to 70 mm. Of the 2 patients with an undetermined pattern, 1 with mucinous bronchioloalveolar carcinoma demonstrated diffuse ground-glass opacities resembling acute exacerbation of IPF (Fig. 2) and the other with adenocarcinoma had extensive pleural thickening mimicking malignant pleural mesothelioma (Fig. 3).

The HRCT findings of 28 nodular lesions are listed in Table 2. A sharp and well-defined interface between the nodule and the surrounding lung was observed in 23 lesions (82.1%). An irregular margin was seen in 22 lesions (78.6%). Lobulation and spiculations were found in 24 (85.7%) and 14 (50.0%) lesions, respectively. Air bronchogram was observed in 16 lesions (57.1%). Cavitation was present in 3 lesions of squamous cell carcinoma. Stippled calcification was recognized in 3 lesions.

In the nodular pattern, all lesions were located in the peripheral area of the lung and all but 1 lesion were in contact with the pleura. Nodular lesions were located in the right upper lobe in 6 patients, the right lower lobe in 9, the left upper lobe in 7, and the left lower lobe in 6.

Seventeen lung cancers were peripheral tumors in association with honeycombing on HRCT (see Fig. 1). Of the remaining 13 cancers, 12 were in the upper lobe and 1 was in the lower lobe. Although these cancers were located away from honeycombing on CT, a reticular pattern indicating fibrosis

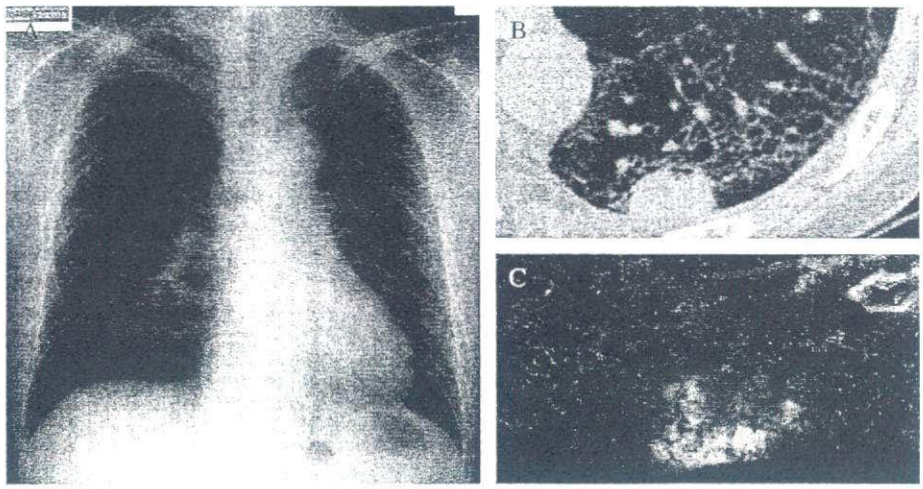

FIGURE 1. An individual with squamous cell carcinoma associated with IPF. A, Chest radiograph shows a reticular pattern. No nodular opacity suggestive of lung cancer is seen. B, High-resolution computed tomography scan at the level of the left lower lung reveals a lobulated nodule located in the peripheral lung field adjacent to honeycombing. C, Gross photograph of the cut surface of the resected left lower lobe shows honeycombing and a lobulated cancerous mass.

was recognized adjacent to the tumor in a subpleural portion (Fig. 4).

Pathologic Findings

The histologic types consisted of 12 squamous cell carcinomas (40%); 12 adenocarcinomas (40%), including 1 mucinous bronchioloalveolar carcinoma; 5 small cell carcinomas (16.7%); and 1 large cell neuroendocrine carcinoma (3.3%) (see Table 1). In 9 surgical and 3 autopsy samples, lung cancer was centered in association with the fibrotic area of the lung, where atypical epithelial proliferation was observed.

DISCUSSION

Our data demonstrated that the characteristic HRCT findings of lung cancer associated with IPF were well-defined, lobulated, nodular lesions with soft tissue attenuation. These CT findings were consistent with those of lung cancer associated with diffuse pulmonary fibrosis as reported by Sakai et al[9] in the context that the shapes of most tumors were round or lobulated with sharp margins. Conversely, our observations were distinctive from those by Lee et al,[8] in which typical CT findings of lung cancer associated with IPF were reported to be ill-defined consolidation-like masses, although HRCT was performed in only 25% of the patients in their study. In addition, the CT findings in our study were different from those of localized bronchioloalveolar carcinoma, which typically represent focal areas of ground-glass opacity.[13,14]

In addition to nodular lesions, we found an undermined pattern in 2 patients, one of which showed diffuse ground-glass opacity attributable to mucinous bronchioloalveolar carcinoma. In this patient, tumor cells spread along the honeycombing wall and did not form a mass lesion. Similarly, Lee et al[8] reported a patient with bronchioloalveolar carcinoma

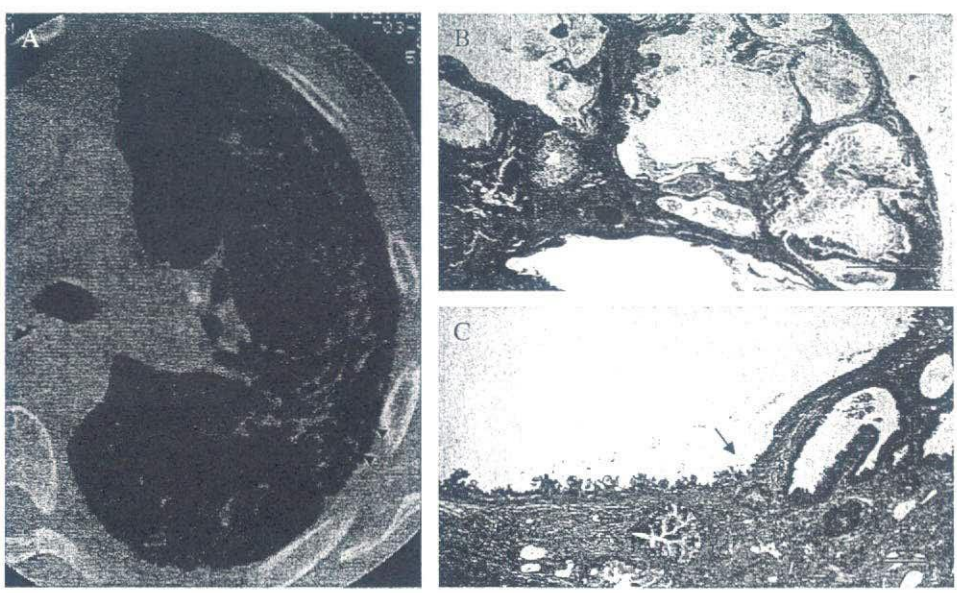

FIGURE 2. Bronchioloalveolar carcinoma associated with IPF. A, High-resolution computed tomography scan reveals peripheral honeycombing (arrowheads) and diffuse ground-glass opacities resembling acute exacerbation of IPF. B, Low-magnification photomicrograph of an autopsied lung specimen shows bronchioalveolar carcinoma invasion of the honeycomb wall. The bar indicates 1 mm (hematoxylin–eosin stain). C, Same as B but higher magnification photograph demonstrates coexistence of bronchiolar metaplasia and bronchioloalveolar carcinoma. The arrow indicates the front of bronchioloalveolar carcinoma. The bar indicates 0.1 mm (hematoxylin–eosin stain).

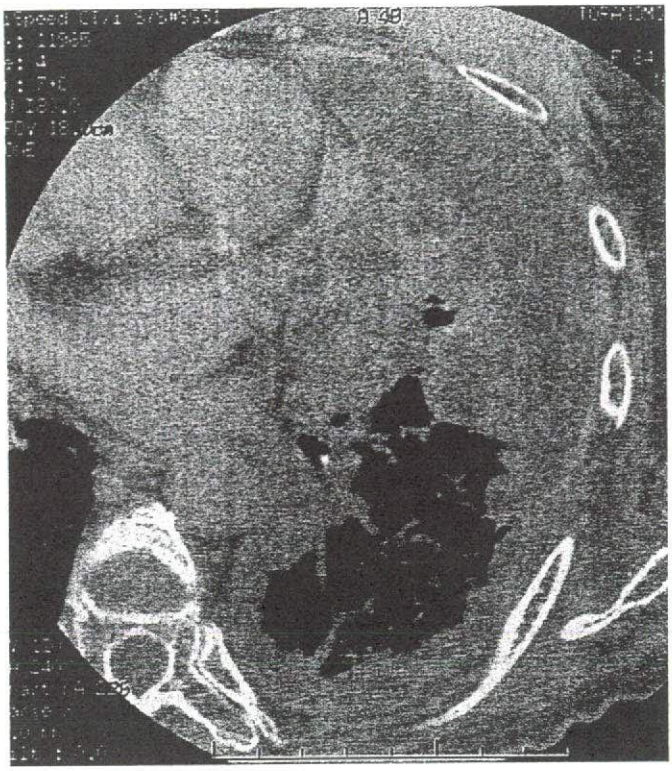

FIGURE 3. High-resolution computed tomography scan of lung adenocarcinoma associated with IPF shows honeycombing and extensive pleural thickening in the left hemithorax resembling malignant pleural mesothelioma.

TABLE 2. High-Resolution Computed Tomography Findings of 28 Nodular Lesions of Lung Cancer Associated With IPF

Parameter	No. Cases (%)
Nodular margin	
Well defined	23 (82.1)
Poorly defined	5 (17.9)
Smooth	6 (21.4)
Irregular	22 (78.6)
Lobulation	24 (85.7)
Spiculation	14 (50.0)
Convergence of peripheral vessels	11 (39.3)
Pleural retraction	9 (32.1)
Internal features	
Air bronchogram	16 (57.1)
Cavitation	3 (10.7)
Calcification	3 (10.7)

who showed diffuse air space consolidation. Diffuse parenchymal opacities should be considered as one of the possible CT appearances of lung cancer associated with IPF.

As for localization, all lung cancers in the present study were located in the peripheral areas of the lung, where fibrosis was more predominant than in the central lung areas. Further, all but 1 lesion was in contact with the pleura. These findings were consistent with those of previous reports.[2–5] Regarding lobar localization, most of the previous studies emphasized a predominance of the lower lobe.[2,3,8,9] A recent study by Park et al[6] demonstrated the presence of 52% of cancers in the upper lobe, however. Our results, in which 46% of cancers were located in the upper lobe, were close to those of Park et al.[6]

In terms of the association between lung cancer and honeycombing, Sakai et al[9] reported that 82% of the tumors were located in the periphery within the areas of honeycombing. Our study showed that 43% of the cancers were located away from honeycombing on CT, however. This rather high frequency could be explained by the fact that cancer originated from the upper lobe in 46% of our patients. Interestingly, these patients had reticular opacities suggestive of fibrosis adjacent to the tumor as well. Therefore, the newly developed nodules in the peripheral lung, even if located in the

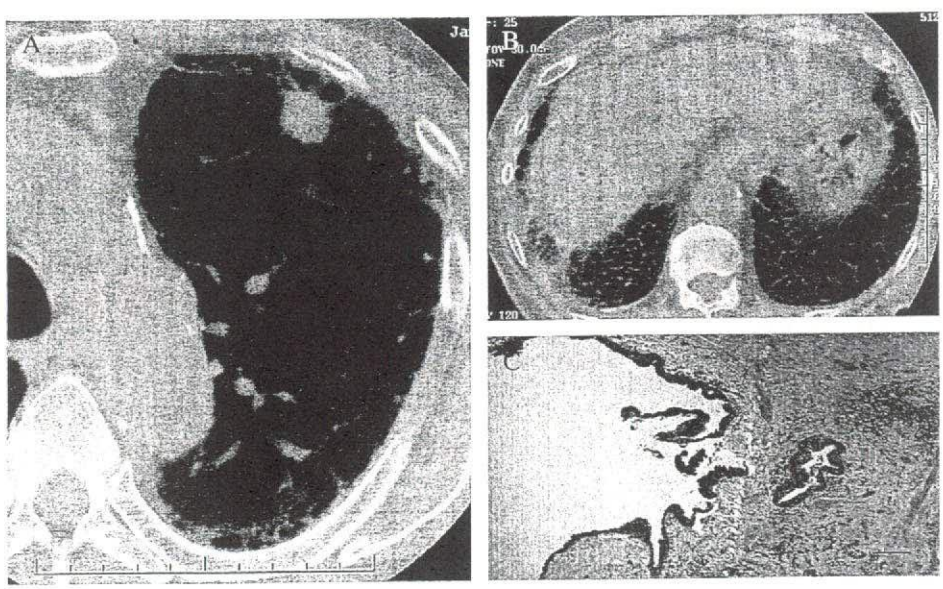

FIGURE 4. Lung adenocarcinoma developing in an individual with IPF. A, High-resolution computed tomography scan reveals a spiculated nodule in an area of subpleural reticulation. B, Computed tomography scan at the level of the lung base demonstrates bilateral honeycombing formation. C, Low magnification of the resected lung shows fibrotic foci and honeycombing lined by adenocarcinoma cells. The bar indicates 0.1 mm (hematoxylin–eosin stain).

upper lobe, where apparent honeycombing is lacking, should be considered as possible lung cancer.

The diversity of histologic types of lung cancer associated with IPF varied among several studies.[1–6,8] Some studies reported that squamous cell carcinoma was the most common histologic type in IPF patients,[1,3,5,6,8,9] whereas other studies showed a predominance of adenocarcinoma.[2,4] In the present study, squamous cell carcinoma and adenocarcinoma were the most frequent histologic types, both accounting for 40%.

It is still unknown why lung cancer is prevalently associated with IPF. Several studies have implicated a close relation between the primary site of lung cancer and fibrosis.[2,4,5,7,9,15,16] For instance, Meyer and Liebow[15] first paid attention to atypical epithelial proliferation in the honeycombing areas in usual interstitial pneumonia and suspected that this might possibly represent a precancerous lesion. This speculation seems to be applicable, because we have also found that lung cancer was situated in association with a fibrotic area in which atypical epithelial proliferation was present. In addition, a smoking habit is likely responsible for the development of lung cancer in the case of preexisting IPF, because, in our study, individuals who had lung cancer with IPF were predominantly men who were current or past smokers, as described in the previous reports.[1–6]

In summary, typical HRCT findings of such lung cancer with IPF are well-defined nodules with lobulation in the peripheral subpleural areas inside or adjacent to the fibrosis. Because it is difficult to find a small-sized lung cancer associated with IPF by chest radiography, routine use of CT is recommended for early detection of lung cancer as well as for evaluating serial changes in IPF.

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間質性肺炎合併肺癌における治療後急性増悪の検討

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要旨 —— **目的.** 間質性肺炎（interstitial pneumonia：IP）合併肺癌における治療後のIP急性増悪の臨床像を明らかにする. **方法.** 1999年6月～2007年4月までに加療した肺癌776例を対象とし，IP合併肺癌の治療後急性増悪について臨床病理学的にretrospectiveに検討した. **結果.** IP合併肺癌は39例（5%）に認めた. 治療後IP急性増悪は39例中6例（15%）に認め，うち4例（10%）が呼吸不全で死亡した. 急性増悪群と非急性増悪群の2群間では肺癌治療前のLDH，KL-6，SP-D，PaO_2，%VC，%DLcoの値には統計学的有意差は認めなかった. 治療法別では化学療法24例中5例（21%），手術療法6例中1例（17%）に治療後急性増悪を認めた. IP分類では，特発性間質性肺炎（idiopathic interstitial pneumonias（IIPs）：idiopathic pulmonary fibrosis（IPF）29例，nonspecific interstitial pneumonia（NSIP）1例）の30例中4例（13%），膠原病随伴性間質性肺炎（collagen vascular disease-IP：CVD-IP）の9例中2例（22%）に急性増悪を認め，死亡した4例中2例はCVD-IPであった. **結語.** IIPsのみならずCVD-IPも急性増悪を念頭に置き肺癌治療にあたることが重要である.（肺癌. 2007;47:849-854）

索引用語 —— 肺癌，間質性肺炎，急性増悪，膠原病

Clinical Characteristics of Acute Exacerbation of Interstitial Pneumonia Associated with Lung Cancer After Anti-cancer Treatment

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ABSTRACT —— ***Objective.*** To demonstrate the characteristic clinical features of acute exacerbation of interstitial pneumonia（IP）associated with lung cancer after anti-cancer treatment. ***Methods.*** Consecutive 776 cases with lung cancer between June 1999 and April 2007 were retrospectively evaluated to clarify the clinicopathological characteristics of acute exacerbation of IP associated with lung cancer after anti-cancer treatment. ***Results.*** Among 776 cases of lung cancer, 39 cases（5%）had concomitant IP. Acute exacerbation of IP after treatment was found in 6 of the 39 cases（15%）, and 4 cases（10%）died of respiratory failure. There were no significant differences in LDH, KL-6, SP-D, PaO_2, %VC, or %DLco between the acute exacerbation group and the non-acute exacerbation group before anti-cancer treatment. Of the 6 cases with acute exacerbation of IP after treatment, exacerbation occurred after chemotherapy in 5 out of 24 cases（21%）, and after surgical resection of the lung cancer in 1 out of 6 cases（17%）. Among the 6 cases with acute exacerbation of IP, the subclassification of IP was IPF in 4 and collagen vascular disease-IP（CVD-IP）in 2. Among the 4 cases who died of respiratory failure after acute exacerbation of IP, the underlying systemic disease was IPF in 2 and CVD-IP in 2. ***Conclusion.*** Both IIPs and CVD-IP should go through the anti-cancer treatment,

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keeping the possibility of acute exacerbation of IP in mind. (*JJLC*. 2007;47:849-854)

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はじめに

間質性肺炎(interstitial pneumonia：以下IP)には高率に肺癌を合併することが知られている.[1-5] しかし，IP合併肺癌症例においては，手術，化学療法などの肺癌治療に伴い致死的なIPの急性増悪が生じうることがあることから，治療法の選択に難渋する場合が多い．IP合併肺癌における治療後のIP急性増悪の実態を明らかにする目的でサブタイプ別，治療法別の発症頻度をretrospectiveに検討した．

対象および方法

1999年6月～2007年4月まで当センターで原発性肺癌で加療を行った776例中，IPに合併した肺癌39例(5%)を対象とした．方法は下記に示す基準に基づき，臨床病理学的に検討した．

1. IPのパターン分類

病理組織学的にusual interstitial pneumonia（UIP）が確認された場合と胸部high resolution CT（HRCT）において大きさ2～10 mm程度の比較的大きさが揃った，壁の厚い嚢胞状病変が集簇した領域（蜂巣肺）が，両側肺底部胸膜直下に優位に存在する場合をUIPパターンとし，それ以外をnon-UIPパターンとした．

また，idiopathic interstitial pneumonias（IIPs)のうちCTで両側肺底部の胸膜直下優位の蜂巣肺を有し①50歳以上，②3ヶ月以上の緩徐な発症，③3ヶ月以上の経過，④両側肺野の捻髪音の4項目中3項目を満たす場合clinical idiopathic pulmonary fibrosis（cIPF）と診断した.[6]

2. 治療後急性増悪の定義

日本呼吸器学会のガイドラインに従い以下のように定義した.[6]

1）肺癌治療後に1ヶ月以内の経過で以下の①～③を満たすものとした．

①呼吸困難の増強，②HRCT所見で線維化所見＋新たに生じたスリガラス陰影＋浸潤影，③動脈血酸素分圧の低下（同一条件下でPaO_2 10 torr以上）．

2）明らかな肺感染症，気胸，悪性腫瘍，肺塞栓や心不全を除外する．CRP，LDHの上昇，KL-6，SP-A，SP-Dなどの上昇を参考所見とした．

3. 統計学的手法

2群間の比較検討にはunpaired-t検定を用い，危険率5%未満を統計上有意差ありとした．

結　果

対象症例の背景をTable 1に示す．男性34例，女性5例，平均年齢は71.5歳（58～87歳）であった．組織型は小細胞癌10例，腺癌9例，扁平上皮癌13例，組織型が確定できなかった非小細胞癌6例，大細胞癌神経内分泌腫瘍1例であった．臨床病期はI期10例，II期3例，III期14例，IV期が12例であった．喫煙歴はcurrent smokerが17例，former smokerが19例，never smokerが3例であった．喫煙指数では960±686と重喫煙者が多く認められた．

IPのパターン分類ではIIPsは30例に合併しており，うちcIPFが21例，IPF/UIPが8例，nonspecific interstitial pneumonia（NSIP)が1例であった．また，膠原病随伴性間質性肺炎（collagen vascular disease-IP：以下CVD-IP)は9例で，うちrheumatoid arthritis(RA)/UIPが7例，systemic sclerosis（SSc)/UIPが1例，SSc/non-UIPが1例であった（Table 2)．

臨床病期および治療では非小細胞肺癌（non-small cell lung cancer：NSCLC）ではI期の8例中5例，II期の3例中1例の，6例に肺葉切除が施行されていた．また，1例に胸腔鏡検査診断が施行されていた．III期以降では化学療法が18例中13例に施行されていた．小細胞肺癌（small cell lung cancer：SCLC）では10例全例に化学療法，胸腔鏡検査診断が3例に施行されていた．胸部放射

Table 1. Patient Characteristics

Age（mean）	58-87（71.5）
Gender	
Male/Female	34/5
Performance status	
0/1/2/3/4	12/21/4/0/2
Histology	
Sm/Ad/Sq/NSCLC/LCNEC	10/9/13/6/1
Clinical stage	
IA/IB/IIA/IIB/IIIA/IIIB/IV	8/2/2/1/3/11/12
Smoking history	
Current/Former/Never	17/19/3
Brinkman index（mean±SD）	960±686

Sm: small cell carcinoma, Ad: adenocarcinoma, Sq: squamous cell carcinoma, NSCLC: non-small cell lung cancer, LCNEC: large cell neuroendocrine carcinoma.

Table 2. Subclassification of Interstitial Pneumonia and Lung Cancer

IIPs	30	
cIPF	21	(Sm 5, Ad 3, Sq 8, NSCLC 5)
IPF/UIP	8	(Sm 1, Ad 3, Sq 3, LCNEC 1)
NSIP	1	(Sm 1)
CVD-IP	9	
RA/UIP	7	(Sm 1, Ad 4, Sq 1, NSCLC 1)
RA/non-UIP	1	(Sm 1)
SSc/UIP	1	(Sq 1)

IIPs: idiopathic interstitial pneumonias, cIPF: clinical idiopathic pulmonary fibrosis, IPF: idiopathic pulmonary fibrosis, UIP: usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, CVD-IP: collagen vascular disease-IP, RA: rheumatoid arthritis, SSc: systemic sclerosis.

Table 3. Clinical Stage and Therapy of Lung Cancer

NSCLC		
I	8	OPE 5, BSC 3
II	3	OPE 1, CTx + RTx 1, BSC 1
IIIA	3	CTx 3
IIIB	7	CTx 5, BSC 2
IV	8	CTx 5, BSC 3
SCLC		
LD	3	CTx 3
ED	7	CTx 7

OPE: operation, BSC: best supportive care, CTx: chemotherapy, RTx: radiotherapy, SCLC: small cell lung cancer, LD: limited disease, ED: extensive disease.

線療法は，胸椎転移に対して緩和目的の放射線治療が1例に施行されていたのみであった（Table 3）．

また，best supportive care（BSC）は9例（23%）と高頻度であった．その理由は高齢（77歳以上）が3例，高齢＋低肺機能が1例，患者治療拒否が3例，低肺機能が2例であった．

化学療法では first line が24/39例（62%）に施行されていた．非小細胞癌の regimen では carboplatin（CBDCA）＋docetaxel（DOC）が7例と最も多く，次いで vinorelbine（VRB）単剤が3例，その他が4例であった．小細胞癌では8例に CBDCA＋etoposide（VP-16），2例に cisplatin（CDDP）＋VP-16が施行されていた．Second line は10例に施行されていた．非小細胞癌の regimen では VRB 単剤，CBDCA＋DOC，gemcitabine（GEM）＋irinotecan（CPT-11），nimustin（ACNU）＋paclitaxel（PAC）が1例ずつであった．小細胞癌は ACNU＋PAC が3例，amrubicin（AMR），CPT-11，

Table 4. Regimen of Chemotherapy for Lung Cancer

1st line（n＝24）				
NSCLC:	CBDCA＋DOC	7	VRB	3
	CDDP＋DOC	1	CDDP＋VRB	1
	UFT	1	DOC	1
SCLC:	CBDCA＋VP-16	8	CDDP＋VP-16	2
2nd line（n＝10）				
NSCLC:	VRB	1	CBDCA＋DOC	1
	GEM＋CPT-11	1	ACNU＋PAC	1
SCLC:	ACNU＋PAC	3	AMR	1
	CPT-11	1	ANV	1

CBDCA: carboplatin, DOC: docetaxel, VRB: vinorelbine, CDDP: cisplatin, VP-16: etoposide, GEM: gemcitabine, CPT-11: irinotecan, ACNU: nimustin, PAC: paclitaxel, AMR: amrubicin, ANV: adriamycin＋nimustin＋vindesine.

Table 5. Response Rate to First Line Chemotherapy

NSCLC:（n＝14）	CBDCA＋DOC	43%（PR 3, SD 2, PD 2）
	VRB	0%（SD 2, PD 1）
	Others	0%（SD 4）
	Total	21%（3/14）
SCLC:（n＝10）	CBDCA＋VP-16	88%（CR 2, PR 5, SD 1）
	CDDP＋VP-16	100%（CR 1, PR 1）
	Total	90%（9/10）

PR: partial response, SD: stable disease, PD: progressive disease, CR: complete response.

adriamycin＋nimustin＋vindesine（ANV）が1例ずつであった（Table 4）．First line の奏効率は NSCLC では21%（3/14）であり SCLC では90%（9/10）であった（Table 5）．

治療後 IP 急性増悪症例は6/39例（15%）で認められ，4例が呼吸不全で死亡した．死亡例のうち2例は RA/UIP 合併肺癌であった．化学療法後急性増悪を発症した regimen は ACNU＋PAC が2例で最も多く，その他は VRB が1例，GEM＋CPT-11 が1例，DOC が1例であった（Table 6）．手術後の IP 急性増悪は6例中1例に認められ，術後3日目に発症し死亡の転帰を辿った．急性増悪の治療ではステロイドパルス療法が6例全例で施行されたが，4例はステロイド抵抗性であった．うち1例には血液浄化療法（polymyxin B-immobilized fiber column hemoperfusion treatment：PMX-DHP）が施行されていた．

手術施行例の手術時間，術中 FiO_2，麻酔法に関して非急性増悪5例と急性増悪1例を比較したが急性増悪の誘因は明らかでなかった（Table 7）．また，診断目的の胸腔

Table 6. Cases with Acute Exacerbation (n=6)

case	age/sex	c-stage, histological type (lung cancer)	subclassification (IP)	therapy (IP)	severity index (IP)	anti-cancer therapy	duration to AE	therapy (AE)	prognosis
1	77/M	T1N2M1, stage IV, Ad	cIPF	-	I	1st line CTx (DOC)	CTx 4 W	mPSL pulse	improved
2	64/M	T4N1M0, stage IIIB, Ad	cIPF	-	I	2nd line CTx (GEM + CPT-11)	CTx 10 D	mPSL pulse	improved
3	79/M	T3N2M1, stage IV, Sq	RA/UIP	PSL 20 mg/D	I	1st line CTx (VRB)	CTx 4 W	mPSL pulse	dead
4	69/M	T1N0M0, stage IA, Ad	RA/UIP	-	I	OPE	OPE 3 D	mPSL pulse PMX-DHP	dead
5	67/M	T2N3M0, stage IIIB, Sm	cIPF	PSL 20 mg/D	IV	2nd line CTx (ACNU/PAC)	CTx 1 W	mPSL pulse	dead
6	58/M	T2N3M0, stage IIIB, NSCLC	cIPF	-	I	3rd line CTx (ACNU/PAC)	CTx 11 D	mPSL pulse	dead

M: male, PSL: prednisolone, D: days, AE: acute exacerbation, W: weeks, PMX-DHP: polymyxin B-immobilized fiber column hemoperfusion treatment.

Table 7. Comparison of Operation Findings Between AE and Non-AE Cases

case	age, sex	p-stage, histological type	operation modality	anesthesia	FiO_2 during operation	operation time	AE
1	69, M	pT1N0M0, Ad	RLL + ND2	TIVA + Epi	0.80-1.0	3 h 30 m	(+)
2	76, M	pT2N0M0, Sq	RLL + ND2	TIVA + Epi	0.50-1.0	3 h 27 m	(−)
3	61, M	pT1N0M0, Ad	RLL + ND2	TIVA + Epi	0.66-0.75	2 h 0 m	(−)
4	65, M	pT1N0M0, Sq	RLL + ND0	IHA + Epi	1.0	1 h 40 m	(−)
5	76, F	pT1N0M0, Ad	LLL + ND2	IHA + Epi	1.0	5 h 10 m	(−)
6	76, M	pT1N0M0, Sq	LUL + ND2	IHA + Epi	0.8-1.0	6 h 36 m	(−)

RLL: right lower lobectomy, ND2: group 2 node dissection, LLL: left lower lobectomy, LUL: left upper lobectomy, TIVA: total intravenous anesthesia, Epi: epidural anesthesia, IHA: inhalation anesthesia, h: hours, m: minutes.

Table 8. Comparison Between AE Group and Non-AE Group Before Anti-cancer Treatment

	AE group (n=6)	non-AE group (n=33)	P value
LDH (IU/l)	473±88	500±184	0.70
KL-6 (U/ml)	728±364	1026±633	0.20
SP-D (ng/ml)	141±140	144±93	0.95
PaO_2 (torr)	84±18	74±13	0.13
%VC (%)	89±13	96±22	0.43
%DLco (%)	64±20	54±20	0.27

鏡検査が4例に施行されたが，急性増悪は生じなかった．

さらに39例中6例の急性増悪群と33例の非急性増悪群の2群間において，肺癌治療前のLDH，KL-6，SP-D，PaO_2，%VC，%DLco値を比較したが統計学的有意差は認められなかった（Table 8）．

考　察

IPには進行性に呼吸不全に至るだけでなく，経過中に気道感染や外傷，外科的侵襲を契機に急性増悪を引き起こし致命的な結果を招く，極めて予後不良の疾患群が含まれる．[1] IP急性増悪の発症機序は，一つの仮説として，線維化刺激に反応しやすい状態の患者に，全身性のサイトカイン血症が引き金となると考えられている．[1]

また，IP，特にIPFは高率に肺癌を合併することが知られており8.7～36%と報告されている．[2-5] 当科における肺癌症例のIP合併頻度は5%であり，病期ごとの治療方法はIP合併のない原発性肺癌とほぼ一致しているが，低肺機能や高齢などの理由より肺癌治療の適応なしとされ，39例中9例（23%）にBSCが施行されていた．

IIP 合併肺癌の治療後急性増悪の発生頻度は化学療法が 8.7～11.5%，放射線治療が 25%，化学療法＋放射線療法が 23.1～36.4%，手術療法が 12.5～22%，と報告されている．[7-11] 本検討では化学療法後は 24 例中 5 例（21%），手術後は 6 例中 1 例（17%）で，諸家の報告と比較すると化学療法後の発症がより高頻度で，術後の発症は諸家の報告と一致していた．

術後の IP 急性増悪の発症要因には①術前の間質性肺炎の高い活動性，②術中高濃度酸素，③長時間の手術侵襲などが挙げられる．[12] IP 合併肺癌における術後の急性増悪の予防としては，高濃度の酸素曝露の回避の他に，erythromycin の術前投与が有効であるとの報告[13] や，手術期におけるステロイド投与の有効性を示している報告[14] もあるものの確立された予防方法はない．さらに，周術期のステロイド剤の投与に関しては，術前投与や減量が術後急性増悪を惹起するとの報告もあり，[2,15] 予防投与したステロイド剤は減量自体のリスクがある．このため，手術施行の 6 例にはステロイドの予防投与は行っていない．また，当科の化学療法においてのステロイド剤は betamethasone 4～8 mg/body を抗癌剤投与日のみに投与している．これは IP 非合併例の化学療法と同用量である．このようなステロイド剤の単回投与が IP 急性増悪の発症因子となりうるかは明らかでない．今回術後の急性増悪を認めた 1 例では手術時間や術中 FiO_2 でも明らかな誘因は認められなかった．現時点では術後の急性増悪を予防する具体的な方法は確立されておらず，術前の十分な IP の活動性の評価に加え，呼吸器外科医，麻酔科医，呼吸器内科医との十分な連携が必要である．

化学療法では，CDDP は VP-16 や VRB との併用で致死的肺障害が認められ，多剤併用療法での危険性が指摘されている．[16] さらに使用薬剤では GEM，CPT-11，AMR は投与禁忌，VRB，DOC，PAC，gefitinib は慎重投与と薬剤添付文書に記載されている．[2] 本検討でも化学療法後に IP 急性増悪を発症した 5 例全例にこれらの抗癌剤が使用されていた．肺小細胞癌に対する CBDCA＋VP-16 は諸家の報告，ならびに本検討をみても急性増悪例は少なく，比較的安全と考えられる．しかし，second line 以降の抗癌剤で，効果，副作用の面を考慮して推奨される抗癌剤はないことが現時点の問題点である．非小細胞肺癌では IP 合併例には慎重投与である DOC，PAC，VRB などとプラチナ製剤との併用が最も多用されている regimen であることが問題点として挙げられる．禁忌薬剤を使用する際には CT 上で IP の合併の有無の確認が重要である．

IP の急性増悪の発症の危険因子として従来より CRP，LDH，WBC などの上昇や，PaO_2，%VC の低下などが報告されている．[9,17,18] しかし，本検討では急性増悪群と非急性増悪群の 2 群間で肺癌治療前の LDH，KL-6，SP-D，PaO_2，%VC，%DLco の値に統計学的有意差は認められなかった．症例数が少ないことも一因と考えられるが，IP の活動性を示す KL-6 は腫瘍マーカーとしての側面を持ち，SP-D も肺癌に発現することがあるので，IP のみの活動性の評価が困難である点も挙げられる．[19,20] 以上より治療前における IP 急性増悪の予測は困難であることが示唆された．

また，本検討では，CVD-IP 合併肺癌の 9 例のうち 2 例（22%）に急性増悪を認めている．これは IIPs の 30 例中 4 例（13%）より高い割合であった．CVD-IP に肺癌を合併する頻度は 2～4% と報告されているが，[21] 辻田らの報告では 155 例中 19 例（12%）と報告されている．[22] CVD-IP は IIPs に比較して急性増悪を起こす頻度は少ないものの，膠原病の死因のうち IP が占める割合は 37.5% と高いことが報告されている．[23] CVD-IP の急性増悪の報告はシェーグレン症候群，RA，SSc，systemic lupus erythematosus，polymyositis/dermatomyositis などで散見されるが，[24-28] CVD-IP に合併した原発性肺癌に関する検討はほとんどない．また，RA/UIP の急性増悪は一般的に治療抵抗性であるとされ，[29] 富山ら[25] もステロイドパルス療法に抵抗性の RA/UIP の急性増悪症例を報告している．本検討でも IP 急性増悪を発症した 4 例中 2 例はいずれも RA/UIP であり，一旦急性増悪した後はステロイド抵抗性で極めて予後不良であった．

以上，IP 合併肺癌において，IIPs のみならず CVD-IP も急性増悪を生じうることを念頭に置き治療すべきであると考えられた．

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