

Spontaneous Pneumothorax and Pneumomediastinum in Patients with Idiopathic Interstitial Pneumonias

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Pneumothorax and pneumomediastinum sometimes occur in patients with idiopathic interstitial pneumonias (IIPs). Although steroid treatment is commonly used for IIPs, some reports indicated that this treatment could cause pneumothorax (PT) or pneumomediastinum (PM) in patients with IIPs. The aim of the present study was to evaluate the clinical features of PT and PM in patients with IIPs, and to assess their association with steroid treatment. We enrolled 77 patients with IIPs and divided them into four groups: (1) idiopathic pulmonary fibrosis (IPF) patients without PT and PM [IPF PT/PM(-) group, n = 38]; (2) IPF patients with PT and/or PM [IPF PT/PM(+) group, n = 6]; (3) non-IPF patients without these complications [non-IPF PT/PM(-) group, n = 29]; and (4) non-IPF patients with PT and/or PM [non-IPF PT/PM(+) group, n = 4]. We reviewed and compared the clinical, radiological and laboratory findings among the four groups. We also focused on the above 10 IIPs patients with PT and/or PM to describe the details of their clinical features. Resultingly, IPF PT/PM(+) and non-IPF PT/PM(+) groups showed low percentage of vital capacity (%VC) compared with IPF PT/PM(-) and non-IPF PT/PM(-) groups, respectively. Six of the 10 cases with PT/PM were treated with steroids about 2 weeks before the development of PT and/or PM. We concluded that PT and PM could arise in patients with IIPs, especially in cases with severe restrictive ventilatory impairment. Our results further suggest that clinicians should be aware of these complications after starting steroid treatment for interstitial lung diseases.

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Introduction

Idiopathic interstitial pneumonias (IIPs) are subsets of acute and chronic lung disorders collectively referred to as interstitial lung diseases or diffuse parenchymal lung diseases of unknown etiology.¹ It has been reported that pneumothorax (PT) and pneumomediastinum (PM) occasionally occur in association with IIPs.²⁻⁴ Although steroid treatment is commonly used for IIPs, some reports indicated that this treatment could cause PT or PM in patients with interstitial pneumonia (IP), especially with collagen vascular disease-related interstitial pneumonia (CVD-IP).⁵⁻⁷

The aim of the present study was to evaluate the clinical features of PT and PM in patients with IIPs and to assess their association with steroid treatment.

Subjects and Methods

The subjects of this study were 77 consecutive patients diagnosed with IIPs at Nagasaki University Hospital between January 2000 and January 2004. In all patients, high-resolution computed tomography (HRCT) showed abnormal interstitial changes in the lungs. The cases of IIPs included 44 patients with idiopathic pulmonary fibrosis (IPF),⁸ 11 with nonspecific interstitial pneumonia, 10 with cryptogenic organizing pneumonia, 1 with respiratory bronchiolitis-interstitial lung disease and 1 with desquamative interstitial pneumonia; final diagnoses were not made in the remaining 10 cases. None of the patients had a history of environmental or occupational exposure, clinical findings of hypersensitivity pneumonitis, or evidence of granulomas. In all patients, current infection caused by bacteria, mycobacteria, or fungi was excluded by negative cultures of bronchoalveolar lavage fluid.

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We classified the subjects into four groups: (1) IPF patients without PT and PM [IPF PT/PM(-) group, n = 38]; (2) IPF patients with PT and/or PM detected by the chest radiography or CT [IPF PT/PM(+) group, n = 6]; (3) non-IPF patients without these complications [non-IPF PT/PM(-) group, n = 29]; and (4) non-IPF patients with PT and/or PM [non-IPF PT/PM(+) group, n = 4]. We reviewed and compared the clinical, radiological and laboratory findings in the four groups. We also focused on the 10 patients with PT/PM to describe the details of their clinical features. None of these patients underwent surgical lung biopsies of PT or PM.

Measurements of continuous variates were all summarized by mean and standard deviation (SD). Fisher's exact test for 2×2 table was used to analyze the qualitative difference. The Mann-Whitney *U*-test was used to compare the difference in the mean of the respective continuous variates between the respective two groups. *P*-values less than 0.05 were regarded as significant. The study protocol was approved by the Human Ethics Review Committee of Nagasaki University School of Medicine and a signed consent form was obtained from each subject.

Results

Table 1 shows the characteristics of all subjects. The IPF group

and non-IPF group differed significantly (data not shown) in smoking habits, duration of IP, proportion of patient on steroid treatment, percentage of vital capacity (%VC), pulmonary bullous and honeycomb changes on HRCT. In patients with IPF, pulmonary function tests in PT/PM(+) group showed a significantly reduced mean %VC and increased forced expiratory volume in one second (FEV1%), but not the percentage of diffusing capacity of the lung for carbon monoxide (%DLCO), compared with PT/PM(-) group. With regard to serum biomarkers for IP, LDH and KL-6 were lower in IPF PT/PM(+) group compared with IPF PT/PM(-) group. In patients with non-IPF, only %VC was significantly reduced in PT/PM(+) group compared with PT/PM(-) group. All four cases in non-IPF PT/PM(+) group had no smoking habits. No significant difference was seen in patient backgrounds between PT cases and PM cases in any of IPF patients, non-IPF patients or both (data not shown).

Table 2 shows the clinical features of all patients with PT and/or PM. IPF cases included 4 cases with PT (Figure 1), 2 cases with PM (Figure 2), and 1 case with both complications simultaneously. On the other hand, non-IPF cases included 1 case with PT, 2 cases with PM, and 1 case with both complications simultaneously. Case 9 was histopathologically diagnosed as nonspecific interstitial pneumonia. When they were diagnosed with PT and/or PM by chest CT, 5 patients were suffering from moderate to severe cough and/or

Table 1. Distribution of characteristics in patients with interstitial pneumonias

Characteristics ^a	IPF ^b		Non-IPF	
	PT/PM(-) ^c	PT/PM(+)	PT/PM(-)	PT/PM(+)
Number of patients	38	6	29	4
Age (years)	67 (8) ^d	65 (11)	62 (15)	69 (1)
Sex (male/female)	30/8	4/2	16/13	1/3
Smoking history (+)	23 (60.5%)	4 (66.7%)	14 (48.3%)	0 (0%)
Duration of IP (month)	43 (43)	27 (22)	15 (18)	24 (16)
Steroid treatment	6 (15.8%)	2 (33.3%)	21 (72.4%)	4 (100%)
<i>Pulmonary function tests</i>				
%VC (%)	81.6 (23.4)	52.2 (13.1)*	90.7 (15.6)	49.4 (1.1) †
FEV1% (%)	79.6 (9.0)	91.3 (11.5)*	76.2 (11.2)	72.4 (27.4)
%DLCO (%)	46.3 (14.9)	59.7 (52.3)	64.0 (19.7)	No data
<i>Laboratory data</i>				
LDH (IU/L)	229 (67)	149 (48)*	218 (88)	248 (144)
KL-6 (U/mL)	1868 (2107)	685 (235)*	1257 (768)	1004 (635)
Surfactant protein-A (ng/mL)	120.7 (59.7)	95.5 (39.3)	103.8 (55.8)	79.4 (52.1)
Surfactant protein-D (ng/mL)	333 (272)	273 (184)	372 (459)	270 (98)
<i>Chest CT findings</i>				
Bullae (+)	22 (57.9%)	6 (100%)	7 (24.1%)	2 (50.0%)
Honeycomb change (+)	36 (94.7%)	6 (100%)	3 (10.3%)	1 (25.0%)

^a%VC=Percentage of vital capacity; FEV1%=Forced expiratory volume in one second; %DLCO=Percentage of diffusing capacity of the lung for carbon monoxide.

^bIPF=Idiopathic pulmonary fibrosis; PT=Pneumothorax; PM=Pneumomediastinum.

^cPT=Pneumothorax; PM=Pneumomediastinum; (+)=Positive; (-)=Negative.

^dMean (standard deviation)

**p*<0.05 compared with IPF PT/PM(-) group; †*p*<0.05 compared with non-IPF PT/PM

Table 2. Clinical features of patients with pneumothorax and/or pneumomediastinum

IPF/non-IPF ^a	Case No.	Age (years)	Sex ^b	PT/PM ^c	Duration of IP (months)	Symptom	Steroid therapy before PT/PM		Therapy for air leak
							Duration (days)	Administered dosed	
IPF	1	63	M	PT	41				rest cure
	2	59	M	PT	12	cough			drainage
	3	74	M	PT	8	dyspnea			resection of bleb
	4	76	F	PT	32		12	mPSL+PSL 40 mg/day	rest cure
	5	47	F	PM	63	cough, dyspnea	15	PSL 40 mg/day	rest cure
	6	74	M	PT/PM	7				rest cure
Non-IPF	7	70	M	PT	20		7	mPSL+PSL 40 mg/day	rest cure
	8	70	F	PM	40	dyspnea	10	mPSL+PSL 50 mg/day	rest cure
	9	67	F	PM	4	cough, dyspnea	28	PSL 40 mg/day	rest cure
	10	70	F	PT/PM	33		14	PSL 40 mg/day	rest cure

^aIPF=Idiopathic pulmonary fibrosis.

^bM=Male; F=Female.

^cPT=Pneumothorax; PM=Pneumomediastin.

^dmPSL=Methylprednisolone pulse therapy; PSL=Prednisolone.

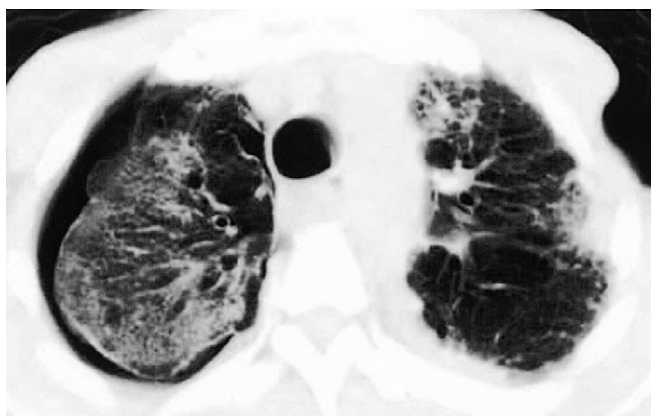


Figure 1. High-resolution computed tomography of the lungs (Case 1), showing reticular and ground glass opacities in both lungs, and pneumothorax in the right thorax.

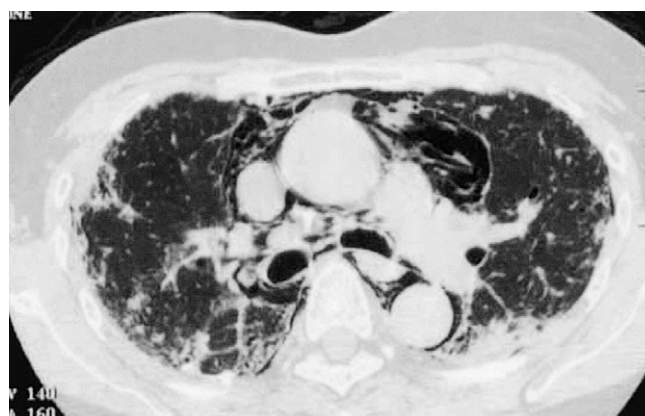


Figure 2. High-resolution computed tomography of the lungs (Case 9), showing bilateral fine reticular opacities and consolidations in both lungs, and air surrounding the mediastinum.

dyspnea. Six of the 10 patients had received oral steroid treatment and 3 of them had received methylprednisolone pulse therapy as well. The other four patients who did not receive steroid treatment had been diagnosed as IPF. The duration of steroid treatment before the development of PT or PM varied from 7 to 28 days with the mean (SD) of 14.3 (7.3) days. Although the PT in Case 2 required suction drainage and that of Case 3 was treated with resection of blebs by video-assisted thoracoscopic surgery, the PT and/or PM in the other cases disappeared spontaneously in a few weeks. None of the patient directly died of PT or PM.

Discussion

It has been reported that PT and/or PM sometimes occur in

association with IIPs and CVD-IP.^{2,4,9} The underlying mechanism of PT in such patients is thought to be associated with formation of subpleural cystic spaces related to diffuse interstitial fibrosis. Thus, the rupture of one of these cystic spaces is most likely the immediate cause of PT.¹⁰ With regard to PM, it has been suggested that rupture of alveoli secondary to increased intrathoracic pressure plays a significant role in the development of PM by allowing air to enter the interstitial space dissecting along the peribronchial sheaths and extending into the mediastinum.^{10,11}

We report here the clinicoradiological features of patients with IIPs complicated with PT and/or PM. These complications were reported in IIPs, especially IPF.^{2,4,12} McLoud¹² and Picado et al.⁴ reported that PT occurred in 7.4% and 3.6% of their IPF cases, respectively. Franquet et al.² also reported that PT occurred in 5.1% and PM in 6.4% of their IPF cases. Our results showed 5 cases (11.4

%) of PT and 2 cases (4.5%) of PM in IPF cases, and 2 cases (6.1%) of PT and 3 cases (9.1%) of PM in non-IPF cases. Two cases of PM in IPF cases were detected by HRCT, but not by the chest radiography. In this context, a small amount of air in the thoracic cavity is often difficult to detect by the chest radiography. Computed tomography is ideally suited for the detection of small air.

Although there were some differences in patient backgrounds between IPF and non-IPF, our cases with PT and/or PM exhibited several important features. Pulmonary function tests of the patients showed significantly reduced %VC, suggesting that PT and/or PM may easily occur in progressive cases of IIPs. KL-6 and LDH are known to be serum markers for the evaluation of disease activity in IIPs.¹³⁻¹⁵ In our cases, the levels of serum KL-6 and LDH in IPF PT/PM(+) group were significantly lower than those in IPF PT/PM(-) group. In addition, serum KL-6 was lower in patients with advanced stage (%VC < 60%) than in those with non-advanced stage (data not shown). These results also suggest that PT or PM in IPF could occur in patients with advanced IPF rather than active IPF. Though not significant, cases of IPF PT/PM(+) group showed pulmonary bullous change in HRCT more frequently than those of IPF PT/PM(-) group, indicating that not only IPF itself but also smoking-related pulmonary bullous change might induce PT or PM. Most of either PT cases or PM cases did not need aggressive treatment, suggesting that these complications in patients with IIPs are not severe, probably due to a decrease in lung compliance or other factors.

The most interesting clinical observation in our cases was that 6 of these 10 patients had received steroid treatment before the development of PT and/or PM, and that the period between the development of PT and/or PM and the commencement of steroid therapy was short (7-28 days). In addition, although all patients with non-IPF complicated with PT and/or PM were non-smokers, they developed PT and/or PM after steroid administration. Yamanishi et al.⁵ postulated that weakening of the interstitial tissues of the lung, caused by steroid therapy, might predispose to PM. Consistent with their findings, Barvaux and colleagues¹⁶ who reviewed the literature on PM associated with dermatomyositis, showed that 18 of 20 cases developed PM during steroid treatment. Our findings suggest that steroid treatment is associated with increased incidence of

PT and PM in patients with IIPs as well as CVD-IP.

In conclusion, PT and PM could arise in patients with IIPs, especially in patients with restrictive ventilatory impairment. Although these complications in our cases were not severe, our results suggest that clinicians should be aware of these complications after starting steroid treatment in patients with interstitial lung diseases.

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