

Influence of Smoking in Interstitial Pneumonia Presenting with a Non-Specific Interstitial Pneumonia Pattern

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Abstract

Objective The influence of smoking on the pathogenesis and clinical course of interstitial pneumonia has recently attracted attention. To clarify the influence of smoking on the clinical patient characteristics and therapeutic effects in patients with interstitial pneumonia presenting with a non-specific interstitial pneumonia (NSIP) pattern, we compared the clinical patient characteristics and therapeutic effects in smokers and non-smokers in this study.

Methods We divided 31 NSIP (16 idiopathic nonspecific interstitial pneumonia and 15 collagen vascular disease-associated nonspecific interstitial pneumonia) patients into smoker and non-smoker groups for each case. The patient characteristics, pulmonary function tests, Krebs von den Lungen 6 (KL-6), surfactant protein D (SP-D), bronchoalveolar lavage fluid findings, and clinical courses for two years were compared between the smoker and non-smoker groups.

Results The smoking subgroup (n=15) of NSIP patients had a significantly lower % diffusing capacity for carbon monoxide/ alveolar ventilation (DL_{CO}/VA) and tended to have higher SP-D values than the nonsmoking subgroup (n=16). Although no difference was observed regarding the prognosis, 5 of 6 cases with NSIP, which had worsening of lung disease were heavy smokers with a pack-year history of 40 or greater.

Conclusion Smoking is thus suggested to negatively influence the diffusing capacity caused by damage to alveolar epithelial cells. In addition, smoking may also be potentially related to resistance to therapy in NSIP cases.

Key words: non-specific interstitial pneumonia, smoking, diffusion capacity, SP-D, therapy resistance

(Intern Med 55: 2939-2944, 2016)

(DOI: 10.2169/internalmedicine.55.6890)

Introduction

The prognosis of patients with non-specific interstitial pneumonia (NSIP) is good and it is suggested that NSIP is a clear clinical entity in many middle-aged females who are nonsmokers (1, 2). However, there are some reports suggesting an influence of smoking in NSIP patients (2-4). Smoking is suggested to be a prognostic factor for NSIP (5), and there may be a relationship between NSIP and pulmonary emphysema (4). However, the relationship between smoking and NSIP has not yet been clarified. To clarify the influence of smoking on the clinical patient characteristics and therapeutic effects in patients with NSIP, we compared both the

characteristics and therapeutic effects in smokers and non-smokers in this study.

Materials and Methods

Patient selection

We conducted a retrospective study of 31 NSIP [16 idiopathic nonspecific interstitial pneumonia (iNSIP) and 15 collagen vascular disease-associated nonspecific interstitial pneumonia (CVD-NSIP)] patients, in which thoracoscopic lung biopsy had been performed and comprehensive diagnoses were made based on both clinical and imaging findings from 1995 to 2012 at Jichi Medical University Hospital (To-

Table 1. Patient Characteristics.

Number	31
Sex (male/female)	11/20
Age	54±10 (40-71)
Smoking history (Never/Ever/Current)	16/15/0
Duration (M)	56±39 (6-166)
Emphysema (+/-)	2/29
Pulmonary function test	
FVC (L)	2.42±0.84 (1.25-3.33)
FVC% predicted (%)	73.8±11.2 (51.1-93.6)
FEV1.0/FVC (%)	84.3±15.3 (68.4-100.0)
DLco/VA% predicted (%)	88.9±19.6 (53.5-126.3)
Serum marker	
KL-6 (U/mL)	2,257±1,488 (445-5,350)
SP-D (ng/mL)	321±212 (48.1-970)

Data are shown as the mean±SD (range).

FVC: forced vital capacity, FEV1.0: forced expiratory volume 1.0 %, DLco/VA: diffusing capacity for carbon monoxide/alveolar ventilation, KL-6: Krebs von den lungen 6, SP-D: surfactant protein-D

chigi, Japan). A specialized pathologist made the pathological diagnosis by investigating all tissue specimens based on the ATS/ERS 2013 standard (2). Any cases for which definite diagnoses were made for malignant conditions at the time of medical examination and follow-up were excluded. CVD was confirmed based on a diagnosis made by a rheumatologist.

Study design

In this study, we investigated the patient characteristics in each case, including the finding of pulmonary function tests, Krebs von den Lungen 6 (KL-6), surfactant protein D (SP-D), bronchoalveolar lavage fluid findings, and clinical courses, thus classifying the patients into 2 groups - one group with and one group without a smoking history. We also divided 31 NSIP patients into 16 iNSIP and 15 CVD-NSIP, and examined them in the same manner. A progression of NSIP was defined as all of the following: 1) a recurrence of subjective symptoms; 2) an increase in consolidation or ground-glass attenuation on chest high-resolution computed tomography images; 3) the need to increase corticosteroid or immunosuppressant medication. In progression cases, infections were excluded if there was no clinical (e.g., grossly purulent sputum absent and patients resistant to antibiotic therapy) or microbiological evidence for infection. All patients were observed for 2 years after treatment. This study was approved by the Bioethics Committee for Clinical Research A, Jichi Medical University Hospital (Approval date: August 4, 2015; Approved A-15-022).

Statistical analysis

The probability of a progression-free survival (PFS) was calculated using the Kaplan-Meier method and the log-rank test was used to compare the PFS in the two groups. A *p* value <0.05 was regarded as statistically significant in all tests. All statistical analyses were performed using the SPSS statistical software package (version 19; SPSS, Inc., Chicago, USA).

Results

Table 1 shows the entire background of the patients and the examination findings for 31 NSIP cases. There were 11 male cases. Regarding age, the patients were 54±10 years old. There was no current smokers. Emphysematous changes on chest computed tomography were observed in 2 cases. In pulmonary function tests, the forced vital capacity (FVC) was 2.42±0.84 L. %FVC was 73.8±11.2%, forced expiratory volume (FEV1.0) /FVC was 84.3±15.3, while % diffusing capacity for carbon monoxide/alveolar ventilation (DLco/VA) was 88.9±19.6%. We thus divided the patients into 16 iNSIP and 15 CVD-NSIP. There were no significant differences in the characteristics between iNSIP and CVD-NSIP patients (Table 2). Table 3 shows the patient backgrounds classified into smoking and non-smoking groups. There were 15 smokers and 16 non-smokers. Emphysematous changes were observed in 2 of 15 cases in the smoking subgroup. Pulmonary function tests showed %FVC to be 74.5±7.5% for the smoking group, which tended to be significantly higher than that of the non-smoking group. FEV1.0/FVC was 78.3±20.4%, and the diffusing capacity in the smoking group was %DLco/VA 72.4±10.6%, which was significantly lower than that of the non-smoking group. The KL-6 levels showed no significant differences between these two groups. The smoking group exhibited significantly higher SP-D scores in the serum. We divided the patients into iNSIP and CVD-NSIP groups, and then examined them in the same manner (Table 4). The iNSIP group consisted of 10 smokers and 6 non-smokers while the CVD-NSIP patients comprised 5 smokers and 10 non-smokers. Emphysematous changes were observed in 2 of 10 cases in the smoking subgroup of iNSIP patients while such changes were noticed in none of the 5 cases in the smoking subgroup of CVD-NSIP patients. In the smoking group iNSIP, lung function tests showed % FVC to be 70.1±4.5% and FEV1.0/FVC to be 75.9±7.4%; while the diffusing capacity in the smoking group was % DLco/VA 71.6±7.5%, which was significantly lower than that of the non-smoking group. %FVC tended to be high, and %DLco/VA was significantly low in the smoking group with CVD-NSIP. The KL-6 levels showed no significant differences between these two groups. The smoking group exhibited significantly higher SP-D scores in the serum in iNSIP. On the other hand, the smoking group with CVD-NSIP showed no significant difference in the SP-D levels, though these tended to be high. According to the above results, the influence of smoking that gave in iNSIP and CVD-NSIP was the same. We examined whether any correlation existed between the pack-years and DLco or SP-D. As a results, a weak correlation was found between the pack-years and DLco and a strong correlation was seen between the pack-years and SP-D (Fig. 1, 2). Fig. 3 shows the Kaplan-Meier curves of PFS in both the smoker and non-smoker groups. PFS was better in the non-smoker group than that in the smoker group (*p*=0.0489). In addition, neither the smoking

Table 2. Patient Characteristics with iNSIP and CVD-NSIP.

	iNSIP	CVD-NSIP	p value
Number	16	15	
Sex (male/female)	8/8	3/12	
Age	53±11 (40-69)	55±8 (43-71)	0.623
Smoking history (Never/Ever/Current)	6/10/0	10/5/0	
Duration (M)	62±34 (4-140)	80±46 (4-166)	0.365
Emphysema (+/-)	2/14	0/15	
Pulmonary function test			
FVC (L)	2.32±0.87 (1.25-3.19)	2.54±0.79 (1.75-3.33)	0.634
FVC% predicted (%)	75.4±7.9 (67.5-83.3)	72.1±14.5 (51.1-93.6)	0.645
FEV1.0/FVC (%)	81.6±6.9 (68.4-100.0)	86.9±5.6 (78.2-97.7)	0.412
DLco/VA% predicted (%)	86.0±22.2 (53.5-126.2)	91.8±17.0 (57.1-126.3)	0.245
Serum marker			
KL-6 (U/mL)	2,721±2,132 (445-5,350)	1,794±845 (698-2,470)	0.128
SP-D (ng/mL)	309±201 (48.1-898)	333±222 (156-970)	0.487

Data are shown as the mean±SD (range).

iNSIP: idiopathic non-specific interstitial pneumonia, CVD: collagen vascular disease, FVC: forced vital capacity, FEV1.0: forced expiratory volume 1.0%, DLco/VA: diffusing capacity for carbon monoxide/alveolar ventilation, KL-6: Krebs von den lungen 6, SP-D: surfactant protein-D

Table 3. Patient Characteristics of Smokers and Non-Smokers.

	NSIP (n=31)		p value
	Smoker	Non smoker	
Number	15	16	
Sex (male/female)	9/6	2/14	
Age	52±12 (43-71)	53±13 (40-69)	0.754
Duration (M)	424±14 (6-140)	53±20 (19-166)	0.768
Emphysema	2	0	
Pulmonary function			
FVC% predicted (%)	74.5±7.5 (67.7-93.6)	59.5±16.4 (51.1-75.5)	0.097
FEV1.0/FVC (%)	78.3±20.4 (51.1-85.5)	79.5±11.3 (72.2-93.6)	0.481
%DLco/VA (%)	72.4±10.6 (53.5-80.0)	113.4±11.9 (101.1-126.3)	0.021*
Serum marker			
KL-6 (U/mL)	2,130±1,573 (663-5,350)	2,490±1,769 (445-4,130)	0.965
SP-D (ng/mL)	487±342 (145-970)	175±79 (48.1-760)	0.049*
BALF total count (×10 ⁵)	3.36±1.29 (2.1-4.5)	2.51±1.19 (1.4-4.1)	0.612
Macrophage (%)	64.1±25.7 (51.1-90.2)	59.2±14.7 (46.2-72.1)	0.688
Neutrophil (%)	8.74±5.75 (3.9-10.2)	6.65±5.75 (0.9-11.4)	0.337
Lymphocyte (%)	21.1±19.5 (10.2-41.1)	29.5±13.1 (14.4-42.6)	0.811
Eosinophil (%)	5.46±4.17 (0.9-8.2)	4.87±2.58 (1.6-6.5)	0.561
CD4/8 (%)	1.87±1.38 (0.5-3.0)	1.54±1.49 (0.1-2.9)	0.356

Data are shown as the mean±SD.

* : statistically significant

FVC: forced vital capacity, FEV1.0%: forced expiratory volume 1.0 %, DLco/VA: diffusing capacity for carbon monoxide/alveolar ventilation, KL-6: krebs von den lungen 6, SP-D: surfactant protein-D, BALF: bronchoalveolar lavage fluid

or non-smoking groups reported any mortality due to a progression of interstitial pneumonia, and no differences were observed in their prognoses. Six of 15 NSIP patients in the smoking group and 2 of 16 cases in the non-smoking group had showed a deterioration of their symptoms during the 2-year period after the start of treatment. Five out of 8 progression cases in the smoking group had a history of more than 40 pack-years (Table 5).

Discussion

In this study, we examined the influence of smoking on interstitial pneumonia exhibiting a nonspecific interstitial pneumonia pattern. Fifteen (48%) of 31 NSIP patients had a smoking history. It has been reported that smoking is closely

related to the onset and progress of lung fibrosis (4-6). According to an ATS statement (2), 20 (31%) of 65 cases with idiopathic NSIP were found to have a history of smoking. Another report suggests that iNSIP is also related to smoking (4). In addition, a further report disclosed that it was difficult to distinguish approximately 30% of desquamative interstitial pneumonia patients with an established tissue diagnosis from fibrotic-NSIP by computed tomography (7).

In addition, since DLco/VA fell to a low level, this implied that smoking negatively influenced their diffusing capacity. It is reported that the smoking in interstitial pneumonia patients leads to gas change disorders due to hypertrophy of the interstitium and a decrease in ventilation efficiency. Moreover, a decrease in hemoglobin, which is responsible for binding oxygen also causes a decrease in

Table 4. Patient Characteristics of Smokers and Non-Smokers with CVD-NSIP and iNSIP.

	iNSIP			CVD-NSIP		
	Smoker	Non smoker	p value	Smoker	Non smoker	p value
Number	10	6		5	10	
Sex (male/female)	7/3	1/5		2/3	1/9	
Age	54±11	52±12	0.724	50±13	55±12	0.724
Duration (M)	42±15	55±22	0.738	45±13	51±14	0.658
Emphysema	2	0		0	0	
Pulmonary function						
FVC% predicted (%)	70.1±4.5	66.4±5.2	0.161	79.9±9.5	67.2±8.6	0.232
FEV1.0%-G (%)	75.9±7.4	79.9±6.3	0.461	82.7±7.4	80.2±7.1	0.562
%DLco/VA (%)	71.6±7.5	103.4±8.7	0.009*	72.4±7.7	91.51±8.1	0.044*
Serum marker						
KL-6 (U/mL)	2,740±2,373	2,690±1,869	0.965	1,382.6±463.8	2,023.7±942.5	0.183
SP-D (ng/mL)	507±322	183±76	0.048*	389±212	172±78	0.097
BALF total count (×10 ⁵)	4.28±3.46	3.33±1.10	0.607	2.30±0.86	2.03±1.10	0.731
Macrophage (%)	62.1±23.6	58.2±4.66	0.808	56.6±15.0	60.4±21.4	0.769
Neutrophil (%)	5.45±4.86	1.43±0.54	0.248	12.9±13.0	8.34±16.1	0.650
Lymphocyte (%)	27.8±25.9	33.4±2.73	0.751	16.6±11.8	27.3±18.6	0.343
Eosinophil (%)	4.58±2.95	6.7±4.07	0.458	7.62±6.65	2.22±1.66	0.087
CD4/8 (%)	1.06±1.63	0.29±0.19	0.495	0.34±0.21	1.95±3.83	0.438

Data are shown as the mean±SD.

*: statistically significant

iNSIP: idiopathic non-specific interstitial pneumonia, CVD: collagen vascular disease, FVC: forced vital capacity, FEV1.0%-G: forced expiratory volume 1.0%-Gaensler, DLco/VA: diffusing capacity for carbon monoxide/alveolar ventilation, KL-6: krebs von den lungen 6, SP-D: surfactant protein-D, BALF: bronchoalveolar lavage fluid

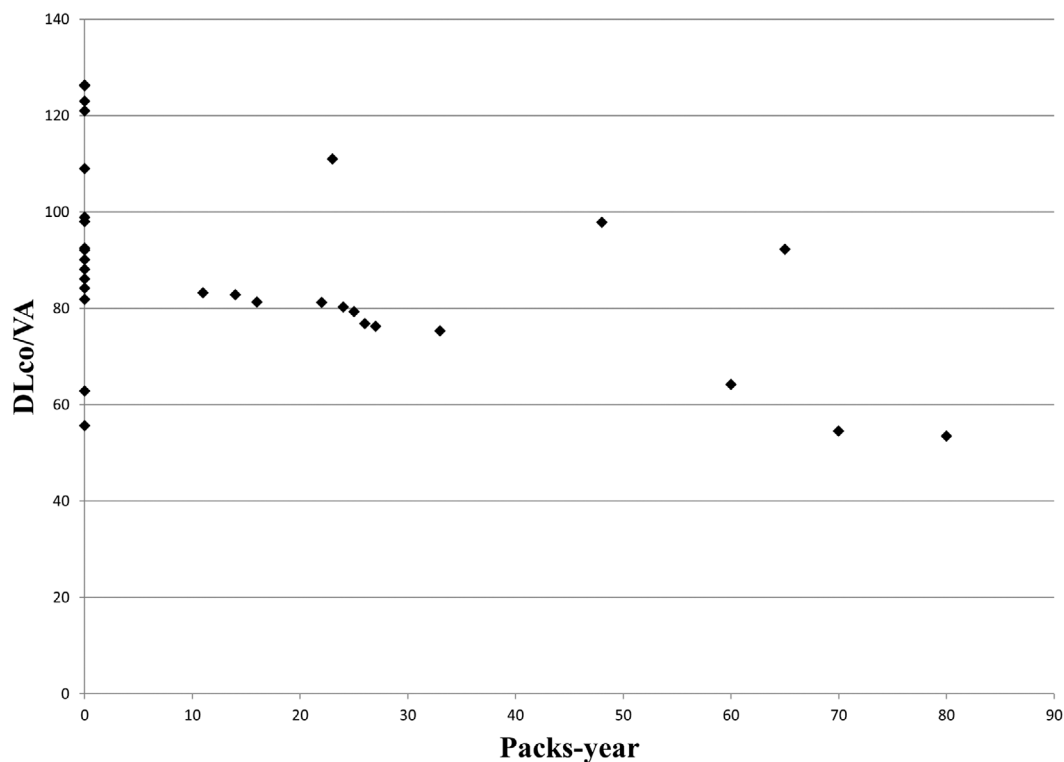


Figure 1. Correlation between pack-years and DLco/VA. There was weak a correlation between pack-years and DLco ($r=-0.483$).

DLco (8). Comparisons between the SP-D values for NSIP in the smoking and non-smoking groups have shown the values to be significantly higher in the smoking group. SP-D, which is a hydrophilic glycoprotein, belongs to one of the C-type lectin subgroups, and it is expressed specifically in type II alveolar epithelial cells (7, 9). The serum SP-D value has been reported to increase in smoker patients, and

a correlation has been reported between smoking and the serum SP-D values (10). Our results were therefore consistent with the findings of previous studies. However, the precise mechanism leading to increased serum levels is unclear. Based on the currently most widely accepted hypothesis, SP-D translocates from the lung to the blood, a process that could be regulated by changes in alveolar-capillary perme-

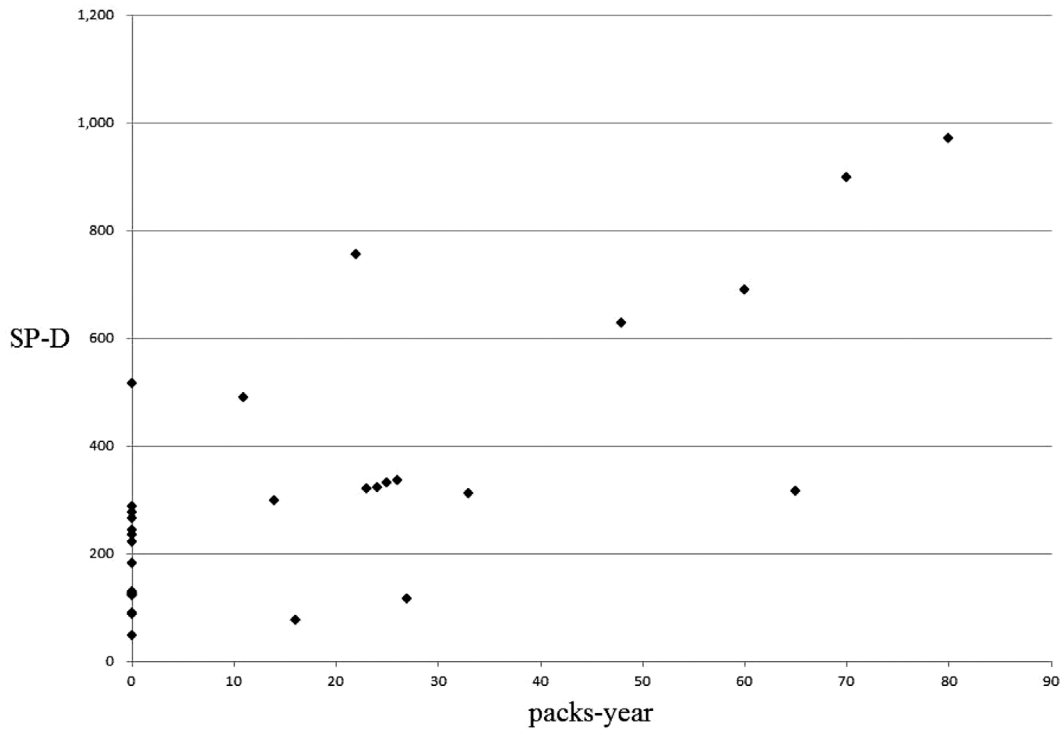


Figure 2. Correlation between pack-years and SP-D. There was a strong correlation between pack-years and SP-D ($r=0.740$).

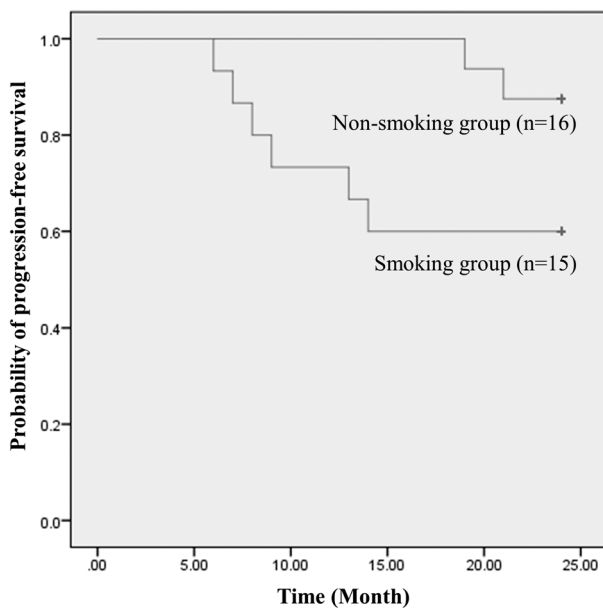


Figure 3. The Kaplan-Meier distribution for the probability of a progression-free survival (PFS) in the patients with NSIP. The p value was calculated using the log-rank test. The blue line represents the smoker group, and the green line represents the non-smoker group. PFS was significantly better in the non-smoker group than that in the smoker group ($p=0.0489$).

ability (11). Additionally, Aoshiba et al. reported that the oxidative stress caused by a smoking stimulus induced the aging of type II alveolar epithelial cells (12, 13).

No mortality due to interstitial pneumonia was found in

Table 5. Pack-year Distribution in the Patients who Showed a Deterioration of Their Symptoms during the 2-year Period after the Start of Treatment.

	Pack-year			total
	-	0-40	≥ 40	
Patients (n=31)	2 (25%)	1 (13%)	5 (63%)	8

either the smoking or non-smoking groups for NSIP and no differences were observed in their prognoses.

However, 6 of 15 NSIP patients in the smoking group and 2 of 16 cases in the non-smoking group showed a deterioration in their symptoms 2 years after the start of medical treatment. Five of the 6 patients showing an exacerbation in the smoking group were heavy smokers, namely those with a history of more than 40 pack-years. These findings suggest that it is necessary to carefully follow up heavy smokers who have a history of more than 40 pack-years.

This study was associated with some limitations including the fact that we were not able to include the degree of severity in NSIP, since this study was retrospective in a single-institution and the number of cases was limited. However, the study parameters were thoroughly measured in all cases at one year and two years later so that the authors could accurately follow the data. Evaluations taking into account the degree of disease severity will thus be needed in the future.

In conclusion, these findings suggested that smoking negatively influences the diffusing capacity caused by damage to alveolar epithelial cells, and that smoking also influences some of the cases that show resistance to treatment

among NSIP patients with a smoking history. It is therefore necessary to examine the influence of smoking on NSIP patients in a greater number of cases in the future.

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

Acknowledgement

We thank Toru Tanaka for his valuable help in making the pathological diagnosis.

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