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

Tetsuro Sawata, Masashi Bando, Masayuki Nakayama, Naoko Mato, Hideaki Yamasawa and Yukihiko Sugiyama

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 (DLCO/VA) and tended to have higher SP-D values than the non-smoking 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-
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).

**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.

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 78.5±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  | 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

|                  | iNSIP       | CVD-NSIP   | p value |
|------------------|-------------|------------|---------|
| 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

|                  | iNSIP       | CVD-NSIP   | p value |
|------------------|-------------|------------|---------|
| 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.

|                  | Smoker       | Non smoker  | p value |
|------------------|--------------|-------------|---------|
| 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 test

|                  | iNSIP       | CVD-NSIP   | p value |
|------------------|-------------|------------|---------|
| FVC% predicted (%)| 74.5±7.5 (67.7-93.6)| 79.5±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

|                  | iNSIP       | CVD-NSIP   | p value |
|------------------|-------------|------------|---------|
| 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 (%)   | 8.7±4.5 (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.

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

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

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

|                  | iNSIP Smoker | Non smoker | p value | CVD-NSIP 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   | 0.046   | 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        | 91.5±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 (×10⁵) | 4.2±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       | 8.3±14.1   | 0.650   |
| Lymphocyte (%)   | 27.8±25.9    | 33.4±2.73  | 0.751   | 16.6±11.8       | 27.3±18.6  | 0.343   |
| Eosinophil (%)   | 4.5±3.9      | 6.7±4.07   | 0.458   | 7.6±6.65        | 2.2±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 a weak 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-
There was a strong correlation between pack-years and SP-D (r=0.740).

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 | Patients (n=31) |
|-----------|----------------|
|           | 0-40 | ≥40 | total |
| Smoking   | 2 (25%) | 1 (13%) | 3 (30%) |
| Non-smoking | 2 (15%) | 1 (7%)  | 3 (20%) |

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).

No mortality due to interstitial pneumonia was found in 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.

References

1. Travis WD, Hunninghake G, King TE Jr, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med 177: 1338-1347, 2008.
2. Travis WD, Costabel U, Hansell DM, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188: 733-748, 2013.
3. Samara KD, Margaritopoulos G, Wells AU, Siafakas NM, Antoniou KM. Smoking and pulmonary fibrosis: novel insights. Pulm Med 2011: 461439, 2011.
4. Marten K, Milne D, Antoniou KM, et al. Nonspecific interstitial pneumonia in cigarette smokers: a CT study. Eur Radiol 19: 1679-1685, 2009.
5. Ma JW, Li ZH, Xu H, Wang HJ, Kang J, Yu RJ. A comparison of clinical features between patients with idiopathic pulmonary fibrosis combined with emphysema and without emphysema. Zhonghua J He He Xi Za Zhi 36: 173-176, 2013 (in Chinese, Abstract in English).
6. Schwartz DA, Merchant RK, Helmers RA, Gilbert SR, Dayton CS, Hunninghake GW. The influence of cigarette smoking on lung function in patients with idiopathic pulmonary fibrosis. Am Rev Respir Dis 144: 504-506, 1991.
7. Wright JR. Immunoregulatory functions of surfactant proteins. Nat Rev Immunol 5: 58-68, 2005.
8. Fujimoto K. Pulmonary function in combined pulmonary fibrosis and emphysema. The Japanese Journal of Chest Diseases 72: S200-S204, 2013 (in Japanese).
9. Goerke J. Lung surfactant. Biochim Biophys Acta 344: 241-261, 1974.
10. Winkler C, Atochina-Vasserman EN, Holz O, et al. Comprehensive characterisation of pulmonary and serum surfactant protein D in COPD. Respir Res 12: 29, 2011.
11. Hermans C, Bernard A. Lung epithelium-specific proteins: characteristics and potential applications as markers. Am J Respir Crit Care Med 159: 646-678, 1999.
12. Aoshiba K, Nagai A. Chronic lung inflammation in aging mice. FEBS Lett 581: 3512-3516, 2007.
13. Tsuji T, Aoshiba K, Nagai A. Cigarette smoke induces senescence in alveolar epithelial cells. Am J Respir Cell Mol Biol 31: 643-649, 2004.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).