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Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP

S. Nagai*, M. Kitaichi**, H.Itoh+, K. Nishimura*, T. Izumi*, T.V. Colby‡

Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. S. Nagai, M. Kitaichi, H.Itoh, K. Nishimura, T. Izumi, T.V. Colby. ©ERS Journals Ltd 1998.

ABSTRACT: Based on past difficulties in clinically differentiating patients with idiopathic pulmonary fibrosis (IPF), bronchiolitis obliterans-organizing pneumonia (BOOP), and nonspecific interstitial pneumonia/fibrosis (NSIP), which all manifest clinically as interstitial lung disease, experience with pathologically confirmed examples of the three diseases was reviewed to compare clinical profiles and prognosis and to define NSIP more clearly.

Thirty-one patients (15 males and 16 females) were pathologically identified as NSIP and subclassified into either the cellular (n=16) or fibrotic group (n=15). All 31 patients were clinically considered to be idiopathic NSIP cases. Patients with idiopathic BOOP (n=16) and IPF (n=64) were compared with the NSIP patients.

Subacute presentation of interstitial lung disease characterized both idiopathic NSIP and idiopathic BOOP. NSIP patients showed volume loss on a chest radiograph (29.0%) and honeycombing on a computed tomography scan (25.8%); these features were not found in BOOP patients. Bronchoalveolar lavage lymphocytosis was characteristic of both BOOP and NSIP. Two subgroups of NSIP can be recognized histologically: patients in the fibrotic group had a less favourable outcome than those in the cellular group. BOOP and NSIP had a more favourable outcome than IPF.

In conclusion, idiopathic nonspecific interstitial pneumonia can be differentiated from other types of idiopathic interstitial pneumonia, both pathologically and clinically.

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Dept of *Respiratory Medicine, Graduate School of Medicine, Kyoto University, and **Laboratory of Anatomical Pathology and +Dept of Radiology, Kyoto University Hospital, Kyoto, Japan. ‡Mayo Clinic, Scottsdale, Arizona, USA.

Correspondence: S. Nagai, Dept of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8507, Japan, Fax: 81 757514643

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The entities included under the heading of idiopathic interstitial pneumonia (IIP) are a subset of the interstitial pneumonia of unknown aetiology, which have been grouped together since the work of LIEBOW [1]. They have undergone considerable changes in classification and some additions since the original classification, which included only chronic interstitial pneumonias, *i.e.* usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with interstitial pneumonia (BIP), lymphocytic interstitial pneumonia (LIP) and giant cell interstitial pneumonia (GIP) [1]. Recently, KATZENSTEIN and coworkers [2–4] have suggested a classification of IIP that includes not only chronic interstitial pneumonias (UIP and DIP), but also acute interstitial pneumonia (AIP) and nonspecific interstitial pneumonia/fibrosis (NSIP). NSIP can be defined histologically since it lacks features of UIP, DIP, bronchiolitis obliterans-organizing pneumonia (BOOP), diffuse alveolar damage (DAD), LIP [1] or GIP [1]. The recognition of NSIP has coincided with clarification of the pathological features of the other lesions, particularly UIP. As a result, UIP is no longer a "wastebasket" histological diagnosis; it now has histological features that are definable and recognizable [4, 5].

BOOP was not included in the classification of IIP by KATZENSTEIN *et al.* [6], because the disease is defined histologically in the airspaces. However, in clinical practice, patients with idiopathic BOOP are often included in the clinical and histologic differential diagnosis of IIP [7–12] and this type of pneumonia has been included in the present study.

A number of NSIP patients were sampled from large numbers of IIP patients [5, 13, 14]. These cases have all been recognized on the basis of histological differences from other IIP cases. Some NSIP patients were found in patients suspected of having BOOP at the time of the initial examination, while others were found in patients initially thought to have idiopathic pulmonary fibrosis (IPF) (UIP). Therefore, it was thought worthwhile to compare the clinical features and prognoses of BOOP, NSIP and IPF (UIP), respectively, and this formed the rationale for the present study.

Although NSIP cases in the original report included interstitial pneumonia, either idiopathic or secondary to an identified context, such as collagen vascular diseases or a drug reaction [4], this comparative study focused on the selection of patients with idiopathic NSIP. Indeed, regarding the prognosis of BOOP, previous studies have revealed differences in clinical outcome between idiopathic and secondary BOOP associated with collagen vascular diseases [15] and between idiopathic UIP and UIP associated with systemic sclerosis [16].

For editorial comments see page 1003.

In this report, the authors' experience with a series of 31 cases of idiopathic NSIP patients is reviewed and compared with cases of IPF (UIP) and idiopathic BOOP, to identify criteria that may be useful in differentiating among these three categories.

Materials and methods

The purpose of the Kyoto conference, organized by T. Izumi and colleagues in 1994, was to review collectively all patients with NSIP identified by pathological examination among the many patients with interstitial pneumonia. The presumed NSIP patients were subsequently evaluated by a panel of nine pathologists using similar histopathological criteria, to determine if an agreement could be reached on whether these patients represented NSIP. In the first conference, 45 IIP patients who were not clearly diagnosed histologically but were considered to be putative examples of NSIP based on surgical (open or thoracoscopic) lung biopsies were selected from 18 medical centres throughout Japan. The biopsies were intensively reviewed by nine Japanese pathologists using a blinded procedure. The pathologists received no information about clinical features, and patients with other types of interstitial lung disease (ILD) were also included to avoid a bias from the exclusive use of NSIP patients.

At a second International Conference in Kyoto in 1995, 31 patients with the histology of NSIP were reselected through intensive review of the previous 45 cases. By definition, 14 patients with collagen vascular diseases, putative drug reactions and identifiable infections were excluded to ensure the validity of comparison with the other IIPs. The 14 patients excluded by the pathology panel were: three with UIP, two with honeycombing (not UIP), two with BOOP, one with fibrotic NSIP associated with Sjögren's syndrome, one with eosinophilic granuloma, one with eosinophilic pneumonia, one with hypersensitivity pneumonitis and bron-chiectasis, one with organizing DAD, one with pulmonary veno-occlusive disease and one with respiratory bronchiolitis associated with ILD (RB-ILD). As a result, three of these cases were redefined as UIP and two as BOOP.

Four pathologists (T.V. Colby, A.M. Churg, J.L. Wright and M. Kitaichi) reviewed the 31 cases. Differential points are summarized in table 1. It was easy to differentiate NSIP from either LIP or DIP, by identifying an absence of desquamation of cells into alveolar spaces, as in DIP, or an absence of a variable spectrum of lymphoid cells, as in LIP.

BOOP, UIP and NSIP are described as follows: BOOP shows oedematous tufts of granulation-type tissue, predominantly within airspaces, usually alveolar tufts, but often involving bronchioles as well. There is a mild-to-moderate interstitial infiltrate in the regions of organization usually associated with a modest type II cell proliferation.

UIP is characterized by patchy scarring of the lung parenchyma with intervening normal or nearly normal alveoli. The most fibrotic zones show honeycombing with complete destruction of the architecture and in these regions inflammation, mucostasis, and metaplastic epithelial changes may all be prominent. The subpleural and paraseptal distribution, the patchy character, and the temporal heterogeneity are the most helpful features in establishing the diagnosis of UIP. Uniform involvement of lung parenchyma, marked chronic inflammation in the interstitium, and prominent pericentral scarring are all features against the diagnosis of UIP.

NSIP represents the heterogeneous group of interstitial pneumonias that histologically do not fit with other categories. However, the key histological features of NSIP in comparison with BOOP are a mild degree of intra-airspace organization and the presence of honeycombing with a loss of alveolar structure, while the key feature of NSIP in comparison with UIP is an absence of temporal heterogeneity of the fibrous tissue.

The 31 patients with NSIP were subdivided into two groups (cellular and fibrotic groups), which were further subcategorized according to the classification system of

Table 1. – Histopathological features of idiopathic nonspecific interstitial pneumonia/fibrosis (NSIP) compared with other types of idiopathic interstitial pneumonia

	Type of pulmonary lesion					
	Cellular NSIP	Fibrotic NSIP	UIP/IPF	DIP	BOOP	DAD/AIP
Distribution of pulmonary lesions	Diffuse	Periacinar predominant/ diffuse	Periacinar predominant/ diffuse	Diffuse	Centrilobular predominant	Diffuse
Type of intra-acinar fibrosis	Homogenous*	Homogenous*	Homogenous+	Homogenous*	Homogenous*	Homogenous*
Density of fibrotic lesions	Loose	Dense/loose	Dense	Dense	Loose	Loose
Honeycombing‡	0	0–+1	+1–+3	0–+1	0	0–+3
Fibrotic lesions with loss of normal alveolar structures‡	0–+2	+1–+3	+1–+3	0–+1	0	0–+3
Hyaline membranes‡	0	0	0	0	0	0–+3
Diffuse cellular infiltration in alveolar walls	+2–+3	+1–+3	±–+1	+3	+1–+2	0–+1
Fibroblastic foci‡	0	0–+2	+1–+3	0	0	0
Granulation tissues formed in terminal air spaces (BOOP) pattern‡	+1–+2	0–+2	0–+1	0	+2–+3	0–+3

Data from Refs. [1–7]. *: temporally homogeneous; +: temporally heterogeneous; ‡: 0: absent; ±: very mild; +1: mild; +2: moderate; +3: marked. UIP: usual interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; DIP: desquamative interstitial pneumonia; BOOP: bronchiolitis obliterans-organizing pneumonia; DAD/AIP: diffuse alveolar damage/acute interstitial pneumonia.

KATZENSTEIN and FIORELLI [4] which was; Group I: cellular interstitial pneumonia, little fibrosis; Group II: cellular interstitial pneumonia, significant admixed fibrosis; and Group III: cellular interstitial pneumonia, severe derangement of lung architecture. The cellular group included group I or II and the fibrotic group included group III [4]. Pathological review focused on the following features: maturity of pulmonary fibrosis (old collagenized fibrous tissue *versus* more recent fibroblastic tissue with little collagen deposition), temporal heterogeneity of the fibrous tissue (a hallmark of UIP) *versus* temporal homogeneity, (a hallmark of AIP, DAD, BOOP and NSIP), whether normal alveolar structures are preserved, distribution of the lesions (patchy or diffuse) and degree of airspace organization.

In addition to the pathological diagnosis by surgical lung biopsy, the following entry criteria were applied: chest symptoms such as cough and exertional dyspnoea in the presence of interstitial shadows on a chest radiograph; restrictive pulmonary dysfunction; performance of computed tomography (CT) of the lungs and bronchoalveolar lavage (BAL) performed before open lung biopsy (OLB), and exclusion of cases associated with collagen vascular diseases, occupational exposure, exposure to drugs, and infection, or prior treatment with corticosteroids or immunosuppressants. Clinical follow-up was performed in the institution where the initial examination had been conducted.

The CT scans were performed without intravenous administration of contrast material, at maximal inspiration in the supine or prone positions. Scans were viewed at a setting appropriate for both lung parenchyma and mediastinum. A variety of scanner equipment was used, *e.g.* at the Chest Disease Research Institute, Kyoto University, the CT scans were performed on a CT X-Vigor CT scanner (Toshiba Corporation, Tokyo, Japan) with 3-collimation, whereas reconstructed images for lung parenchyma were obtained by a high spatial-resolution algorithm in the majority of patients.

Four experienced chest radiologists reviewed the cases during the conference. The following items on the chest radiograph were evaluated: airspace consolidation; reticular, nodular shadows, cystic formation, which suggests the presence of honeycombing; bilateral patchy infiltrate; linear opacities; migration of the shadows; and distribution of the lesions (upper, middle and lower lung areas). Chest CT findings were evaluated by identifying the presence of cystic formation, ground glass opacities, airspace consolidation, emphysematous changes, pleural lesions, and bronchovascular bundle thickening, in the referred areas (upper, middle, lower, subpleural, central, random, patchy or diffuse).

Serial changes in shadows on chest radiographs were followed by focusing on each of six areas (right and left; upper, middle and lower lung fields). Thus, Š20% changes in the involved areas on chest radiographs were defined as significant changes (improved or worsened) in the involved areas.

To assess therapeutic responses, five different prognostic categories were defined: died of progressive lung disease, condition worsened (radiographically and functionally), condition unchanged (radiographically and functionally), improved with or without treatment, and complete remission (cured without treatment). Clearance of Š20% in the areas of shadows on chest radiographs was evaluated as improved and an increase of Š20% or more of the areas of shadows was defined as worsened. In addition, changes of ±20% in the measured values of pulmonary functions were evaluated as improved or worsened, respectively.

For comparison, 34 patients with idiopathic BOOP were selected (all of whom were diagnosed by G.R. Epler, T.E. King Jr, U. Costabel, T.V. Colby and Japanese chest physicians and pathologists at the BOOP meeting in Kyoto in 1991) [7, 8, 10], 16 of whom were followed prospectively for 5 yrs), along with 64 patients with biopsy-confirmed IPF (UIP) and clinical features of IPF who had been followed longitudinally, and selected from the files of the Chest Disease Research Institute in Kyoto [3]. All patients satisfied the same entry criteria as used for NSIP. Informed consent was obtained from each patient. The study was approved by the Ethical Committee of the Chest Disease Research Institute, Kyoto University.

Statistical methods

For statistical analysis, JMP Statistical Software running on an Apple Macintosh personal computer (SAS Institute, Cary, NC, USA) [17] was used. To measure the relationship between two or more ordinal variables, the rank test (Pearson test or likelihood ratio) was used. To evaluate the relationship between two or more measured variables, analysis of variance (ANOVA) (Wilcoxon Kruskal–Willis test) was used. *Post hoc* analysis between two variables was performed using Fisher's Exact test or the Chi-squared test for two ordinal variables and Student's t-test for two measured variables [18]. Statistical significance was assumed at p-values <0.05. In the results of the rank test, only the statistically significant data are summarized. Except where indicated, values were expressed as mean±SD, or median (range).

Results

Histopathological features and subclassification of NSIP

Thirty-one patients were diagnosed as having idiopathic NSIP (table 2).

Of the 31 patients with idiopathic NSIP, 16 we classified into the NSIP cellular group, a group which included both Katzenstein groups I and II NSIP [4]. The cellular group (fig. 1) showed diffuse interstitial cellular infiltrates, and relatively little intra-airspace organization, in contrast to that seen in patients with BOOP [10]. Interstitial fibrosis with loss of normal alveolar structures was observed in the majority of patients in the NSIP group, but not in any of the patients with BOOP. None of the 31 patients with NSIP showed any temporal heterogeneity of fibrosis. These features were in marked contrast to those of IPF (UIP).

Fifteen patients were designated as the NSIP fibrotic group (Katzenstein group III). These patients had a patchy distribution of fibrosis predominantly in the subpleural regions, with some intermingling with normal alveolar walls (fig. 2). When compared with the histopathology of UIP, the patchy distribution of fibrotic changes was similar, but the fibrotic processes of NSIP were characterized

Table 2. – Histology and prognosis with idiopathic nonspecific interstitial pneumonia/fibrosis (NSIP)

Patient No.	Age yrs	Sex	Smoking	Mode of onset days*	Histology‡	Honeycombing in biopsy	BALF lymphocytes %	Honeycombing on CT-scan	Treatment	Prognosis at 2 yrs+
1	46	F	NS	30	C (I)	(-)	70.4	(-)	None	R
2	50	F	NS	90	C (I)	(-)	30.7	(-)	CS	I
3	63	F	NS	90	C (II)	(-)	2.7	(-)	None	U
4	54	F	NS	60	C (II)	(-)	18.8	(-)	None	I
5	62	F	NS	90	C (II)	(-)	-	(-)	None	R
6	51	F	NS	30	C (II)	(-)	60.0	(-)	CS+IS	I
7	55	M	S	30	C (II)	(-)	20.0	(+)	CS+IS	I
8	58	M	S	8	C (II)	(-)	-	(-)	CS	I
9	40	F	NS	6	C (II)	(-)	-	(-)	CS	U
10	69	M	Ex	960	C (II)	(-)	45.4	(-)	CS	I
11	63	M	S	30	C (II)	(-)	52.7	(-)	None	R
12	66	M	S	60	C (II)	(-)	48.2	(-)	None	R
13	58	M	Ex	22	C (II)	(-)	55.8	(-)	None	I
14	64	F	S	60	C (II)	(-)	38.0	(-)	None	I
15	66	F	NS	20	C (II)	(-)	50.0	(-)	CS	I
16	58	M	S	30	C (II)	(-)	26.8	(-)	CS	I
17	54	F	Ex	60	Fb (III)	(+)	76.1	(+)	CS+IS	D
18	63	F	NS	30	Fb (III)	(+)	38.0	(+)	None	R
19	51	F	NS	60	Fb (III)	(+)	66.0	(+)	CS+IS	I
20	57	M	Ex	40	Fb (III)	(-)	7.0	(+)	CS+IS	I
21	66	M	S	12	Fb (III)	(-)	-	(-)	None	I
22	66	M	S	90	Fb (III)	(-)	22.3	(+)	CS	I
23	72	F	Ex	15	Fb (III)	(-)	68.6	(-)	CS+IS	D
24	49	M	S	180	Fb (III)	(+)	50.3	(-)	CS+IS	I
25	62	M	S	60	Fb (III)	(+)	4.4	(-)	CS	I
26	56	M	S	60	Fb (III)	(+)	-	(-)	None	U
27	66	F	NS	90	Fb (III)	(-)	48.0	(-)	None	I
28	41	M	S	720	Fb (III)	(+)	4.0	(+)	CS+IS	W
29	56	M	S	90	Fb (III)	(+)	1.5	(+)	CS	W
30	45	F	NS	7	Fb (III)	(-)	-	(-)	CS	W
31	63	F	NS	30	Fb (III)	(+)	27.0	(-)	CS	I

*: days from onset of symptoms to visiting the clinic; +: 2 yrs after detection; ‡: classification of NSIP in the study by KATZENSTEIN and FIORELLI [4]. BALF: bronchoalveolar lavage fluid; CT: computed tomography; F: female; M: male; NS: nonsmokers; Ex: exsmokers; S: current smokers; C: cellular group; Fb: fibrotic group; CS: corticosteroid; IS: immunosuppressant; R: remission; I: improved; U: unchanged; D: died; W: worsened.

as temporally homogeneous and recent in age, as opposed to IPF [3, 15].

Among the 31 patients with NSIP summarized in table 2, honeycombing was observed in nine patients in the idiopathic NSIP group, but the honeycombing spaces were smaller (usually <1 mm in outer diameter) than those in the patients with IPF (UIP).

Comparison of clinical profiles at the time of initial examination

In spite of a female preponderance among the patients with idiopathic BOOP and a significant male preponderance among the patients with IPF, sex-related differences were not found in patients with idiopathic NSIP (table 3).

The duration of symptoms (number of days from the onset of symptoms such as dyspnoea, cough, and fever to consultation in the clinic) in both idiopathic NSIP and idiopathic BOOP patients was subacute (median 60 and 30 days, respectively), contrasting markedly with that in patients with IPF, who showed an insidious onset of symptoms (1 or 2 yrs after the detection of the shadows by a health survey). Constitutional symptoms such as fever were commonly found in NSIP (32.3%) and BOOP (43.8%), but not in IPF (0.0%) ($p<0.0001$).

Clubbing was found in 3/31 (9.7%) of patients with idiopathic NSIP, although it was not detected in any pa-tients with idiopathic BOOP. In contrast, 42/64 (65.6%) of the patients with IPF had clubbed fingers ($p<0.0001$).

Pulmonary function tests and arterial blood oxygen tension

A majority of the patients with idiopathic NSIP showed a mild decrease in vital capacity (VC), similar to that found in patients with idiopathic BOOP and IPF (UIP) (table 4). Although a decrease in the diffusion capacity of the lung for carbon monoxide was present in all three disease groups, it was more severe in IPF (UIP). Arterial oxygen tension P_{a,O_2} was lower in patients with fibrotic NSIP than in those with BOOP or IPF.

Radiographic findings

Based on conventional chest radiographs of the patients with the three diseases, bilateral patchy infiltrates were the

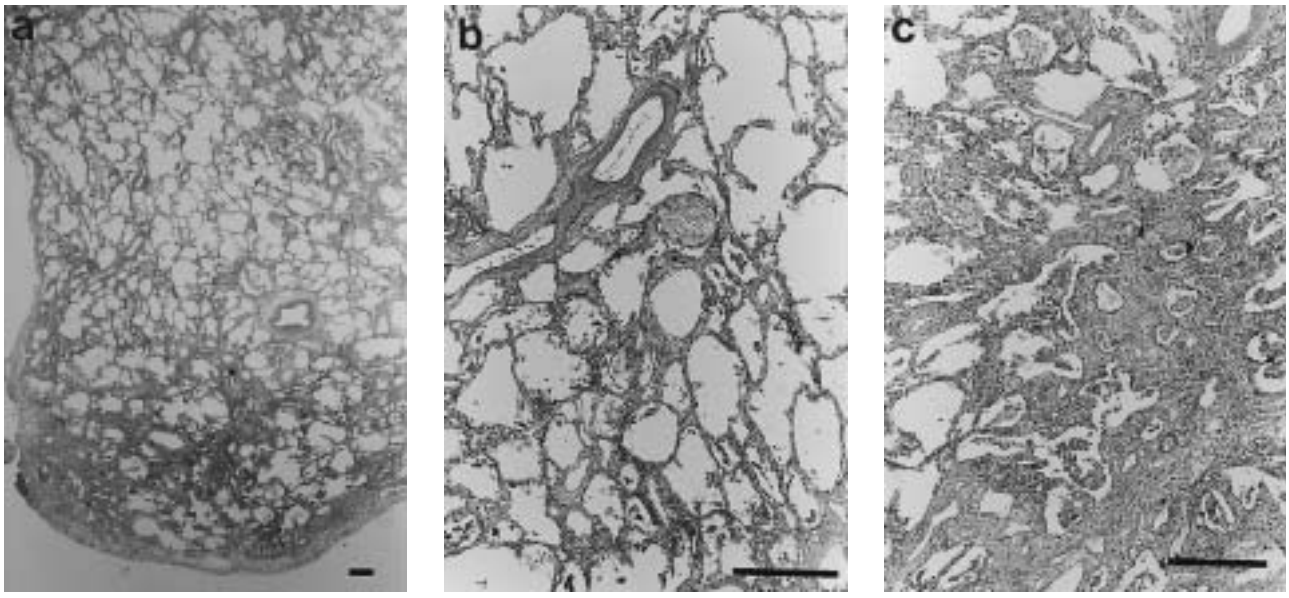

Fig. 1. – Cellular nonspecific interstitial pneumonia/fibrosis (NSIP group II) (patient 11 in table 1). a) Low-magnification photomicrograph of the surgical lung biopsy specimen showed a moderate degree of diffuse interstitial infiltration of the mononuclear cells admixed multifocally with temporally homogenous fibrotic lesions that were associated with a loss of normal alveolar structures. b) Higher magnification of the left middle portion of a) showing a granulation tissue that was formed in an alveolar duct (middle centre). The focal finding was the intra-airspace bud which is frequently found in the lesion of bronchiolitis obliterans-organizing pneumonia (BOOP). c) However, another higher magnification view of the lower right portion of a) showed fibrotic lesions accompanied by loss of normal alveolar structures. This finding contraindicated a histological diagnosis of BOOP. (Haematoxylin and eosin staining; internal scale bars = 400 μm).

major finding in BOOP and NSIP (24/31, 77.4% *versus* 13/16, 81.3%, NSIP *versus* BOOP), as compared with IPF (26/64, 40.6%) (table 5). Reticular and nodular shadows were found in 6.3% of the patients with idiopathic cellular NSIP ($p<0.0001$), in 22.5% of patients with NSIP overall ($p<0.05$) and in 59.4% of those with IPF. No difference was found between the BOOP and NSIP cases.

In the fibrotic NSIP group bilateral patchy shadows (66.7%) and reticular shadows (80.0%) were seen less frequently than in the cellular group, with patchy shadows in 93.8% and reticular shadows in 50.1%. While CT scans depicted cystic formation, suggesting the presence of honeycombing, in 8/31 (25.8%) of the patients with idiopathic NSIP (6.3% in the cellular group and 46.7% in the fibrotic

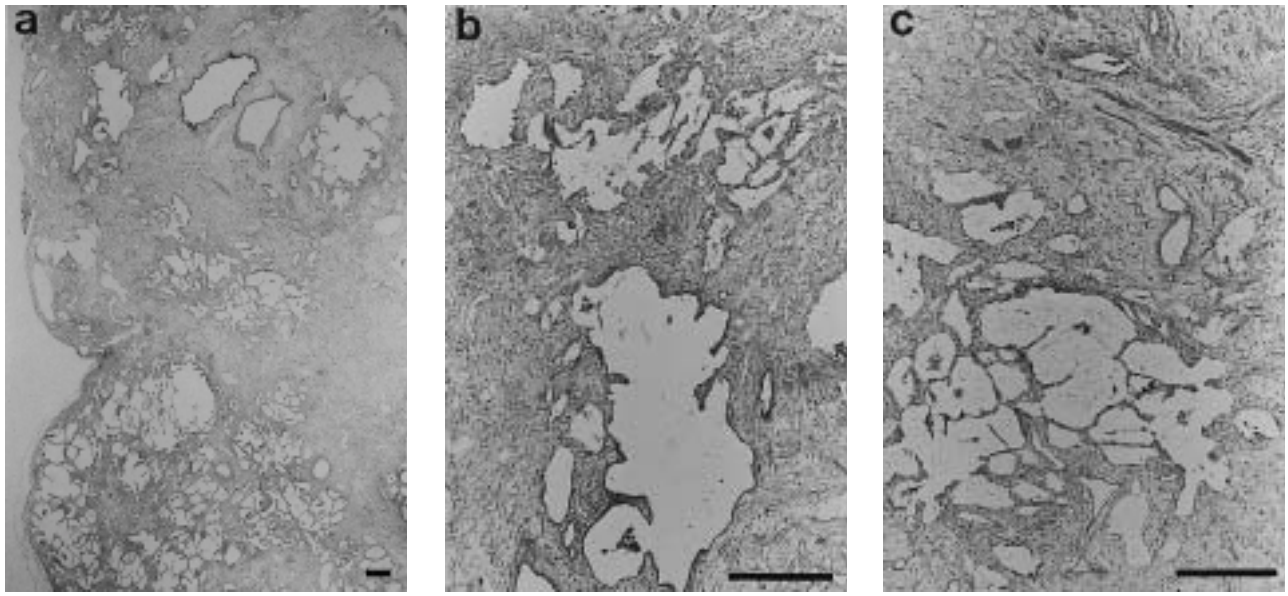

Fig. 2. – Fibrotic nonspecific interstitial pneumonia/fibrosis (NSIP group III) (patient 18 in table 1). a) Low-magnification photomicrograph of the surgical lung biopsy specimen showing subpleural-dominant patchy fibrotic lesions and honeycombing. The distribution pattern of fibrotic lesions was similar to that of usual interstitial pneumonia (UIP) on the low-magnification view. b) However, a higher magnification of the upper left portion of a) showed that the extensive fibrotic lesions surrounding the honeycombing airspaces were less dense than those in UIP. The fibrotic lesions in this case were temporally homogenous, which contradicted a histological diagnosis of UIP. c) Another higher magnification of the middle centre area of a) showing a mild-to-moderate degree of smooth muscle proliferation in the loose fibrotic lesions (upper centre). In the adjacent alveolar area (lower centre), there were a few normal or nearly normal alveolar walls without hyaline membranes. Finding of these alveolar walls in the diseased lung tissue contradicted a histological diagnosis of diffuse alveolar damage. (Haematoxylin and eosin staining; internal scale bars = 400 μm).

Table 3. – Clinical profiles at the time of detection

	Idiopathic NSIP			Idiopathic BOOP	Idiopathic UIP
	Cellular	Fibrotic	Overall		
Cases n	16	15	31	16	64
Sex M/F	6/10	8/7	15/16	6/10	55/9
Age detection yrs*	57.7±8.0	57.8±8.7	57.7±8.2	56.9±8.6	59.5±10.0
Smoking NS/Ex/S	8/2/6	5/3/7	13/5/13	11/2/3	11/29/24
Duration days+	30 (6–960)	60 (7–720)	60 (6–960)	30 (5–120)	1–2 yrs
Symptoms %					
None	0.0	0.0	0.0	6.3	0.0
Chest‡	100.0	100.0	100.0	93.8	100.0
Fever	6.3	53.3	32.3	43.8	0.01
Clubbing %	6.3	13.3	9.7	0.0	65.6
Crackles %	75.0	92.9	80.6	93.7	93.8
Results of rank tests# p-values§					
Sex	<0.0001	<0.0001	<0.001	<0.0001	
Smoking habits	<0.01	<0.0001	<0.0001	<0.0001	
Symptoms	<0.001	<0.0001	<0.0001	<0.0001	
Clubbing	<0.0001	<0.0001	<0.0001	<0.0001	

*: mean±SD; +: days from onset of symptoms to visiting the clinic with median (range); ‡: cough, dyspnoea on exertion, sputum; #: comparison with idiopathic pulmonary fibrosis/usual interstitial pneumonia (UIP). NSIP: nonspecific interstitial pneumonia/fibrosis; BOOP: bronchiolitis obliterans-organizing pneumonia; M: male; F: female; NS: nonsmokers; Ex: exsmokers; S: smokers. § :p-value associated with the overall comparison across histopathological groups using Wilcoxon Kruskal–Wallis test for continuous variables and Pearson χ^2 test for categorical variables.

group), no cystic formation was observed in any of the BOOP cases (p<0.0001).

Laboratory findings

An increase in both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) was common in all disease groups (ESR in NSIP: 46.3±36.2 mm·h^{-1}, mean±SD; in BOOP: 74.0±52.0; in UIP: 34.6±27.8; CRP-positive in NSIP: 53.3%; in BOOP: 68.7 %; in UIP: 67.2%). In the two subgroups of idiopathic NSIP, ESR tended to be increased to a greater extent in the fibrotic group (cellular: 34.8±34.6 *versus* fibrotic: 58.8±35.1 mm·h^{-1}). No differences were found in other laboratory data among these three diseases (data not shown).

Bronchoalveolar lavage fluid cell findings

An increase in both cell recovery and the percentage of lymphocytes, along with a decrease in the CD4/CD8 ratio, were found in patients with NSIP, as well as in those with BOOP (table 6). No increase in BAL fluid lymphocytes was found in patients with IPF (UIP) (p<0.0001) (table 6). An increase in neutrophils or eosinophils was found in all disease groups, compared with the healthy subjects in a previous report [19].

Treatment and prognosis

Orally administered corticosteroids were prescribed to 11/31 (35.5%) of the idiopathic NSIP patients, 12/16 (75.0%) of the idiopathic BOOP patients and 23/64 (36.0%) of the IPF patients. In addition, combined therapy with corticosteroids and immunosuppressants was administered to 8/31 (25.8%) of the idiopathic NSIP patients and 7/64 (10.9%) of the IPF patients (table 7). In total, 19/31 (61.3%) of the patients with NSIP were treated with corticosteroids. The corticosteroids were used according to the severity of the

Table 4. – Pulmonary function results

	Idiopathic NSIP			Idiopathic BOOP	Idiopathic UIP
	Cellular	Fibrotic	Overall		
VC % pred	74.8±18.1	72.6±19.4	73.8±3.3	74.3±4.7	69.6±21.7
FEV1/FVC %	83.6±11.2	82.5±10.4	83.1±10.7	77.7±14.4	81.5±11.1
$D_{L,CO}$ %	57.6±14.4	53.9±22.1	56.1±17.5	58.3±24.7	43.6±15.4
P_{a,O_2} mmHg	73.7±11.9	64.5±11.7	69.7±12.5	70.7±14.0	76.1±13.2
P_{a,CO_2} mmHg	38.0±3.7	40.3±3.5	39.0±4.6	38.1±3.2	39.3±5.2
Results of rank tests* p-values+					
$D_{L,CO}$	<0.05	NS	NS	<0.05	
P_{a,O_2}	NS	<0.05	<0.05	NS	

Values are mean±SD; *: comparison with idiopathic pulmonary fibrosis/usual interstitial pneumonia (UIP). NSIP: nonspecific interstitial pneumonia/fibrosis; BOOP: bronchiolitis obliterans-organizing pneumonia; VC: vital capacity; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; $D_{L,CO}$: diffusion capacity of the lung for carbon monoxide; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension. (1 mmHg=0.133 kPa.) +: p-value associated with the overall comparison across histopathological groups using Wilcoxon Kruskal–Wallis test for continuous variables.

Table 5. – Radiographic findings

	Idiopathic NSIP				
	Cellular n=16	Fibrotic n=15	Overall n=31	Idiopathic BOOP n=16	Idiopathic UIP n=64
Shadows on chest radiographs					
Reticular/nodular	1 (6.3)	5 (33.3)	7 (22.5)	3 (18.8)	38 (59.4)
Bilateral patchy	8 (50.0)	3 (20.0)	11 (35.5)	13 (81.3)	26 (40.6)
Both	7 (43.8)	7 (46.7)	13 (41.9)	0 (0.0)	0 (0.0)
Migratory shadows	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.5)	0 (0.0)
Volume loss	4 (25.0)	5 (33.3)	9 (29.0)	0 (0.0)	24 (37.7)
CT findings					
Cystic formation	1 (6.3)	7 (46.7)	8 (25.8)	0 (0.0)	63 (97.9)
Ground glass opacity	13 (80.7)	14 (93.3)	26 (83.9)	16 (100.0)	0 (0.0)
Airspace consolidation	13 (81.3)	01 (66.7)	23 (74.2)	16 (100.0)	0 (0.0)
Results of rank tests* p-values+					
Reticular/nodular	<0.0001	NS	<0.05	<0.05	
Bilateral patchy	NS	<0.05	NS	<0.0001	
Both	<0.0001	<0.0001	<0.0001	NS	
Migratory shadows	NS	NS	NS	<0.0001	
Volume loss	NS	NS	NS	<0.0001	
Cystic formation	<0.0001	<0.01	<0.01	<0.0001	
Ground glass opacity	<0.0001	<0.0001	<0.0001	<0.0001	
Airspace consolidation	<0.0001	<0.0001	<0.0001	<0.0001	

Values are n (%). *: comparison with idiopathic pulmonary fibrosis/usual interstitial pneumonia (UIP). NSIP: nonspecific interstitial pneumonia/fibrosis; BOOP: bronchiolitis obliterans-organizing pneumonia; CT: computed tomography. +: p-value associated with the overall comparison across histopathological groups using Pearson χ^2 test for categorical variables.

initial signs and symptoms. Cyclophosphamide or azathioprine was used as an immunosuppressant whenever the initial response to corticosteroids was ineffective.

In total, 15/16 (93.8%) of the idiopathic BOOP patients and 23/31 (74.2%) of the idiopathic NSIP patients showed either improvement or remission, but three (20.0%) worsened and two (13.3%) patients died in the fibrotic group of idiopathic NSIP; one patient died of the progression of NSIP, and another died of cytomegalovirus pneumonia when placed on combination therapy for progressive NSIP. No improvement was seen in any patient with IPF (UIP).

Discussion

In this study, the clinical profiles and outcomes of patients with idiopathic NSIP were characterized in comparison to those with idiopathic BOOP and IPF (UIP). The term "nonspecific interstitial pneumonia" has been used in the literature in other settings such as human immunodeficiency virus (HIV)-related [20–22] and chemotherapy-related interstitial pneumonia [23], but it has also recently been applied to a subset of idiopathic interstitial pneumonias that do not share histological features of AIP, BOOP, DIP or UIP.

In this study, cases of NSIP of known cause or association (such as collagen vascular diseases) were excluded arbitrarily in order to make a valid comparison with other idiopathic interstitial pneumonias. As cellular NSIP may also overlap with chronic hypersensitivity pneumonitis, all patients were interviewed in detail, but no identifiable exposure or precipitating antibodies to various putative agents in blood were found. Furthermore, in clinical practice, patients with interstitial lung disease associated with collagen vascular diseases are usually separated from IIP, partly because the prognosis of the same histological lesion may

Table 6. – Bronchoalveolar lavage fluid cell findings

	Idiopathic NSIP				
	Cellular	Fibrotic	Overall	Idiopathic BOOP	Idiopathic UIP
Cell recovery $\times 10^5 \cdot mL^{-1}$	3.17±2.65	5.89±9.84	4.41±6.86	3.52±2.54	1.87±0.87
Cell differentials %					
Macrophages	51.8±20.6	42.3±27.3	47.4±5.2	45.5±7.1	83.0±14.7
Lymphocytes	40.0±19.2	34.4±27.3	37.3±5.2	44.4±7.3	7.2±7.4
Neutrophils	2.5±3.9	13.9±18.4	8.0±2.8	6.4±3.7	5.9±9.8
Eosinophils	5.7±12.7	5.4±7.4	5.5±7.1	2.2±3.1	3.3±5.1
CD4/CD8 ratio	0.30±0.17	1.20±1.63	0.63±1.08	0.97±1.35	1.65±1.71
Results of rank test* p-value+					
Macrophages	<0.0001	<0.0001	<0.0001	<0.0001	
Lymphocytes	<0.0001	<0.0001	<0.0001	<0.0001	
CD4/CD8 ratio	<0.0001	<0.05	<0.001	<0.01	

Values are mean±SD; *: comparison with idiopathic pulmonary fibrosis/usual interstitial pneumonia (UIP). NSIP: nonspecific interstitial pneumonia/fibrosis; BOOP: bronchiolitis obliterans-organizing pneumonia; +: p-value associated with the overall comparison across histopathological groups using Wilcoxon Kruskal–Wallis test for continuous variables.

Table 7. – Treatment and prognosis

	Idiopathic NSIP				
	Cellular n=16	Fibrotic n=15	Overall n=31	Idiopathic BOOP n=16	Idiopathic UIP n=64
Treatment					
None	8 (50.0)	4 (26.7)	12 (38.7)	4 (25.0)	34 (53.1)
CS	6 (37.5)	5 (33.3)	11 (35.5)	12 (75.0)	23 (36.0)
CS+IS	2 (12.5)	6 (40.0)	8 (25.8)	0 (0.0)	7 (10.9)
Prognosis					
Improved	10 (62.5)	8 (53.3)	18 (58.1)**	13 (81.3)+	0 (0.0)‡
Remission	4 (25.0)	1 (6.7)	5 (16.1)**	2 (12.5)+	0 (0.0)‡
Unchanged	2 (12.5)	1 (6.7)	3 (9.7)**	1 (6.2)+	13 (20.0)‡
Worsened	0 (0.0)	3 (20.0)	3 (9.7)**	0 (0.0)+	2 (3.4)‡
Died	0 (0.0)	2 (13.3)	2 (6.5)**	0 (0.0)+	49 (76.7)‡
Results of rank tests# p-values§					
Treatment					
None	NS	<0.01	NS	<0.0001	-
CS	NS	NS	NS	<0.0001	-
CS+IS	NS	<0.05	<0.05	<0.001	-
Prognosis					
Improved	<0.0001	<0.0001	<0.0001	<0.0001	-
Remission	<0.0001	<0.01	<0.0001	<0.01	-
Unchanged	NS	<0.01	<0.01	<0.01	-
Worsened	NS	<0.0001	NS	NS	-
Died	<0.0001	<0.0001	<0.0001	<0.0001	-
Results of rank tests$					
Treatment	<0.05*				

Values are n (%). **: 2 yrs, +: 5 yrs and ‡: 7 yrs after detection. #: comparison with idiopathic pulmonary fibrosis (IPF) usual interstitial pneumonia (UIP), made between IPF/UIP and each other group, respectively, usual cross-table analysis. NSIP: nonspecific interstitial pneumonia/fibrosis; BOOP: bronchiolitis obliterans-organizing pneumonia. CS: corticosteroids; IS: immunosuppressants. $: comparison was made between BOOP and others, respectively, between cellular and fibrotic NSIP. *: BOOP *versus* NSIP overall, BOOP *versus* fibrotic NSIP. §: p-values associated with the overall comparison across histopathological groups using Pearson χ^2 test for categorical variables. NS: nonsignificant (p>0.05).

differ according to whether it is idiopathic or associated with collagen vascular disease [15, 16]. In the authors' experience, the incidence of patients whose pulmonary lesions precede extrathoracic lesions of collagen vascular diseases is <5% among idiopathic cases diagnosed by surgical lung biopsy at the time of initial examination (unpublished data).

This series of biopsy-proven IPF patients was followed longitudinally from the detection by mass survey (early stage of IPF) to the final outcome or the last evaluation (unpublished data). Based on the authors' experience at the time of initial examination, the majority of patients tended to show relatively good values of P_{a,O_2} at rest (table 4), although prominent decreases in P_{a,O_2} were noted during exercise. The validity of the diagnosis of IPF (UIP) is clinically and histologically reliable in this study.

Thirty-one NSIP patients were selected from a large number of cases of IIP. At the time of initial examination, clinical profiles of idiopathic NSIP are more similar to those of idiopathic BOOP than to other types of interstitial pneumonia. Nonetheless, the prognosis of NSIP lay between that of idiopathic BOOP [7, 8] and idiopathic UIP [24–29]. When the clinical profiles and outcomes were compared between cellular and fibrotic groups of idiopathic NSIP, the latter group had a less favourable outcome. The fibrotic group of NSIP could be differentiated from idiopathic UIP based on: subacute mode of onset; BAL fluid lymphocytosis with decreased CD4/CD8 ratio, a finding that usually is not seen in patients with IPF (UIP) [19, 30]; and a significantly more favourable prognosis. Finally, in definition, the NSIP fibrotic group did not fulfil the current histological criteria of UIP [1, 3, 5, 14]; primarily, they showed a lack of temporal heterogeneity, and fibrotic changes in NSIP were homogeneous (diffuse in dis-tribution with recent fibrosis), in a manner similar to those in patients with AIP and BOOP.

There is one confusing report in which "IPF with organizing pneumonia" was characterized based on an approach by transbronchial lung biopsy [31]. In this report, although the mode of onset and clinical findings were similar to those of NSIP, the histology was different. Namely, "features of IPF with organizing pneumonia" can be found when patients with IPF show an acute exacerbation during the clinical course. When this occurs, two spectra of lesions can be seen: one is UIP as a background lesion and the other is organizing pneumonia (BOOP or DAD) as newly superimposed lesions. Differences in histopathological findings can only be clearly recognized between "IPF with organizing pneumonia" and NSIP by surgical lung biopsy and not by transbronchial lung biopsy.

Differences between NSIP and BOOP were not readily apparent either on chest radiographs [13, 32, 33] or on the basis of BAL fluid cell findings [19, 30].

Although the follow-up period for evaluation of clinical outcome was not exactly the same for the three diseases, the clinical outcomes of idiopathic NSIP clearly differed from those of the other two diseases. Five years after detection, 15/16 idiopathic BOOP patients showed an improvement and none showed a deterioration. Two-year outcomes

were favourable in the majority of patients with idiopathic NSIP, but deterioration was found among the 15 cases in the fibrotic group, of whom two died and three worsened. Cellular NSIP did not differ appreciably from BOOP. In patients with IPF (UIP), no improvement was seen, and over half of the patients (76.7%) died of the disease within 7 yrs after the detection of dyspnoea. The unfavourable prognosis of IPF (UIP) 2 yrs after detection can be also supported by the results obtained from a previous study of 52 patients with IPF (UIP) of whom 14 patients (27%) died within 2 yrs of OLB [34], and about 35% of 234 IPF patients died 2 yrs after the detection of exertional dyspnoea in a nationwide survey (unpublished data).

Thus, the final questions to address are whether cellular NSIP is simply a variant of BOOP and whether the fibrotic category of NSIP is simply a variant of UIP. The first question can be refuted histologically (if not clinically) because of a conspicuous lack of intra-airspace organization in NSIP and the presence of multifocal fibrotic lesions with loss of normal alveolar structures in the NSIP cellular group compared with BOOP. The second question can be refuted clinically (as well as histologically) by the difference in response to corticosteroids and clinical outcomes, and by the difference between NSIP and IPF (UIP) patients with respect to the histological age of fibrosis (*i.e.* temporal homogeneity in NSIP). Furthermore, it remains to be discussed whether some fibrotic NSIP cases can progress to UIP; namely, whether NSIP is an early manifestation of UIP. Early fibrotic lesions of UIP show dense fibrotic and temporally heterogeneous changes even in the earliest subpleural or periacinar lesions in asymptomatic cases detected by mass survey [35]. In addition, the authors have not yet come across any incidence of subacute or acute type pneumonia in the previous history of IPF (UIP) patients. Therefore, it is unlikely that the fibrotic group of NSIP is an early phase of IPF (UIP) from either a clinical or a histopathological point of view.

In conclusion, idiopathic nonspecific interstitial pneumonia is a subacute idiopathic pneumonia which can be differentiated from the other types of idiopathic interstitial pneumonia both pathologically and clinically. In general, clinical profiles of idiopathic nonspecific interstitial pneumonia are more similar to those of idiopathic bronchiolitis obliterans-organizing pneumonia than to other types of idiopathic interstitial pneumonia. Two groups of nonspecific interstitial pneumonia/fibrosis can be recognized: cellular and fibrotic. Patients in the fibrotic nonspecific interstitial pneumonia group who need to be distinguished from cases of idiopathic pulmonary fibrosis (usual interstitial pneumonia) have a less favourable outcome than those in the cellular group.

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