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Idiopathic non-specific interstitial pneumonia: as an ''autoimmune interstitial pneumonia''

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Summary Recently, we have experienced significant number of patients diagnosed with non-specific interstitial pneumonia (NSIP) by open lung biopsy or video-assisted thoracoscopic surgery. The purpose of this study is to compare clinical and pathological features of idiopathic NSIP and NSIP associated with underlying diseases (mainly autoimmune disorders). Forty-six patients with histologically proven NSIP were retrospectively collected. Twenty-four patients had underlying diseases (12 polymyositis/dermatomyositis, 5 systemic sclerosis, 2 rheumatoid arthritis, 2 Sjogren's syndrome, 1 ulcerative colitis, 1 primary biliary cirrhosis, and 1 multiple myeloma). Twenty-two of the 46 patients had no underlying diseases. It was very difficult to distinguish idiopathic NSIP and NSIP associated with underlying diseases, clinically and radiologically. Pathologically, lymphocytic pneumonitis was demonstrated in both groups, and it was impossible to distinguish idiopathic NSIP and NSIP associated with underlying diseases. Since generalized symptoms were not observed in patients with idiopathic NSIP, and clinical and pathological features were identical to NSIP with several autoimmune disorders, we postulate new clinical entities of ''autoimmune interstitial pneumonia'' in cases without underlying diseases.

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Introduction

In 1994, Katzenstein and Fiorelli reported the histologic features and clinical significance of non-specific interstitial pneumonia (NSIP).[1] The histologic features of NSIP include a varying degree of interstitial inflammation and fibrosis which appear to develop over a specific time; the process is temporarily uniform.[1] Since then, clinico-pathological features of NSIP have been well-characterized.[2–17] A recent international consensus report[18] defines this entity more specifically, on the basis of the histopathological appearances of idiopathic nature, thus distinguishing it from usual interstitial pneumonia.

More recently, pathological classification of lung fibrosis has been reevaluated and it has been reported that the NSIP pattern is frequently observed in interstitial pneumonia associated with polymyositis/dermatomyositis,[19–22] progressive systemic sclerosis,[23–25] and Sjogren's syndrome.[26] However, a significant portion of NSIP is considered to be unassociated with collagen vascular disorder, but idiopathic nature.

In the present report, we describe clinical features of histologically proven idiopathic NSIP and conclude that idiopathic NSIP should be considered an ''autoimmune interstitial pneumonia'' since it was impossible to distinguish idiopathic NSIP and NSIP associated with underlying diseases (mainly autoimmune disorders), clinically as well as pathologically.

Materials and methods

Subjects

Between March 1990 and June 2003, 46 patients with a pathological diagnosis of NSIP were entered in this study. No patients had histories of occupational inhalation of dust or demonstrated digital clubbing. In auscultatory findings, inspiratory fine crackles in the back lower lung fields were observed in all patients. Since, there was no improvement of symptoms or radiological findings during the hospital stay, and no antibodies to *Trichosporon cutaneum* were demonstrated, we believe that patients with hypersensitivity pneumonitis were not included in our study.

In all patients, high-resolution computed radiographic scanning of the lungs (HRCT) was performed. HRCT was performed by making 12 slices from above the aortic arch to the diaphragm with 5 mm collimation in a bone detail algorithm during moderate inspiration. Most subjects underwent pulmonary function testing before treatment. None of the patients received immunosuppressive treatment such as corticosteroid or cyclophosphamide at the time of open lung biopsy. The diagnoses of interstitial pneumonia were made on clinical, radiological, physiological, and histological grounds. In all patients, the diagnosis was made by means of surgical lung biopsy.

Pathological criteria

All pathologic specimens were analyzed by lung pathologists (IY and YO) according to the criteria of NSIP described by Katzenstein and Fiorelli.[1] Briefly, NSIP represented a pattern of chronic interstitial pneumonia that lacked characteristic features of other specific entities such as UIP, DIP, hypersensitivity pneumonitis, BOOP, Langerhans' cell granulomatosis, or chronic eosinophilic pneumonia. Lung biopsies in this group were characterized by varying proportions of chronic interstitial inflammation and fibrosis, which was temporarily uniform. This was in sharp contrast to the temporarily heterogeneous pattern of UIP, related in part to an admixture of recent organization (fibroblastic foci) and old collagen-rich scars.

Blood samples

Peripheral venous blood samples with and without ethylenediamine tetraacetic acid (EDTA) were obtained before breakfast. After centrifugation at 1000*g* for 10 min at 4 °C, the serum was frozen and stored at −70 °C until used. Arterial blood samples were analyzed for PaO_2 and $PaCO_2$ using a blood gas analyzer. In serum, we measured C-reactive protein (CRP), lactate dehydrogenase (LDH), and immunoglobulin G (IgG). In peripheral venous blood, the white blood cell numbers (WBC) were measured.

Bronchoalveolar lavage (BAL)

Among 46 patients, BAL was performed in 30 patients. After the upper airway was anesthetized with topical lidocaine, a flexible fiberoptic bronchoscope was wedged into the lower respiratory tract under visualization. To sample the lower respiratory tract, BAL was performed by infusing three 50 ml aliquots of sterile saline at the site of the anterior segment of the right lower lobe. The last two aliquots were preserved for evaluation. The fluid was filtered through gauze, and cells were separated from alveolar lavage fluid by centrifugation (300*g* for 10 min). BAL fluid (BALF) was frozen

and stored at −70 °C until used. In BALF, cell differentiations and OKT4/OKT8 ratios were measured.

Results

Twenty-two of 46 patients with histologically proven NSIP had no underlying diseases. Characteristics of these patients are demonstrated in Table 1. There were 12 females and 10 males (median age of 61.5). Eighteen patients were diagnosed with NSIP group II and 4 patients were diagnosed with NSIP group III according to the Katzenstein's criteria.[1] Although apparent collagen vascular disorders were not demonstrated, autoantibodies (rheumatoid factor, anti-nuclear factor, or anti-Jo-1 antibody) were demonstrated in 6 patients (27.3%).

Twenty-four patients with histologically proven NSIP had underlying diseases (12 polymyositis/dermatomyositis, 5 systemic sclerosis, 2 rheumatoid arthritis, 2 Sjogren's syndrome, 1 ulcerative colitis, 1 primary biliary cirrhosis, and 1 multiple myeloma). Characteristics of these patients are demonstrated in Table 2. There were 19 females and 5 males (median age of 58.5). Autoantibodies were demonstrated in 19 of 24 patients (79.2%).

Table 3 shows the results of laboratory findings, therapy, and prognosis of 22 patients with secondary NSIP. Patients had a relatively high IgG (1774 ± 1096 mg/dl, mean ± standard deviation), WBC count (8010 ± 2720/μl), CRP (3.3 ± 5.5 mg/dl), and LDH (385 ± 138 U/l). Their percent vital capacity (69.4 ± 12.8%) and PaO_2 (69.4 ± 12.8 Torr) were decreased. In BALF, an increase of lymphocytes (30.4 ± 29.3%) with an even CD4/CD8 ratio (1.10 ± 1.07) was demonstrated. Steroid therapy was performed in 18 patients, and steroid plus cyclophosphamide was administered in 3 patients. A good response was defined as improvement of PaO_2 and chest CT findings. A poor response was defined as no improvement of either PaO_2 or chest CT findings. Nineteen of the 22 patients (86.4%) showed a good response. Poor responses were experienced in 3 patients. In 3 patients, although steroid therapy was effective at first, they became resistant later. Five patients (22.7%) died of respiratory failure.

Table 4 shows the results of laboratory findings, therapy, and prognosis of 24 patients with secondary NSIP. Patients had a relatively high IgG (2024 ± 1245 mg/dl, mean ± standard deviation), WBC count (7292 ± 3075/μl), CRP (1.7 ± 1.7 mg/dl), and LDH (488 ± 274 U/l). Their percent vital

Table 1 Patient characteristics of idiopathic non-specific interstitial pneumonia.

Case	Age and sex	Background	Autoantibodies	Symptoms at the onset	Pathological diagnosis
1	69 F	(−)	RF*	Cough, dyspnea	NSIP (group II)
2	66 M	(−)	RF	Cough, fever, dyspnea	NSIP (group II)
3	62 F	(−)	(−)	Cough, dyspnea	NSIP (group II)
4	67 F	(−)	(−)	Cough, fever, dyspnea	NSIP (group II)
5	52 M	(−)	(−)	Cough, dyspnea	NSIP (group III)
6	52 F	(−)	RF	Cough	NSIP (group II)
7	69 M	(−)	ANF†	Cough, dyspnea	NSIP (group II)
8	66 M	(−)	(−)	Cough, fever, dyspnea	NSIP (group II)
9	77 M	(−)	(−)	Dyspnea	NSIP (group III)
10	51 F	(−)	(−)	Cough, fever	NSIP (group II)
11	55 F	(−)	RF, ANF	Cough	NSIP (group II)
12	53 F	(−)	(−)	Cough, fever, dyspnea	NSIP (group II)
13	60 F	(−)	Jo-1	Cough	NSIP (group II)
14	62 M	(−)	(−)	None	NSIP (group II)
15	74 M	(−)	(−)	Cough, dyspnea	NSIP (group III)
16	59 M	(−)	(−)	Cough, fever, dyspnea	NSIP (group II)
17	68 F	(−)	(−)	Cough, dyspnea	NSIP (group III)
18	61 F	(−)	(−)	Cough, fever, dyspnea	NSIP (group II)
19	57 M	(−)	(−)	Cough, dyspnea	NSIP (group II)
20	44 F	(−)	(−)	Cough, dyspnea	NSIP (group II)
21	48 F	(−)	(−)	Cough, fever	NSIP (group II)
22	63 M	(−)	(−)	Cough	NSIP (group II)

*Rheumatoid factor.
†Anti-nuclear factor.

Table 2 Patient characteristics of secondary non-specific interstitial pneumonia.

Case	Age and sex	Background	Autoantibodies	Symptoms at the onset	Pathological diagnosis
1	55 F	Dermatomyositis	RF*, ANF†, Jo-1	Dyspnea	NSIP (group II)
2	44 F	Dermatomyositis	ANF	Fever, dyspnea	NSIP (group II)
3	45 F	Dermatomyositis	ANF	Cough, dyspnea	NSIP (group II)
4	47 F	Dermatomyositis	(−)	Cough, dyspnea	NSIP (group III)
5	58 M	Dermatomyositis	(−)	Dyspnea	NSIP (group II)
6	70 F	Dermatomyositis	RF	Cough	NSIP (group II)
7	69 F	Dermatomyositis	(−)	Cough, fever	NSIP (group II)
8	56 F	Polymyositis	Jo-1	Dyspnea	NSIP (group III)
9	61 F	Polymyositis	RF, ANF, Jo-1	Cough, dyspnea	NSIP (group III)
10	57 M	Polymyositis	ANF	Cough, dyspnea	NSIP (group II)
11	62 F	Polymyositis	Jo-1	Cough, dyspnea	NSIP (group II)
12	71 F	Polymyositis	SS-A	Cough	NSIP (group II)
13	58 F	Systemic sclerosis	SCL-70	Cough, fever, dyspnea	NSIP (group II)
14	57 F	Systemic sclerosis	RF	Cough, fever, dyspnea	NSIP (group II)
15	50 F	Systemic sclerosis	(−)	Cough, fever, dyspnea	NSIP (group II)
16	34 M	Systemic sclerosis	ANF	Dyspnea	NSIP (group II)
17	60 F	Systemic sclerosis	ANF, SCL-70	Cough, dyspnea	NSIP (group II)
18	57 F	Rheumatoid arthritis	RF	Cough	NSIP (group II)
19	52 F	Rheumatoid arthritis	RF	Cough, dyspnea	NSIP (group II)
20	71 F	Sjogren's syndrome	SS-A	Cough, dyspnea	NSIP (group II)
21	59 F	Sjogren's syndrome	SS-A	Cough, fever	NSIP (group II)
22	67 M	Ulcerative colitis	(-)	Cough, dyspnea	NSIP (group II)
23	67 F	Primary biliary cirrhosis	RF, ANF	Cough, dyspnea	NSIP (group II)
24	74 M	Multiple myeloma	RF, ANF	Dyspnea	NSIP (group II)

*Rheumatoid factor.
†Anti-nuclear factor.

Table 3 Laboratory findings, therapy, and prognosis of patients with idiopathic non-specific interstitial pneumonia.

Case	IgG (mg/dl)	WBC (/μl)	CRP (mg/dl)	LDH (U/l)	PaO_2	%VC	BAL (%LYM)	OKT4/ OKT8	Therapy	Response	Prognosis
1	1847	5000	<0.25	408	67	71.3	40	1.1	Steroid	Good	Alive
2	2033	8400	12	328	65.7	39.7	8	NA	Steroid	Good→poor	Dead
3	1260	7000	1.7	492	52.9	60.17	80	0.3	Steroid	Good	Dead
4	5756	10,900	4.7	328	42	62.1	20	0.55	Steroid	Good	Alive
5	1835.8	8300	0.6	381	91.9	93.3	0	0.08	Steroid	Poor	Alive
6	1603	7500	<0.25	487	88	56.7	20	0.37	Steroid	Good	Alive
7	1645	4600	0.1	288	78.8	101.1	5	4.02	Steroid	Good	Alive
8	1449	10,900	21.7	441	57.2	NA	3	0.65	Steroid	Good	Alive
9	NA*	15,700	8	426	78.1	60.9	16	0.5	Steroid	Good	Alive
10	928	6300	0.25	239	74	39.2	47	0.74	Steroid	Good	Alive
11	1330	4100	1.27	254	72	62.1	NA	1.92	Steroid	Good	Alive
12	NA	8300	1.2	778	50	47.7	NA	NA	Steroid	Good→poor	Dead
13	1430	5400	0.2	410	68	70.1	95	0.29	Steroid	Good	Alive
14	NA	7790	0.4	220	65.7	91.2	2	3.3	Steroid	Good	Alive
15	NA	4800	0.2	196	79	93.8	NA	NA	Steroid	Poor	Alive
16	1369	8200	1.5	261	70.2	97.4	21	1.91	Steroid+cyclophosphamide	Poor	Dead
17	1600	7300	0	558	66.5	83	8	1.85	Steroid	Good→poor	Dead
18	1192	8100	0.4	468	88.1	62.5	71	1.02	Steroid	Good	Alive
19	NA	11,100	1.5	273	72.4	81.8	57	0.91	Steroid	Good	Alive
20	1620	10,400	0.2	304	79.6	81.4	15	0.94	Steroid+cyclophosphamide	Good	Alive
21	NA	6340	4.92	553	53	NA	59	0.31	Steroid+cyclophosphamide	Good	Alive
22	1480	9800	11.5	376	67.6	57.1	10	0.16	Steroid	Good	Alive

*Not analyzed.

Table 4 Laboratory findings, therapy, and prognosis of patients with idiopathic non-specific interstitial pneumonia.

Case	IgG (mg/dl)	WBC (/μl)	CRP (mg/dl)	LDH (U/l)	PaO_2	%VC	BAL (%LYM)	OKT4/ OKT8	Therapy	Response	Prognosis
1	1495	9600	1.5	1068	68	73.2	NA	NA	Steroid+cyclophosphamide	Good	Alive
2	2036	2700	2.1	460	84.3	86.3	21	2.16	Steroid+cyclophosphamide	Poor	Dead
3	1690	10,800	4.18	318	72	53	16	1.54	Steroid	Good	Alive
4	1500	3900	0.2	1019	68.4	65.8	53.8	0.002	Steroid+cyclophosphamide	Good	Alive
5	2200	6000	4.7	695	54.7	NA	82.4	0.66	Steroid+cyclosporin A	Poor	Dead
6	2640	9000	3.1	839	77.5	45.1	NA	NA	Steroid+cyclophosphamide	Good→poor	Dead
7	1350	3200	3.9	480	73.2	76.5	NA	NA	Steroid	Poor	Alive
8	1160	11600	0.7	1039	72.1	83.8	NA	NA	Steroid+cyclophosphamide	Good	Alive
9	1360	9100	0.3	616	83.9	83.5	NA	NA	Steroid	Good	Dead*
10	1210	9200	0.3	576	94.1	51.2	NA	NA	Steroid+cyclophosphamide	Good	Alive
11	1430	12,400	0.4	603	85.1	71.4	NA	NA	Steroid+cyclophosphamide	Good	Alive
12	NA†	7000	0.4	428	71.5	55.3	NA	NA	Steroid	Good	Alive
13	1630	10,900	3.6	266	81	104	6.4	1.8	Steroid	Good	Alive
14	2300	5600	0	248	98.7	63	6.5	0.8	Steroid	Poor	Alive
15	1080	1000	NA	478	62	28.7	NA	NA	Steroid	Poor	Dead
16	1985	9600	1.19	266	82.1	57.1	NA	NA	Steroid	Poor	Alive
17	NA	5100	0.3	233	100	94	NA	NA	Steroid	Poor	Alive
18	NA	10000	5.68	174	81	65.3	NA	NA	Steroid	Good	Alive
19	2382	6700	1.1	168	76	68.1	1.2	0.71	Steroid	Good	Alive
20	1780	5500	0.1	506	81.6	60.2	91	0.083	Steroid	Good	Alive
21	NA	6300	1.1	404	71.6	61.8	20	0.3	Steroid	Good	Alive
22	2201	9800	2.8	251	74.9	70.8	36	0.7	Steroid	Good	Alive
23	6960	5000	0.27	287	81	54.2	NA	NA	Steroid	Good	Dead*
24	2087	5000	0.1	286	65.2	57.2	15	0.29	Steroid	Good	Dead*

*Died of other diseases.
†Not analyzed.

capacity (66.5±16.7%) and PaO_2 (77.5±10.8 Torr) were decreased. In BALF, an increase of lymphocytes (31.8±30.9%) with a low CD4/CD8 ratio (0.82±0.71) was demonstrated. Steroid therapy was performed in 16 patients, steroid plus cyclophosphamide were administered in 7 patients, and steroid plus cyclosporin A were administered in 1 patient. Seventeen of the 24 patients (70.8%) showed a good response. Poor responses were experienced in 7 patients. In 1 patient although steroid plus cyclophosphamide were effective at first, the patient became resistant later. Four patients died of respiratory failure and 3 patients died of other diseases.

The predominant CT features of NSIP of both groups were interstitial and patchy parenchymal opacification in both lungs, predominantly in the middle and lower lung zones. Scattered ground-glass opacities were also the most common manifestation. Among all patients, neither honeycombing nor pleural effusions were seen on the initial CT scan.

We also compared pathological features between idiopathic NSIP and NSIP with underlying diseases. However, there were no apparent differences between these 2 groups as previously reported.[27,28]

Discussion

In the present study, we clearly demonstrate the difficulty of distinguishing idiopathic NSIP and NSIP associated with collagen vascular disorders, clinically, radiologically, and pathologically.

Although, in several organs, autoimmune inflammation has been well described (for example; autoimmune thyroiditis, autoimmune hepatitis, primary biliary cirrhosis, autoimmune pancreatitis), there have been no reports about autoimmune pneumonitis. However, the lung is a large organ with a huge area directly connected to the atmosphere. In addition, several exogenous materials such as pathogens (virus, bacteria, and fungi), dust, chemicals, and organic substances enter the lung directly. Therefore, it is supposed that antigen stimulation frequently take place in the lung.

The pathogenesis of NSIP involves injury, an immune/inflammatory response and fibrosis. In

the present study, we demonstrate that autoantibodies were detected in 6 of 22 patients with idiopathic NSIP. In addition, we have previously demonstrated that autoantibodies against cytokeratin 8 [29] cytokeratin 18 [30] cytokeratin 19 [31] and vimentin[32] are frequently demonstrated in patients with NSIP. Although the cause of injury is unknown, frequent identification of serum autoantibodies makes an autoimmune etiology attractive. Furthermore, since it is well known that NSIP is frequently associated with autoimmune disorders such as polymyositis/dermatomyositis,[19–22] progressive systemic sclerosis,[23–25] and Sjogren's syndrome,[26] it is possible to speculate that autoimmune etiology should cause NSIP pattern in the lung. More importantly, we followed up most patients with idiopathic NSIP for up to 5 years, with no apparent collagen vascular disorder, suggesting that inflammation was restricted to the lung and not systemic nature.

Previously, we reported lymphocyte subsets, distribution of myofibroblasts, and the appearance of S-100 positive cells in patients with idiopathic NSIP.[27] Although the distribution of myofibroblasts differs between idiopathic NSIP and NSIP associated with collagen vascular disorders,[28] it is difficult to distinguish the histological differences between these 2 groups.[28] In addition, antigen-presenting cells (S-100 positive cells), frequent autoantibody formations, and histological evidence of lymphocytic pneumonitis suggest that the autoimmune process takes place in the pathogenesis of idiopathic NSIP.

Based on this evidence, only clinical features of associated underlying diseases (mainly autoimmune disorders) distinguished idiopathic NSIP and NSIP with underlying diseases. In addition, in the idiopathic NSIP group, there were no apparent collagen vascular disorders even after long-term follow-up, suggesting that autoimmune disorder was restricted only to the lung. Therefore, we propose that idiopathic NSIP could be considered to be an "autoimmune interstitial pneumonia".

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