The Korean Journal of Internal Medicine
Vol. 11, No. 2, June, 1996

Clinical Features of Interstitial Lung Diseases

Gune-il Lim, M.D., Kwang Hee Lee, M.D., Seong Whan Jeong, M.D.
Soo-taek Uh, M.D., So Young Jin, M.D.[1], Dong Hwa Lee, M.D.[1]
Jai Soung Park, M.D.[2], Deuk Lin Choi, M.D.[2]
Chang Hee Kang, M.D.[3] and Choon Sik Park, M.D.

Division of Allergy and Respiratory Medicine, Department of Medicine,
Anatomic Pathology[1], Diagnostic Radiology[2] and Thoracic Surgery[3]
Soon Chun Hyang University Hospital, Seoul, Korea

Objectives: *Interstitial lung diseases (ILD) are heterogenous groups of disorders that involve the interstitium of the lung. Lung biopsy is mandatory in most cases of ILD for diagnosis. In Korea, a few clinical data about ILD were analyzed on the basis of pathologic proof. Thus, we analysed the clinical profiles of patients with ILD who had lung biopsy in a tertiary university hospital.*

Methods: *Clinical and pathologic data concerning 100 patients who had open lung biopsy (OLB) and/or transbronchial lung biopsy (TBLB) were prospectively analysed. Two patients were excluded because one patient was proven to have metastatic cancer and the other to have miliary tuberculosis. One patient had two combined diseases: rheumatoid arthritis and pneumoconiosis. Thus, 99 cases were analysed from 98 patients. Demographic characteristics, pulmonary functions and pathologic findings were analysed according to the disease entities of ILD. Pathologic findings were classified only in patients who had OLB. Clinical courses were also analysed during follow-up.*

Results: *OLB was performed on 68 cases with concomittant TBLB in 18 cases and 30 cases had TBLB only. Mediastinal lymph node biopsy has performed on one case. The most common cause of ILD was IPF (51.5%), which was followed by CVD-PF (15.2%) and HP (9.1%). Average age of 51 cases with idiopathic pulmonary fibrosis (IPF) was 60 ± 11 years, that of 15 cases with collagen vascular disease associated pulmonary fibrosis (CVD-PF) was 46 ± 17 years and that of 9 cases with hypersensitivity pneumonitis (HP) was 53 ± 8.1 years. In IPF, CVD-PF AND HP, male to female ratio was equal. But female was dominant in sarcoidosis and male was dominant in pneumoconiosis. Pulmonary function tests (PFT) in IPF, CVD-PF and HP were restrictive patterns in half of the cases. In pneumoconiosis and sarcoidosis, PFT showed normal pattern. Usual interstitial pneumonia (UIP) was the most common pathologic type in IPF and CVD-PF. The most common cause of CVD-PF was rheumatoid arthritis. The overall mortality rate was 12.1%.*

Conclusion: *We reported that the ILD had a variety of disease entities and pathologic types even in one tertiary referral hospital. We hope that a multi-center study will be performed on the basis of pathologic proof in the future.*

Key Words: *Interstitial lung disease, open lung biopsy, pulmonary functions.*

INTRODUCTION

Interstitial lung diseases (ILD) are uncommon disorders involving interstitium of the lung. The term "interstitium of the lung" refers to a potential space interposed between the basement membranes of the alveolar lining epithelium and the capillary endothelium[1]. This space contains connective tissue elements and the matrix components, and consists of several macromolecules including collagen, proteoglycans and glycoproteins, as well

Address reprint requests to: Choon Sik Park, M.D., Ph.D., Associate Professor of Medicine, Division of Allergy and Respiratory Medicine, Soon Chun Hyang University Hospital 657 Hannam Dong, Yongsan Ku, Seoul, 140-743, Korea

as the noncollagenous proteins, including fibronectin and laminin[2]. Also present are small numbers of interstitial macrophages, fibroblasts and myofibroblasts. Additionally, the alveolar wall becomes anatomically altered by a variety of inflammatory cells, hyperplastic alveolar epithelial lining cells, proliferating fibroblasts, disordered collagen deposition and smooth muscle proliferation. These changes in interstitium lead to derangements of the alveolar walls and loss of functional alveolar capillary units.

Although ILDs are composed of many diverse disorders, ILDs have common features, including similarity of clinical symptoms, comparable appearance of chest readiographs, consistent alterations in pulmonary physiology and typical histology and typical histologic features[3]. In recent years, there has been heightened interest in this area of pulmonary disease with an increasing number of cases reported[4].

Gaensler and colleaques, from Boston University, USA, reported the clinical review of 502 cases who had open lung biopsy (OLB) due to chronic diffuse infiltrative lung diseases during 30 years[5]. In Korea, clinical data of 982 patients who were diagnosed as ILD from 1980 to 1990 at nine university hospitals and one general hospital in the Seoul area were analysed. Among the 982 patients, only 275 cases (28%) performed TBLB (207 cases, 21%) or OLB (68 cases, 7%), and the others were diagnosed by clinical findings and/or roentgenographic findings[6]. The scientific committee of the Korean Academy of Tuberculosis and Respiratory Diseases undertook a national survey to estimate the incidence of sarcoidosis in Korea. That was limited to sarcoidosis[7], not extended to other ILD.

Overall incidence of ILD is uncertain in Korea so far; moreover, analysis of patients with ILD, proven by pathologic findings, was rare in Korea in terms of etiologic and pathologic classifications. Thus, to evaluate the incidence of disease entities and histopathology in ILDs, we analysed 100 patients with ILD who had TBLB or OLB in a tertiary referal university hospital.

MATERIALS AND METHODS

1. Study Populations

We prospectively analysed 100 patients who were admitted with ILD to Soon Chun Hyang University Hospital from 1984 to May 1995. All patients had TBLB and/or OLB. A standardized history was obtained from each of the study patients. The duration of pulmonary symptoms, occupational history, medications taken prior to the onset of diseases, history of medications, previous pulmonary diseases, smoking and family history were reviewed.

The diagnostic criteria of IPF were that (1) known causes of ILD were excluded, (2) HRCT or chest PA findings were a lower lung zone predominant reticular pattern, consisting of thickened interlobular septa and intralobular lines, honeycombing, traction bronchiectasis, and subpleural fibrosis, and (3) compatible histopathology was found[1]. The diagnostic criteria of HP included; (1) exposure to offending antigens revealed by history, or by environmental measurement, and/or (2) compatible symptoms with HP, and (3) presence of noncaseating granuloma in pathology[8].

The serologic tests for antinuclear antibody (ANA), rheumatoid factor, LE cell test and anti-ds-DNA antibody were routinely performed. Collagen vascular diseases (CVD) were confirmed by the criteria provided by the American Rheumatism Association (ARA). Serologic tests for viruses were sent to the Department of Microbiology, Korea National Institute of Health, when viral diseases were suspected.

2. Pulmonary Function Tests

Pulmonary function tests were initially performed prior to diagnostic procedures including OLB, TBLB or BAL, and repeated at the second and fourth week and every third month interval after diagnosis. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), single breath diffusion capacity for carbon monoxide (DLco) and total lung capacity (TLC) were measured with pulmonary function analyzer ERS-150 (Fukuda-Sangyo Co., Ltd., Tokyo, Japan). TLC was measured by helium dilution technique.

We divided PFT results into 4 categories; restrictive, obstructive, combined and normal patterns. Restrictive pattern was defined when FVC was less than 80% of the predicted value and/or TLC was less than 80% of the predicted value. Obstructive pattern was defined when FEV_1 was less than 75% of the predicted value[9]. Combined patterns had both obstructive and restrictive patterns.

3. Procedure for Tissue Biopsy

The site of biopsy was chosen in conjunction with radiologic predominancy. In all of the 100 patients, tissue biopsy was performed. 51 patients had open lung biopsy. TBLB were performed on 30 patients. 18 patients had open lung biopsy and TBLB. In one patient with sarcoidosis, tissue was obtained from the mediastinal lymph node. Obtained tissues were sent to the Department of Pathology in our hospital and some cases were referred to Professor kitaichi in Kyoto University, Japan. Pulmonary fibrosis was subdivided with UIP, desquamative interstitial pneumonia (DIP)[10], nonspecific intersitial pneumonia/fibrosis (NIP)[11], acute interstitial pneumonia (AIP) and lymphocytic interstitial pneumonia (LIP)[12].

4. Clinical Course and Treatment Protocol

Treatment consisted of supportive care and corticosteroids. Indications of corticosteroids were 1) progressive worsening of symptoms and physiological parameters and 2) life threatening conditions of respiratory difficulty more than grade III dyspnea, classified by the American Thoracic Society Scale for dyspnea[13]. If patients complained of severe dyspnea above grade III or had a progressive derangement in PFT, we started high-dose steroid (2 mg/kg/day). If the patient was stable and better than grade II dyspnea, we managed with symptomatic care only until dyspnea aggravated.

When the patients did not response to steroids, cyclophophamide was tried.

RESULTS

1. Incidence of Disease Entities and Diagnostic procedures in ILD

Among 100 patients, two cases were excluded from the study because one case was proven as metastatic cancer and the other as miliary tuberculosis. Because one patient had rheumatoid arthritis and coal worker's pneumoconiosis concomittantly, he was regarded as two separated cases. Thus 99 cases were analysed from 98 patients.

IPF was the most common disease (51 cases, 51.5%), which was follwed by CVD associated with pulmonary fibrosis (CVD-PF) (15 cases, 15.2%), HP (9 cases, 9.1%), sarcoidosis (5 cases, 5.1%), pneumoconiosis (4 cases, 4.1%), bronchiolitis obliterance with organizing pneumonia (BOOP) (4 cases, 4%), diffuse panbronchiolitis (DPB) 3 cases, 3%), drug-induced lung disease (2 cases, 2%), viral pneumonia (2 cases, 2%) and lipoid pneumonia (1 case, 1.0%). Among 3 cases of BOOP, 2 cases were idiopathic type and the other one was associated with adenoviral infection.

Among 15 cases with CVD, rheumatoid arthritis (RA) was the most frequent (6 cases, 40%), followed by Sjogren's syndrome (3 cases), MCTD (2 cases), polymyositis (2 cases) and systemic lupus erythematosus (SLE) (1 case).

The cause of eosinophilic pneumonia (EP) was parasite infestations in two cases, pentastomiasis and anisakiasis. The former was confirmed by the presence of pentastomia in OLB specimen, and the latter by a positive serology to anisakiasis. The other case of EP was suspected to be due to drugs, but a challenge test was not done. The causes of drug-induced ILD were methotrexate and amiodaron. A female patient had taken intermittently 5 to 10 mg/day of methotrexate to treat psoriasis for 15 years. She had acute-onset of ILD, which completely subsided after the withdrawal of methotrexate. Two cases of viral pneumonia were caused by influenza a virus, which were confirmed by serology and pathologic findings of open lung biopsy. Lipoid pneumonia developed in a chronic alcoholic, but he had no history of aspiration.

In 51 cases with IPF, 35 cases had OLB. The number of OLB was 10 cases in 15 cases with CVD, 4 cases in 9 cases with HP and 2 cases in 5 cases with sarcoidosis. All patients with BOOP, DPB, eosinophilic pneumonia, viral pneumonia and lipoid pneumonia had OLB. Amiodaron-induced lung disease had OLB and methotrexate-induced lung disease had TBLB (Table 1).

2. Demographic Characteristics and Types of Tissue Biopsy

Mean age of IPF was 60 years, which was followed by that of BOOP, HP, pneumoconiosis, CVD, sarcoidosis and diffuse panbronchiolitis (DPB). Mean age of DPB was 23 years. Current smokers were relatively frequent in IPF, pneumoconiosis and BOOP. Female was predominant in sarcoidosis and, on the contrary, male was predominant in pneumoconiosis. This may be due to occupational characteristics (Table 2).

3. Pulmonary Function Tests

Initial pulmonary functions were evaluated in 91 cases among 99 cases with ILD. 8 cases were not able to do PFT before the diagnosis because of severe dypnea on admission. 49 cases among 51 cases with IPF had PFT, 25 cases (51%) showed restrictive patterns and 6 cases showed combined patterns (12%). 31 cases among 51 cases in IPF showed restrictive patterns of PFT WITH concomittant obstructive pattern in 6 cases. 5 cases (10%) showed obstructive disease pattern with reduction of lung volume. 13 cases showed normal PFT. 13 cases among 15 cases with CVD-PF had pft, restrictive pattern was observed in 7 cases (58%), obstructive pattern in 3 cases (25%) and normal pattern in 3 cases (25%). PFT was done in all cases with HP and 5 cases among them showed restrictive patterns. In 4 cases with pneumoconiosis, 2 cases showed a normal pattern, and 3 cases among 4 cases with sarcoidosis showed normal pulmonary function tests. In BOOP, there was no dominant

Table 1. Disease Entities and Methods of Tissue Biopsies in 99 Cases of ILD

Diseases entity	Number		Diagnostic methods			
			OLB only	OLB with TBLB	TBLB only	Lymph node
Idiopathic pulmonary fibrosis	51	(51.5%)	22	13	16	
CVD-PF	15	(15.2%)	10	0	5	
Hypersensitivity pneumonitis	9	(9.1%)	3	1	5	
Sarcoidosis	5	(5.1%)	2	0	2	1
Pneumoconiosis	4	(4.1%)	2	2	0	
Silicosis	3					
Caplan's syndrome	1					
BOOP	4	(4.0%)	4	0	0	
idiopathic	3					
adenovirus-associated	1					
Diffuse panbronchiolitis	3	(3.0%)	1	1	1	
Eosinophilic pneumonia	3	(3.0%)	2	1	0	
Drug-induced lung disease	2	(2.0%)	1	0	1	
Methotrexate	1					
Amiodarone	1					
Virus pneumonia	2	(2.0%)	2	0	0	
Lipoid pneumonia	1	(1.0%)	1	0	0	
Total	99	(100.0%)	50	18	30	1

*CVD-PF; collagen vascular disease-associated pulmonary fibrosis
OLB; open lung biopsy
TBLB; transbronchial lung biopsy
L/N; lymph node

Table 2. Demographic Characteristics of the Study Populations

Disease	No. of Case	Age, yr	Sex (M/F)	smoker/nonsmoker
IPF	51	60±11	26/25	18/33
CVD	15	46±17	7/ 8	3/12
HP	9	53±8.1	4/ 5	3/ 6
Sarcoidosis	5	37± 9	0/ 5	0/ 5
Pneumoconiosis	4	47±13	4/ 0	3/ 1
BOOP	4	46±19	2/ 2	3/ 1
DPB	3	23± 5	1/ 2	0/ 3

*All data were represented as mean±SD.

Table 3. Patterns of Pulmonary Function Tests in Study Populations

Diseases	Normal	Restrictive	Obstructive	Combined	Total
IPF	13	25	5	6	49
CVD-PF	3	7	3		13
HP	2	5	1	1	9
Sarcoidosis	3	1			4
Pneumoconiosis	2	1	1		4
BOOP	1	2		1	4
DPB		1		2	3
Eos. pneumonia		2		1	3
Drug-induced	1				1
Viral pneumonia				1	1
Total	25	44	10	12	91

Table 4. Mean Values of Pulmonary Function Tests in the Study Populations

Disease	Number	FVC (% predicted)	FEV_1/FVC (%)	TLC (% predicted)	DLco (% predicted)
IPF	49	69.4±20.8	80.8±13.5	74.5±18.3	51.8±19.6
CVD-PF	13	63.4±26.8	84.3± 7.7	79.8±29.1	47.1±17.0
HP	9	67.9±18.3	79.6±13.1	68.7±22.4	56.4±27.6
Sarcoidosis	4	87.6±16.6	83.9± 9.5	96.0±14.1	48.5±18.5
Pneumoconiosis	4	86.5±10.0	80.1±18.2	110.5± 6.4	62.5±16.3
BOOP	4	73.5±10.2	78.1±18.1	76.2± 8.0	51.1±11.6
DPB	3	59.3± 6.7	71.0±13.0	85.0± 2.8	48.5± 9.2
Eos. pneumonia	3	68.3± 3.5	90.0±19.5	81.5± 3.5	85.5±17.7

*All data were represented as mean±SD.

pattern (Table 3). The mean values of lung function tests for each group are shown in Table 4. Reduction in FVC was greater in CVD-PF, which was followed by HP, IPF and BOOP. DLco was markedly reduced in all groups of ILDs. The overall incidence of restrictive pattern in ILD was dominant. However the incidence of normal pattern was observed in 28% in ILD.

4. Pathologic Classifications of ILD

Pathologic classifications were analysed only in patients who had OLB. Among 35 cases with IPF, the number of usual interstitial pneumonia (UIP) was most frequent (26 cases, 50%), which was followed by non-specific interstitial pneumonitis/fibrosis (NIP) (8 cases, 15%) and acute interstitial pneumonia (AIP) (1 case, 2%) (Table 5). Among 10 cases of CVD-PF, UIP was most frequent (5 cases, 50%), which was followed by diffuse alveolar damage (DAD, 3 cases) and necrobiotic nodule (1 case) (Table 6).

The number of BOOP was 4 cases (idiopathic, 3 cases and adenovirus-induced, 1 case). The number of patients with DPB was 3 cases. 2 cases of viral pneumonia due to influenza a showed DAD patterns on pathology.

Table 5. Numbers of Cases on Whom Open Lung Biopsy was Hergormed According to Pathologic Classifications

	IPF	CVD	Virus	Total
Usual interstitial pneumonia	26	5		31
NIP	8			8
AIP	1			1
LIP		1		1
BOOP			1	4
DPB				3
DAD		3	2	5
Necrobiotic nodule		1		1
Total number	35	10	3	54

5. Treatment and Clinical Courses

Among 99 cases, 51 cases were treated with steroids. Among them, 12 cases were treated with combined cyclophosphamide. 48 cases received supportive care only.

In 51 cases of IPF, 28 cases were treated with steroids. Among them, 8 cases were treated with combined cyclophosphamide. 23 cases were not given any specific therapy. 7 cases with IPF expired during treatment. The most common form of pathology in the dead patients with IPF was UIP (4 cases), followed by AIP (1 case). The remaining two cases were not classified into pathologic form. The causes of death were infections in 5 cases, bronchopleural fistula (BPF) in one case and cor pulmonale in one case.

In 15 cases with CVD-PF, 10 cases were treated with steroids. Among them, 5 cases were treated with combined cyclophophamide. 4 patients with CVD-PF expired due to infections. Three patients died in the treatment groups and one patient died in the untreated group. In dead patients with CVD-PF, underlying diseases were RA (2 cases), SLE (1 case) and polymyositis (1 case). According to the pathology of CVD-PF, the most common type of pathology in the expired patients was diffuse alveolar damage (3 cases) (Table 7).

One case of BOOP died of pneumocystis carinii pneumonia.

Lung cancer (squamous cell cancer) occurred in one patient with UIP after follow-up during 7 years.

Table 6. Numbers of Patients with CVD-PF According to Pathologic Classifications

	Number	UIP	DAD	LIP	necrobioitic nodule
Rheumatoid arthritis	3				
RA only	2	1	2		
Caplan's syndrome	1				1
Sjogren's syndrome	2	2			
Mixed connective tissue disorder	2				
DM*+Sjogren's syndrome	1	1			
SLE+RA	1			1	
Polymyositis	2	1	1		
SLE	1		1		
Total number	10	5	3	1	1

*DM; Dermatomyositis

Table 7. Treatment and Prognosis of Patients with ILD (n=99)

	IPF (51)	CVD (15)	HP (9)	sarcoid (5)	BOOP (3)	Other (15)	Total (99)
Steroid therapy	28	10	6	3	4	0	51
only steroid	20	6	6	3	4		38
death	2	2	0	0	1		5
infection	2	2			1		5
Combined cyclophosphamide	8	4					12
death	5	1					6
infection	3	1					4
BPF	1						1
cor pulmonale	1						1
No therapy	23	5	3	2		15	48
death	0	1	0	0			1
infection		1					1
Total deaths	7	4			1		12

Table 8. Comparison of Incidence of ILD in Several Studies

	Our study	Gaensler (1980)*	Multi-center (Korea, 1990)*	Denver (1993)[1]
IPF	51 (51.5%)	130 (25.9%)	261 (42.6%)	144 (27.4%)
CVD-PF	15 (15.2%)	no classification	152 (24.8%)	89 (16.9%)
HP	9 (9.1%)	9 (1.8%)	4 (0.7%)	79 (15.0%)
Sarcoidosis	5 (5.1%)	63 (12.5%)	17 (2.8%)	76 (14.4%)
Pneumoconiosis	4 (4.1%)	74 (14.7%)	42 (6.9%)	44 (8.4%)
BOOP	4 (4.0%)	11 (2.2%)	3 (0.5%)	25 (4.8%)
DPB	3 (3.0%)			
Eos. pneumonia	3 (3.0%)	17 (3.3%)		7 (1.3%)

*Reorganization after exclusion of malignant disease and miliary tbc

DISCUSSIONS

The epidemiology of ILD is not carefully defined, but it is estimated that their prevalence is approximately 20 to 40 per 100,000 of the population in the United States[14]. Winterbauer and colleagues reported male predominance in patients with diffuse interstitial pneumonitis[15].

Gaensler and colleagues reviewed clinical, physiological and histological data concerning 502 patients who had open lung biopsy for chronic interstitial lung disease[5]. The numbers of patients with interstitial pneumonia were 130 (25.9%), granulomatous group 63 (12.5%) and pneumoconioses 74 (14.7%). In Korea, multi-center study revealed the frequency of the underlying disease for the diffuse pulmonary infiltrates. The most common etiology was miliary tuberculosis (38%), which was followed by idiopathic pulmonary fibrosis (27%), CVD-PF (15%) and diffuse pulmonary infiltrates by malignancy (10%)[6]. If malignancy and infectious cause are removed from the multi-center study, the frequency of underlying diseases are similar to our study.

Our study showed that IPF was the most common disease entity (52.6%), followed by CVD (14.4%) and HP (8.5%). The proportion of IPF in ILD is higher than other studies. The incidence of noncaseating granulomatous diseases, including sarcoidosis, is relatively lower in Korea than the USA, which may be the reason why our study had more IPF and less sarcoidosis than those of Gaensler's study (Table 8).

We included virus-induced ILD, though considered as an infectious process, because patterns of their diseases showed the typical view of ILD.

Table 9. Comparison of Pathologic Classification of IPF in Several Studies

	Our study	Gaensler	Kyoto Univ.
UIP	26 (50%)	64 (52%)	73 (91%)
NIP	8 (15%)	no classify	4 (5%)
AIP	1 (2%)	8 (7%)	1 (1%)
DIP	0	50 (41%)	1 (1%)
LIP	0		1 (1%)

Causative agents were two cases of influenza a virus and one case of adenovirus. Pathologic features were two cases of DAD and one case of BOOP pattern. BOOP pattern was induced by adenovirus.

In patients with IPF in our study, the most common type of pathology is UIP, followed by NIP (8 cases, 15%) and AIP. NIP is relatively more frequent in our study than the report of Kyoto University. They reported 5% incidence of NIP among 87 patients with ILD. DIP, which is not a rare type of IPF in the USA, was not found in our study. Multi-center study in Korea reported only 2 cases of DIP among 261 patients with IPF[6]. In data of Kyoto University from 1966 to 1991, they reported 1% incidence of DIP[16]. The reason why incidence of DIP is lower in Korea and Japan than that of the USA is unclear (Table 9).

The inidence of HP in our study is much higher than those in other studies. Especially, the incidence of HP in multi-center study in Korea was 0.7% and 1.8% in Gaensler's study. There is no good explanation for this difference in the incidence of ILD.

The incidence of BOOP was much higher than that of multi-center study[6].

Only 3 cases of 99 cases in our study were diagnosed as DPB.

In the remaining patients (31.4%) who had TBLB,

biopsy specimens were too small to be clarified pathologically.

Our study showed that male to female ratio was equal in IPF. This difference originated from female predominance in NIP of our study. Age of patients with IPF was higher than that of other disease groups. In CVD-PF, male to female ratio was nearly equal. Interestingly, the age of onset in most patients with DPB is over 40 years old in Japan but, in our study, the mean age was 23 years, which is younger than that in Japanese cases.

Regarding the usefulness of PFT in assessing patients with ILD, lung volumes, DLco and arterial oxygen pressure with exercise were considered to be the best index of the overall disease process[17]. IPF, CVD-PF and HP showed restrictive pattern of PFT in more than half of the patients, but sarcoidosis and pneumoconiosis had mainly normal PFT findings. In sarcoidosis, we had 3 patients with Stage 1 and one patient with Stage 3. The patients with Stage 1 had normal ventilatory function and the patients with Stage 3 had restrictive pattern. Because there were no complicated cases of pneumoconiosis in our study, PFT seemed to be the normal pattern. Combined obstructive and restrictive pattern was predominant in DPB. In BOOP, it did not show a specific pattern due to the small number of cases.

In CVD-PF, the most common underlying disease was RA. Lower incidence of SLE may be due to avoidance of OLB in cases of lupus pneumonitis because obvious serologic and other non-invasive diagnostic approaches are possible. The most common type of pathology in CVD-PF was UIP and DAD. Kazenstein reported the association of CVD with NIP, but we did not find any NIP in CVD-PF.

Treatment is usually offered to patients with ILD, including advanced fibrotic disease. A trial of steroids is the first line of medication. Should the disease not respond or be progressive. the dosage of prednisone can be increased, or immunosuppression with cyclophosphamide should be considered[18].

In our study, the most common cause of death was infection and the most common type of pathology in dead patients was UIP. The focus of infection was the lung. Therefore, pneumonia was the major cause. Panos and co-workers reported studies of the clinical course of IPF. In their study, mortality was most frequently due to respiratory failure; other causes of death included heart failure, bronchogenic carcinoma, ischemic heart disease, infection and pulmonary embolism[19]. Epler et al. analysed 48 patients with BOOP. Among them, 37 cases were treated by steroid and 4 cases of treated patients expired due to progressive disease (2 cases) or other cause (2 cases)[20]. Guerry-Force and associates described that patients with UIP died of respiratory illness (10 of 17 cases) more than patients with BOOP (4 of 15 cases)[21]. Carrington performed a 24-year period of observation of patients with UIP and patients with DIP. The result was that only one fourth of the patients with DIP died, and nearly one third had fully recovered 11 to 22 years later, but nearly all patients with UIP progressed, and two thirds died. So, they suggested that DIP should have a better prognosis because the criteria of DIP include the absence of marked fibrosis[22]. In the USA, CVD-PF accounts for 1600 deaths per year. This number represents 25 percent of all ILD mortality and 2 percent of all respiratory deaths. In our study, patients with CVD-PF composed 14.4% of the entire number of ILD, AND the death rate was 26.7% of patients with CVD-PF. Among 12 dead patients of ILD, the dead patients with CVD-PF were 4 cases (33.3%). This incidence is comparative to that in the USA.

In general, patients with ILD who received immunosuppressants, including steroids and cyclophosphamide, had been faced with difficult problems of infection with bacteria, virus or protozoa. To these patients, infection was fatal. In our study, the group treated with steroids had a higher mortality rate than the group treated with no steroids. This finding must be interpreted in consideration that patients receiving steroids were more severe than patients without steroid treatment.

Another problems in patients with ILD is pulmonary hypertension. In our study, one case died of corpulmonale. Kennedy and et al. researched the prevalence of pulmonary hypertension in patients with ILD. 70% had ausculatory findings consistent with pulmonary hypertension[23]. Current data suggest that the etiology of pulmonary hypertension in the interstitial disease is multifactorial and involves the following: 1) primary lesions of the pulmonary vessels (e.g., vasculitis in sarcoidosis)[24], 2) compression and/or destruction of pulmonary vessels by the interstitial process[25] and 3) vasoconstriction of vessels mediated by hypoxia or

acidosis[26].

Also, during follow-up, squamous cell lung ca developed in one case with UIP. Patients with IPF have an increased risk of developing bronchogenic carcinoma. In a retrospective review of 205 patients with pulmonary fibrosis, Turner-Warwick and co-workers found the 20 (9.8%) had developed bronchogenic carcinoma. The excess relative risk of lung cancer in patients with fibrosis compared with the general population was 14.1, controlling for age, sex and smoking history[27].

Further evaluation about ILD and long-term follow-up must be done.

REFERENCES

1. Schwarz MI, King TE. *Interstitial lung disease. 2nd ed. p 1-22, St. Louise, Mosby-Year book Inc. 1993.*
2. Campbell EJ, Senior RM, Welgus HG. *Extracellular matrix injury during lung inflammation. Chest 1987; 92:161-167.*
3. Reynolds HY. *Classification, definition and correlation between clinical and histologic staging of interstitial lung disease. Semin Respir Med 1984; 6:1-19.*
4. DeRemee RA. *Diffuse interstitial pulmonary disease from the perspective of the clinicians. Chest 1987; 92: 1068-1073.*
5. Gaensler EA, Carrington CB. *Open biopsy for chronic diffuse infiltrative lung disease: Clinical, roentgenographic and physiological correlations in 502 patients. Ann Thorac Surg 1980; 30:411-426.*
6. Kim JH, Choi SJ, Kim DS, You JH, Kang HM, You SH, Jo DI, Kim JW, Han SK, Kim KY, Kim YS, Park CS, etc. *The etiology of the diffuse infiltrative disease of the lung in Korea. Tuberculosis and respiratory disease (Korean) 1990; 38:1-7.*
7. Scientific Committee of the Korean Academy of Tuberculosis and Respiratory Disease. *National survey of sarcoidosis in Korea. Tuberculosis and Respiratory Disease (Korean) 1992, 39:453-473.*
8. Terho EO. *Diagnostic criteria for farmer's lung disease. Am J Ind Med 1986; 10:329.*
9. Conrad SA, Kinasewitz GT, George RB. *Pulmonary function testing: principles and practice. 1st ed. p. 206-13 New York, Churchill Livingstone 1984.*
10. Liebow AA, Steer A, Billingsley JG. *Desquamative interstitial pneumonia. Am J Med 1965; 39:369-404.*
11. Katzenstein AA, Fiorelli RF. *Nonspecific interstitial pneumonia/fibrosis: Histologic features and clinical significance. Am J Surg Pathol 1994; 18:136-147.*
12. Liebow A. *Definition and classification of interstitial pneumonias in human pathology. Prog Resp Res 8:1, 1975.*
13. Brooks SM (chairman). *Task group on surveillance for respiratory hazards in the occupational setting. Surveillance for respiratory hazards. ATS News 1982; 8:12-16.*
14. Wyngaarden JB, Smith LH, Bennett JC. *Cecil textbook of medicine. 19th ed. p. 396-409, Philadelphia, WB Saunders Co 1992.*
15. Winterbauer RH, Hammar SP, Hallman KO, Hays JE, Pardee NE, Morgan EH, Allen JD, Moores KD, Bush W, Walker JH. *Diffuse interstitial pneumonitis: Clinicopathologic correlations in 20 patients treated with prednisone/azathioprine. Am J Med 1978; 65:661-672.*
16. Kitaichi M. *Bronchiolitis obliterance organizing pneumonia (BOOP). In Basic and clinical aspects of pulmonary fibrosis, ed by Takishima T. Boca Raton, CRC press. 463-488, 1994.*
17. Keogh BA, Crystal RG. *Pulmonary function testing in interstitial pulmonary disease; What does it tell us ? Chest 1980; 78:856-865.*
18. Murray JF, Nadel JA. *Textbook of respiratory medicine. 2nd ed. p. 1827-1848, Philadelphia, WB Saunders Co. 1994.*
19. Panos RJ, Mortenson RL, Niccoli SA, King TE. *Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med 1990; 88:396-404.*
20. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. *Bronchiolitis obliterance organizing pneumonia. N Engl J Med. 1985; 312:152-158.*
21. Guerry-Force ML, Muller NL, Wright JL, Wiggs B, Coppin C, Pare PD, Hogg JC. *A comparison of bronchiolitis obliterance with organizing pneumonia, usual interstitial pneumonia and small airway disease. Am Rev Respir Dis 1987; 135:705-712.*
22. Carrington CB, Gaesler EA, Coutu RE, FitzGerald MX, Gupta RG. *Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 298:801-809, 1978.*
23. Kennedy JI, Fulmer JD. *Pulmonary hypertension in the interstitial lung disease. Chest 87:558-560, 1985.*
24. Battesti JP, Georges R, Basset F, Saumon G. *Chronic cor pulmonale in pulmonary sarcoidosis. Thorax 1978; 33:76-84.*
25. Fishman AP. *Chronic cor pulmonale. Am Rev Respir Dis 1976; 114:775-794.*
26. Fishman AP. *Vasomotor regulation of the pulmonary circulation. Ann Rev Physic 1975; 88:248-255.*
27. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. *Cryptogenic fibrosing alveolitis and lung cancer. Thorax 1980; 35:496-499.*