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Bronchoalveolar lavage in fibrotic idiopathic interstitial pneumonias

Yon Ju Ryu[a], Man Pyo Chung[b,*], Joungho Han[c], Tae Sung Kim[d], Kyung Soo Lee[d], Eun-Mi Chun[a], Sun Young Kyung[e], Sung Hwan Jeong[e], Thomas V. Colby[f], Hojoong Kim[b], O. Jung Kwon[b]

[a]*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Dongdaemun Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea*
[b]*Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-Dong, Kangnam-Ku, Seoul, 135-710, Republic of Korea*
[c]*Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[d]*Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[e]*Division of Pulmonology, Department of Internal Medicine, Gachon Medical School, Gil Medical Center, Incheon, Republic of Korea*
[f]*Department of Pathology, Mayo Clinic, Scottsdale, AZ, USA*

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Summary
The purpose of this study was to assess the role of bronchoalveolar lavage (BAL) in differentiating usual interstitial peumonia (UIP) from non-specific interstitial pneumonia (NSIP) and in predicting the prognosis in fibrotic idiopathic interstitial pneumonia (IIP). A retrospective review of 122 patients (age 58±8 years, 70 male) with UIP ($n = 87$) and NSIP ($n = 35$) was carried out. Prior to surgical lung biopsy, all of them underwent BAL and high-resolution-computed tomography (HRCT) of the chest. Neutrophil count in BAL fluid was higher in UIP (7.0%) than NSIP (3.0%) ($P = 0.027$). In contrast, BAL lymphocyte count was significantly higher in NSIP (29.0%) than UIP (5.5%) ($P < 0.0001$). In 62 patients whose HRCT findings were atypical for UIP, BAL lymphocytosis was more frequently observed in NSIP (20/33) than UIP (4/29) ($P < 0.001$) and the absence of BAL lymphocytosis suggested a diagnosis of UIP rather than NSIP (odds ratio 12.7, $P < 0.001$). Pathologic diagnosis of NSIP was the only independent factor predicting a longer survival of our patients (median follow-up 21 months) (hazard ratio (HR) 0.035, $P = 0.005$). When NSIP was not included in the survival analysis, higher BAL lymphocyte count was the only independent predictor of a

*Corresponding author. Tel.: +82 2 3410 3423; fax: +82 2 3410 6956.
E-mail address: mpchung@smc.samsung.co.kr (M. Pyo Chung).

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longer survival (HR 0.909, $P = 0.029$). BAL is an useful non-invasive tool in fibrotic IIP, not only for excluding a variety of specific non-IIP diseases but also for narrowing the differential diagnosis and predicting the prognosis in the absence of the histopathologic diagnosis.

Introduction

Idiopathic interstitial pneumonias (IIP) are a heterogeneous group of diffuse parenchymal lung diseases of unknown etiology.[1] Because of the differences in the clinical manifestations, the radiographic features and the prognosis, IIP are classified into seven histopathologic entities that include idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP).[1] Surgical lung biopsy, however, is not feasible in all the patients with IIP since it requires general anesthesia and adequate interpretation by an experienced lung pathologist. In addition, lobar histologic variability and inter-observer variation in the histopathologic interpretation of IIP make it less reliable to use the histology alone as the diagnostic "gold standard".[2–5] A recent report by Nicholson et al.[6] showed that more than half of the inter-observer variation in the histopathologic interpretation was related to the diagnosis of NSIP and its distinction from usual interstitial pneumonia (UIP). Separating NSIP from UIP is important because NSIP has a better prognosis than UIP.[7–12]

Bronchoalveolar lavage (BAL) is a non-invasive diagnostic procedure in interstitial lung diseases (ILD), not only for the diagnosis of certain non-IIP diseases such as hypersensitivity pneumonitis, sarcoidosis or pulmonary alveolar proteinosis but also for the exclusion of infection or malignancy.[13–15] In the patients suspected to have UIP or NSIP, analysis of the differential white blood cell counts in BAL fluid can be also helpful. In the past, BAL lymphocytosis was known to be a good prognostic factor while BAL neutrophilia or eosinophilia denoted a poor clinical outcome in the patients with UIP.[16–21] After the first description of NSIP in 1994, BAL lymphocytosis is more likely suggestive of NSIP rather than UIP.[20] A few recent studies have also shown that BAL could provide substantial diagnostic information on UIP and NSIP.[8,9,22] Veeraraghavan et al.,[23] however, reported that BAL had neither diagnostic role nor prognostic value in 54 patients with either IPF or idiopathic NSIP. Therefore the role of BAL in fibrotic IIP is still controversial.

This retrospective study was undertaken to identify the role of BAL in the separation of NSIP from UIP in the large number of patients with fibrotic IIP. We also evaluated whether the BAL findings can predict the prognosis in the absence of the histopathologic diagnosis.

Methods

Between May 1995 and April 2004, a total of 122 patients with UIP ($n = 87$) or idiopathic NSIP ($n = 35$) were pathologically confirmed by surgical lung biopsy. During this period, open thoracotomy or video-assisted thoracoscopic surgery was performed for a diagnostic purpose in 313 patients with ILD at Samsung Medical Center, which is a tertiary referral hospital in Korea. Following the investigation for collagen vascular diseases including the examination by a rheumatologist and serologic tests, a standardized evaluation for environmental or occupational exposure, and a search for the ingestion of any drugs known to cause ILD, 193 patients were confirmed to have IIP. Among them, 148 patients underwent BAL procedures prior to surgical lung biopsy. Lung biopsy specimen was obtained from at least two different lobes. The pathology slides of 148 patients were independently reviewed by two experienced lung pathologists (J.H. and T.C.). Except for age, sex and the site of biopsy, clinical information was not provided to the pathologists. The kappa coefficient used to measure the agreement between the two pathologists was 0.67. Twenty-six patients were excluded from the study because the pathologic diagnosis did not concur. A total of 122 patients (87 patients with UIP and 35 patients with idiopathic NSIP) were finally included in the study. The patients with NSIP were further divided into those with cellular NSIP ($n = 6$) and fibrotic NSIP ($n = 29$).[7,12]

Following a review of the medical records, the data on the age at the time of diagnosis, the gender, the smoking history, the respiratory symptoms and their duration, arterial blood gas analysis when breathing room air, the medical treatment, and the final clinical outcome were obtained. The forced vital capacity (FVC) ($n = 111$), total lung capacity (TLC) ($n = 82$) and diffusing capacity of the lung (DLco) ($n = 84$) were examined with pulmonary function units (SensorMedics, Yorba Linda, CA, USA). Pulmonary function tests could not be performed in all the patients because of intractable coughing, dyspnea or poor cooperation.

High-resolution-computed tomography (HRCT) of the chest was done prior to surgical lung biopsy in all the patients. Two chest radiologists (TS K. and KS L.) reached decisions on CT findings by consensus. The typical HRCT findings of IPF are areas of irregular linear opacity, traction bronchiectasis and honeycombing that predominantly involve the basal and subpleural lung with minimal ground-glass attenuation.[24,25] If the HRCT findings were typical for IPF, the radiographic diagnosis was "confident IPF".

BAL was performed as previously described.[26] A flexible bronchoscope (EVIS BF 1T240, Olympus, Japan) was wedged into a segmental or subsegmental bronchus of the most involved segment, or of the right middle lobe or the lingular segment. Warm saline was then infused in five 30–50 ml aliquots up to total volume of 150–200 ml. After each instillation of saline, BAL fluid was retrieved by gentle suction and the samples were pooled. The recovery percentage of BAL fluid ranged between 45% and 68%, with an average rate of 56%. Cytocentrifuge preparations were

made using a Shandon Cytopsin-3 (Shandon Ltd, Runcorn, UK), and the differential cell count was performed with using Wright–Giemsa staining. A total of 300–500 cells from a cytospin slide were counted. The results of differential cell counts in BAL fluid were classified as BAL lymphocytosis (lymphocytes >20% of total white blood cells) or BAL neutrophilia (neutrophils >5% of total white blood cells).[20,21] BAL eosinophilia was absent in our patients.

Medical treatment consisted of corticosteroids (1 mg/kg/day of prednisolone for 1–2 months with subsequent tapering) with or without either azathioprine (2–3 mg/kg/day to a maximum dose of 150 mg/day) or cyclophosphamide (2 mg/kg/day to a maximum dose of 150 mg/day).[20] Some patients were managed with symptomatic supportive care ($n = 19$) or subcutaneous injection of interferon-gamma ($n = 24$). Serial changes in the respiratory symptoms, chest radiography and pulmonary function tests were evaluated at 3–6 month intervals. Survival and the causes of death were identified from the medical records, by interviews with the patients' families/doctors or by accessing the national death registry data.

For statistical analysis, SPSS version 11.5 was used. A *P*-value of less than 0.05 was considered significant. Group comparisons for categorical variables were made with using Pearson χ^2 test or Fisher's exact test. To compare between the three groups for the continuous variables, ANOVA test for the normally distributed data or Kruskal–Wallis test for the data that was not normally distributed was performed. For comparison between two groups, student *t*-test for the normally distributed data or Mann–Whiney *U*-test for the data that was not normally distributed was used. For survival analysis, Kaplan–Meier analysis with a log-rank test was used. Time zero was determined as the date of surgical lung biopsy. Cox proportional hazard multivariate analysis was performed to identify the independent factors that were closely related to death.

Results

Baseline characteristics of the patients

Among 122 patients, there were 70 male and 52 female patients with a mean age of 58±8 years. Compared to UIP, the patients with NSIP had a younger age, a female predilection, more non-smokers and a shorter duration of respiratory symptoms ($P < 0.05$) (Table 1). Initial FVC, DLco and arterial oxygen tension when breathing room air were not different between the two groups. The proportion of patients who received corticosteroids and/or cytotoxic agents was not different either.

Diagnostic value of BAL in separating NSIP from IPF

Neutrophil count in BAL fluid was significantly higher in UIP (7.0%) than NSIP (3.0%) ($P = 0.027$) (Table 2). The patients showing BAL neutrophilia was also much more in UIP (49/87) than NSIP (12/35) ($P = 0.028$). In contrast, lymphocyte count in BAL fluid was significantly higher in NSIP (29.0%) than UIP (5.5%) ($P < 0.0001$). BAL lymphocytosis was more frequently found in NSIP (20/35) than UIP (14/87) ($P < 0.0001$). When compared between UIP and fibrotic NSIP, these differences were also observed. After adjusted for smoking, BAL neutrophilia ($P = 0.040$) and BAL lymphocytosis ($P = 0.026$) were still more frequently present in UIP and fibrotic NSIP, respectively.

Among the 60 patients whose HRCT diagnosis was confident UIP, 58 patients (97%) were confirmed to have UIP on surgical lung biopsy. In particular, all of 35 patients with BAL neutrophilia showed UIP pathologically. In the remaining 62 patients whose HRCT features were atypical for UIP, BAL lymphocytosis was more frequently observed in NSIP (20/33) than UIP (4/29) ($P < 0.001$) while the absence of

Table 1 Baseline clinical profiles of the patients with IPF and idiopathic NSIP.

Variables	IPF ($n = 87$)	Idiopathic NSIP			*P*-value*
		Cellular ($n = 6$)	Fibrotic ($n = 29$)	Both ($n = 35$)	
Age (years)	59±7	51±4	55±12	54±11	<0.05
Gender (M:F)	62:25	0:06	8:21	8:27	<0.05
Smoking history					
Never smoker (number)	32	6	23	29	
Ex-smoker (number)	28	0	5	5	<0.05
Current smoker (number)	27	0	1	1	
Duration of symptoms (months)	12 (0–120)	2 (1–4)	5 (1–72)	4 (1–72)	<0.05
Pulmonary function at diagnosis					
PaO_2 at room air (mmHg)	82.4±13.1	74.1±11.9	82.2±16.0	81.2±15.6	NS
FVC (% predicted)	75.0±16.5	70.2±8.8	67.4±17.2	67.9±16.1	NS
TLC (% predicted)	78.7±18.3	73.0±19.5	73.0±17.6	73.0±17.5	NS
DLCO (% predicted)	66.4±18.2	74.5±16.3	62.5±15.1	64.2±15.5	NS
Immunosuppressive therapy (%)	70	100	93	94	NS

Values are expressed as means±SD, medians (ranges) or frequencies (%).
*When compared between IPF and idiopathic NSIP. NS: Not significant.

Table 2 Bronchoalveolar lavage (BAL) findings and their relationship with HRCT diagnosis in IPF and idiopathic NSIP.

Variables	IPF ($n = 87$)	Idiopathic NSIP			*P*-value*
		Cellular ($n = 6$)	Fibrotic ($n = 29$)	Both ($n = 35$)	
BAL neutrophils					
Counts (%) (ranges)	7.0(0–85)	3.5(1–25)	3.0(0–38)	3.0(0–38)	<0.05
Neutrophilia (+) (*n*)	49	2	10	12	<0.05
BAL lymphocytes					
Counts (%) (ranges)	5.5(0–68)	40.5(29–76)	19.0(4–71)	29.0(4–76)	<0.05
Lymphocytosis (+) (*n*)	14	6	14	20	<0.05
HRCT diagnosis					
Confident IPF (*n*)	58	0	2	2	<0.05
BAL neutrophilia (+)	35/58	0	0	0	NS
BAL lymphocytosis (+)	10/58	0	1/2	1/2	NS
Not confident IPF (*n*)	29	6	27	33	<0.05
BAL neutrophilia (+)	14/29	2/6	10/27	12/33	NS
BAL lymphocytosis (+)	4/29	6/6	14/27	20/33	<0.05

Values are expressed as medians (ranges) or as the number of patients.
*When compared between IPF and idiopathic NSIP.

BAL lymphocytosis suggested a diagnosis of UIP (odds ratio (OR) 12.7, $P < 0.001$). The presence of BAL neutrophilia, however, could not predict a diagnosis of IPF ($P = 0.343$).

The value of BAL for the prediction of survival in patients with IPF and NSIP

The patients were followed for a median of 21 months (range 0–104 months). The median survival time was 71 months (36–106 months) for the patients with UIP and 95 months (90–100 months) for the patients with idiopathic NSIP ($P = 0.0001$) (Fig. 1). A total of 36 patients died during the follow-up. Progression of interstitial pneumonia was the cause of death in 29 patients (acute exacerbation in 20 and slow progression in 9). Among the 29 patients, 28 patients had UIP. The seven patients who died of other causes, such as lung cancer ($n = 3$), infectious pneumonia ($n = 3$) and post-operative acute respiratory distress syndrome ($n = 1$), were excluded from the survival analysis. In multivariate survival analysis with a Cox proportional hazards model, the pathologic diagnosis of NSIP was the only independent predictive factor for a longer survival (hazard ratio (HR) 0.035, $P = 0.005$). When the pathologic diagnosis was not included in the analysis, higher lymphocyte count in BAL fluid was the other only predictive factor for a longer survival (HR 0.909, $P = 0.029$). As shown in Fig. 2, survival was not different between UIP patients with BAL lymphocytosis and NSIP patients without BAL lymphocytosis ($P = 0.743$). The patients with UIP showing BAL lymphocytosis had a tendency of better survival than those without BAL lymphocytosis, but it did not reach a statistical significance ($P = 0.073$). Kaplan–Meier survival analysis showed that BAL lymphocytosis was associated with better survival (Fig. 3). The survival was not affected by age

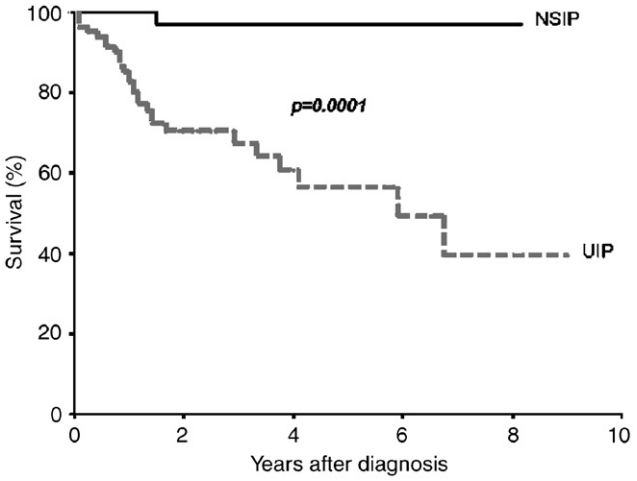

Figure 1 The Kaplan–Meier survival curve of 122 patients with IPF ($n = 87$) and idiopathic NSIP ($n = 35$).

($P = 0.779$), sex ($P = 0.079$) and the treatment with corticosteroids and/or cytotoxic agents ($P = 0.167$).

Discussion

Our study showed that analysis of the differential white blood cell count in BAL fluid was useful not only for separating NSIP from UIP, but also for predicting the prognosis in patients with fibrotic IIP. In particular, the presence or absence of BAL lymphocytosis was important. Unless pathologic diagnosis was confirmed, it can be an independent predictor of good prognosis in fibrotic IIP.

Our observations are meaningful from a clinical aspect because BAL could give valuable information on the

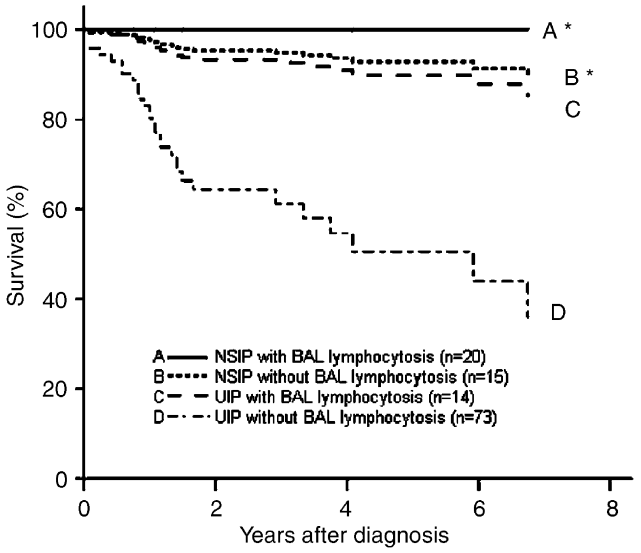

Figure 2 Survival of the patients with UIP and NSIP according to the presence and absence of BAL lymphocytosis. *P-value < 0.05 when compared with D group.

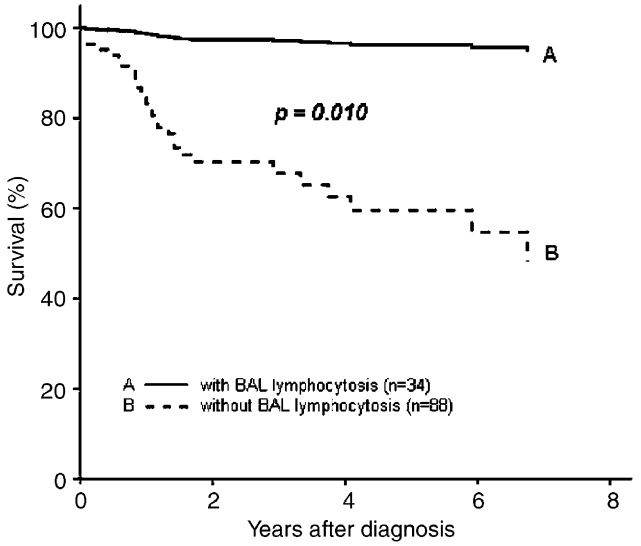

Figure 3 Survival of patients with fibrotic idiopathic interstitial pneumonia in relation to BAL lymphocytosis.

differential diagnosis and prognosis in those patients who are suspected of having UIP or idiopathic NSIP. Old age, decreased lung function and coexisting illnesses of the patients with fibrotic IIP can make surgical lung biopsy difficult to perform. When the risk of undergoing surgical lung biopsy exceeds the benefit, the patients with IIP should be evaluated by non-invasive procedures. HRCT is a crucial tool for the differential diagnosis and for predicting the reversibility of lung lesion in IIP.[1,3,24,25] In our study, 97% of the patients with HRCT diagnosis of confident UIP were confirmed to have UIP on surgical lung biopsy. When both HRCT diagnosis of confident UIP and BAL neutrophilia were present, all of them were pathologically diagnosed as UIP. In the 62 patients whose HRCT diagnosis was not confident UIP, the absence of BAL lymphocytosis suggested a diagnosis of UIP. When HRCT findings are atypical for UIP, the current recommendation by ATS/ERS is to get a histopathologic diagnosis with or without performing BAL prior to surgical lung biopsy.[20] Our results suggest that BAL is at least complementary to HRCT in the non-invasive diagnostic evaluation of IIP. Therefore, BAL as well as chest HRCT should be performed as a routine procedure in IIP.

Previous studies suggested that patients with BAL neutrophilia showed a poor prognosis in UIP/NSIP.[16,17,20,21] BAL neutrophilia, however, had no prognostic value in our study. It might be because the follow-up duration of our patients was relatively short. Regardless of the presence of BAL neutrophilia, our data suggests that BAL lymphocytosis can be an independent prognostic factor in IIP. UIP is an ultimately fatal disease unresponsive to corticosteroids and/or cytotoxic agents, but NSIP usually shows a favorable treatment response.[7–12] When surgical lung biopsy is not feasible in patients with fibrotic IIP, BAL lymphocytosis can be an objective parameter predictive of a good treatment response.[16,18–20]

Our result is contrasted with the report by Veeraraghavan et al.[23] which concluded that the BAL findings in 54 patients with a clinical diagnosis of UIP had no diagnostic role in discriminating between UIP and NSIP. The most plausible explanation for this discrepancy is the difference in the number of patients. The number of our patients is 122, much more than that of Veeraraghavan's study. Since the histopathologic distinction between UIP and fibrotic NSIP is very difficult in some cases,[4,5] increasing the number of patients could decrease the error in the histologic diagnosis. As we had already excluded 26 patients whose histopathologic diagnosis was uncertain, the possibility of histopathologic misclassification in 122 patients would be very low. The typical pattern of the differential cell count in BAL fluid has also been reported in individual entity of IIP in other studies.[8,9,20,22,27]

Our study has several drawbacks. It is a retrospective study in nature; hence, our observations remain to be confirmed in a prospective study. Second, our patients might have less severe disease since all of them tolerated surgical lung biopsy under general anesthesia. The longer median survival of our patients compared to the previous reports[10,12,19] may well reflect this. Thirdly, since our follow-up duration is relatively short, the role of BAL in predicting prognosis needs to be verified in a long-term follow-up study. Lastly, BAL findings had no prognostic value once the histologic distinction between UIP and NSLP had been made.

In conclusion, BAL is useful not only in diagnosing a variety of specific non-IIP diseases but also in narrowing the differential diagnosis and predicting the prognosis in fibrotic IIP. Therefore, BAL should be performed in IIP whenever possible. A long-term prospective study will be needed to define the role of BAL more clearly in IIP.

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