Significance of Bronchoalveolar Lavage for the Diagnosis of Idiopathic Pulmonary Fibrosis

Shinichiro Ohshimo[1], Francesco Bonella[1], Ai Cui[1], Martin Beume[2], Nobuoki Kohno[3], Josune Guzman[4], and Ulrich Costabel[1]

[1]Medical Faculty, University of Duisburg-Essen, and Department of Pneumology/Allergy, Ruhrlandklinik, Essen, Germany; [2]Radiology Unit, Klinikum Niederberg, Velbert, Germany; [3]Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; and [4]General and Experimental Pathology, Ruhr-University, Bochum, Germany

***Rationale*: According to the 2002 ATS/ERS Consensus Classification, a confident diagnosis of idiopathic pulmonary fibrosis (IPF) without surgical lung biopsy is made with consistent clinical/physiological findings and the typical features on high-resolution computed tomography (HRCT). Bronchoalveolar lavage (BAL) and/or transbronchial biopsy, one of four major criteria in the 2000 ATS/ERS IPF Statement, was no more essential in the diagnostic algorithm of 2002 ATS/ERS Consensus Classification.**

***Objectives*: To evaluate the additional utility of BAL for the diagnosis of IPF.**

***Methods*: A total of 101 patients with suspected IPF on HRCT were studied. Twenty-seven patients were excluded because of lack of functional impairment (n = 20), an underlying condition causing fibrosis (n = 5), or a clinical history inconsistent with IPF (n = 2). The remaining 74 patients met all the criteria recommended in the 2002 ATS/ERS Consensus Classification for making a diagnosis in the absence of surgical biopsy. The final diagnosis was made with further examinations, including pathological analysis, in patients who showed inconsistent findings for IPF on BAL.**

***Measurements and Main Results*: A cut-off level of 30% for lymphocytes in BAL demonstrated a favorable discriminative power for the diagnosis of IPF. Six of the 74 patients (8%) showed a lymphocytosis of 30% or greater in BAL. Their final diagnoses were idiopathic nonspecific interstitial pneumonia (n = 3) and extrinsic allergic alveolitis (n = 3). The change in perception of the diagnosis was validated by a surgical biopsy in two cases and by subsequent outcome in four cases.**

***Conclusions*: BAL lymphocytosis changed the diagnostic perception in six of 74 patients who would have been misdiagnosed as having IPF without BAL.**

Keywords: lymphocytosis; extrinsic allergic alveolitis; nonspecific interstitial pneumonia

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive interstitial lung disease (ILD) of unknown etiology (1). It is histologically characterized by the usual interstitial pneumonia (UIP) pattern. Because of its poor prognosis and no established effective therapy, the differential diagnosis of IPF from other ILD is important (2–5). Previous studies have demonstrated considerable interobserver variation (6) and interlobar variability (7) in the histopathologic interpretation of ILD. It is, therefore, less reliable to use histopathologic examination alone as a pivotal diagnostic procedure for ILD. In addition, previous studies have demonstrated interobserver variation in the interpretation of high-resolution computed tomography (HRCT) (8–11) and discrepancies between pathological and HRCT findings (3).

Bronchoalveolar lavage (BAL) is a well-tolerated diagnostic procedure in ILD. In addition to BAL cell differentials, morphologic features are beneficial for the diagnosis of extrinsic allergic alveolitis (EAA), sarcoidosis, *Pneumocystis carinii* pneumonia, and malignancy. BAL and/or transbronchial biopsy were considered requirements for the exclusion of other diseases in a patient with IPF who did not undergo surgical lung biopsy as one of the four major criteria for making a clinical diagnosis of IPF according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) IPF Statement of 2000 (12). In the ATS/ERS international consensus classification of idiopathic interstitial pneumonias (IIPs) of 2002 (1), BAL analysis was no more found to be important in the diagnostic work-up of IPF. In that statement, a confident CT diagnosis of IPF with consistent clinical features was considered to be sufficient to make an accurate diagnosis of IPF without surgical biopsy.

The aim of this study was to evaluate the diagnostic contribution of BAL cell differentials in patients with clinicoradiologically suspected IPF. Some of the results of this study have been previously reported in the form of an abstract (13).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

According to the 2002 ATS/ERS Consensus Classification, the analysis of bronchoalveolar lavage fluid, which was essential in the 2000 ATS/ERS IPF Statement (one of four major criteria), is no longer essential in the diagnostic algorithm for idiopathic pulmonary fibrosis.

What This Study Adds to the Field

Bronchoalveolar lavage lymphocytosis changed diagnostic perception in 6 of 74 suspected cases of idiopathic pulmonary fibrosis. Brochoalveolar lavage cell differentials may be of additional diagnostic benefit in this clinical setting.

MATERIALS AND METHODS

Study Subjects

We retrospectively collected all patients with a confident CT diagnosis of IPF who were admitted to Ruhrlandklinik (Essen, Germany) between 2003 and 2007 and who had a BAL performed during the initial diagnostic work-up. BAL is a routine diagnostic procedure at our hospital for every patient with undiagnosed interstitial lung disease. According to our database, only 3% of patients do not undergo BAL because of contraindications or refusal by patients. There were a total of 101 patients. All patients showed bilateral, subpleural, and basal distribution of a reticular and honey-combing pattern on HRCT and absence of significant ground glass opacification or nodular changes.

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Correspondence and requests for reprints should be addressed to Ulrich Costabel, M.D., Ph.D., University of Duisburg-Essen, and Department of Pneumology/Allergy, Ruhrlandklinik Tueschener Weg 40, 45239 Essen, Germany. E-mail: ulrich.costabel@ruhrlandklinik.de

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Two observers (U.C. and M.B.) independently evaluated the HRCT findings blinded to the BAL results and other clinical data and reached a consensus. Next, the patients were evaluated whether they fulfilled the major and minor criteria (except for the BAL/transbronchial biopsy criterium) of the 2000 ATS/ERS Consensus Classification (12). Seventeen patients were excluded because they had no evidence of restriction (VC >80% predicted and TLC >80% predicted), three patients were excluded because they had no impairment of gas exchange [single-breath D_{LCO} >80% predicted and $P(A–a)_{O_2}$ >25 mm Hg], five patients were excluded because they had evidence of collagen vascular disease–associated interstitial pneumonia or drug-induced pneumonia, and two patients were excluded because they lacked the clinical history for IPF (Figure 1). A total of 74 patients were included in this study. All patients met the following three major criteria: (*1*) exclusion of other known causes of ILD, (*2*) abnormal pulmonary function, including evidence of restriction and impaired gas exchange, and (*3*) bibasilar reticular abnormalities on HRCT scans; and at least three of four following minor criteria: (*1*) age greater than 50 years, (*2*) insidious onset of otherwise unexplained dyspnea on exertion, (*3*) duration of illness more than 3 months, and (*4*) bibasilar, inspiratory crackles as recommended by the ATS/ERS (1, 12).

Pulmonary Function Tests

Vital capacity and FEV_1 were analyzed by using spirometry (ZAN 400 Sniff; ZAN Messgeraete GmbH, Ober-thulba, Germany). TLC and D_{LCO} were analyzed using body plethysmography (Slativ ZAN 500; ZAN Messgeraete GmbH). Arterial blood gas was analyzed using ABL 800 Flex (Radiometer GmbH, Denmark). Values were expressed as percentages of predicted normal values.

BAL

BAL was performed as previously described (14). In brief, a flexible bronchoscope was wedged into a segmental bronchus of the middle lobe or the lingula. Sterile isotonic saline was instilled in five to ten 20-ml aliquots up to a total volume of 100 to 200 ml, with immediate aspiration by gentle suction after each aliquot. The recovered BAL fluid was immediately processed in the laboratory. The fluid was pooled, filtered through two layers of gauze, and centrifuged at 500 × *g* for 10 minutes at room temperature. The cells were counted in a hemocytometer. Slides were stained with May-Grünwald-Giemsa stain (Merck, Darmstadt, Germany), and a total of 600 cells were counted for the cell differentials. A trypan blue exclusion test was performed for evaluating cell viability.

Statistical Methods

Data were expressed as mean ± SD. Comparison of nonnormally distributed variables between two groups was done with the Mann-Whitney *U* test. Comparison of categorical variables between two groups was done with the Fisher's exact probability and the χ^2 test. All statistical analyses were done using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL). Differences were considered statistically significant at $P < 0.05$.

RESULTS

Characteristics of the Enrolled Patients

Among the 74 eligible patients with a clinical diagnosis of IPF according to the 2002 ATS/ERS Consensus Classification (1),

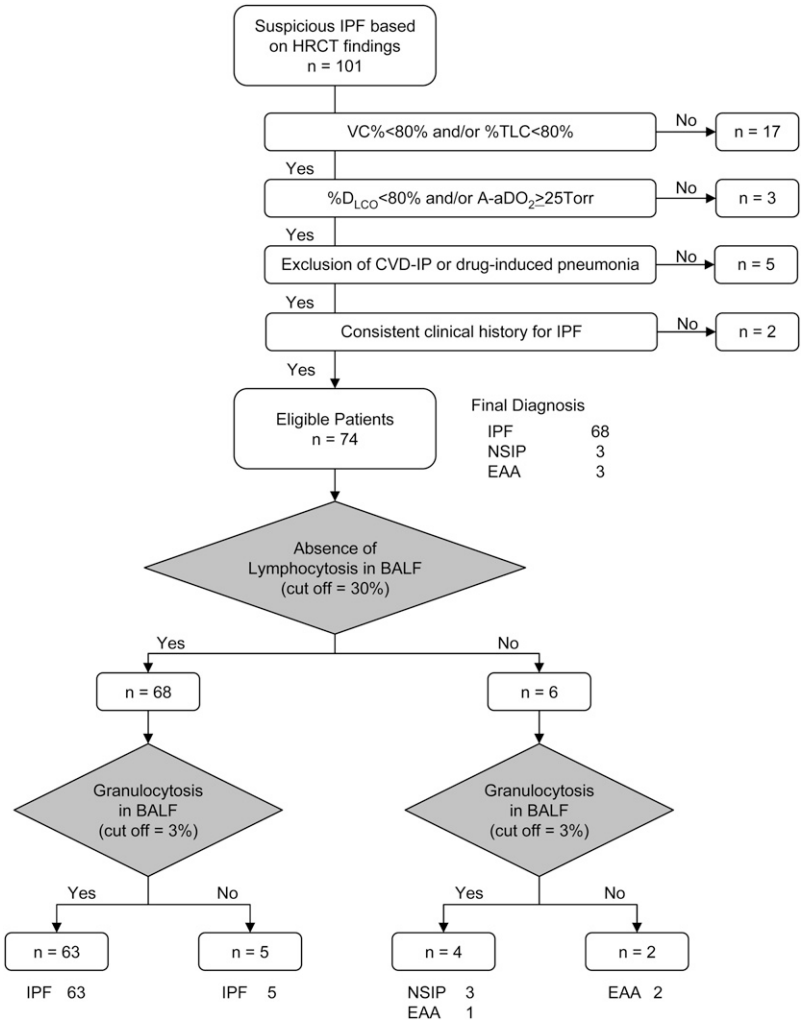

Figure 1. Selection of patients and the categorization of patients according to the bronchoalveolar lavage findings.

TABLE 1. CHARACTERISTICS OF THE ENROLLED PATIENTS

Variables	Total	IPF	Non-IPF	*P* Value
n	74	68	6	
Gender, male/female	60/14	54/14	6/0	0.49
Age, years, mean ± SD	69 ± 8	69 ± 8	72 ± 10	0.58
Age range, years	52–84	52–83	60–84	
Smoking status, current/ex/non, n	5/40/29	5/34/29	0/6/0	0.06
Duration of symptoms before diagnosis, years, mean ± SD	3.2 ± 4.5	3.4 ± 4.7	1.3 ± 1.1	0.18
Relevant concomitant medications, n (%)				
Corticosteroids and/or immunosuppressants	17 (23)	17 (25)	0 (0)	0.37
Oxygen use	7 (9)	7 (10)	0 (0)	0.92
Pulmonary function tests, mean ± SD				
VC, % predicted	71 ± 17	70 ± 18	77 ± 9	0.20
FEV_1, % predicted	72 ± 18	71 ± 18	78 ± 17	0.38
D_{LCO}, % predicted	47 ± 17*	47 ± 17	48 ± 13	0.68
TLC, % predicted	64 ± 12†	63 ± 2	72 ± 7	0.08
$P(A–a)_{O_2}$, mm Hg, mean ± SD	31 ± 10	30 ± 9	40 ± 10	0.04

Definition of abbreviation: IPF = idiopathic pulmonary fibrosis.
* n = 67.
† n = 72.

there were 60 male and 14 female patients with a mean age of 69 ± 8 years (Table 1). No significant differences were observed between the IPF and the non-IPF group regarding gender, age, smoking status, and the duration of symptoms before diagnosis. The numbers of patients who received corticosteroids, immunosuppressants, and/or oxygen were not significantly different between both groups. No significant differences were seen between both groups regarding pulmonary function tests, including VC, FEV_1, D_{LCO}, and TLC, except for the $P(A–a)_{O_2}$ ($P = 0.04$).

Final Diagnosis of the 74 Patients

The final diagnoses of the 74 patients are shown in Figure 1. Sixty-eight patients were diagnosed as having IPF, three patients were diagnosed as having idiopathic nonspecific interstitial pneumonia (NSIP), and three patients were diagnosed as having EAA. The precise clinical characteristics of the six non-IPF patients are shown in Table 2.

TABLE 2. CLINICAL CHARACTERISTICS OF THE SIX PATIENTS WITH DIAGNOSES OF NON-IPF

	Patient No.					
	1	2	3	4	5	6
Final diagnosis	NSIP	NSIP	NSIP	EAA	EAA	EAA
Age	60	65	82	84	67	71
Sex	M	M	M	M	M	M
Smoking history	Ex	Ex	Ex	Ex	Ex	Ex
History of antigen exposure	No	No	No	Yes	Yes	Yes
Type of exposure	NA	NA	NA	Birds and mold	Humidifier water	Moldy hay
Positive precipitins	No	ND	No	Yes	No	Yes
Type of biopsy	SLB	SLB	ND	TBB	TBB	TBB
Biopsy result	NSIP	NSIP	NA	EAA	NSIP	Not diagnostic
BALF analysis						
TCC, $\times 10^6$ cells/ml	0.03	0.15	0.11	0.53	0.43	0.32
Lymphocytes, %	30	67	41	63	68	70
Granulocytes, %	30	21	8	15	1	12
Neutrophils, %	27	10	5	1	1	1

Definition of abbreviations: BALF = bronchoalveolar lavage fluid; EAA = extrinsic allergic alveolitis; Ex = ex-smoker; IPF = idiopathic pulmonary fibrosis; M = male; NA = not applicable; ND = not done; NSIP = nonspecific interstitial pneumonia; SLB = surgical lung biopsy; TBB = transbronchial biopsy; TCC = total cell count.

BAL Findings

The differential cell counts of the IPF and the non-IPF group are shown in Table 3. The absolute number and the percentage of lymphocytes was significantly higher in the non-IPF group than in the IPF group ($P = 0.0007$ and $P = 0.0001$, respectively). Accordingly, the percentage of macrophages was significantly lower in the non-IPF group than in the IPF group ($P = 0.0001$). No significant differences were found between both groups regarding the numbers of granulocytes, neutrophils, and eosinophils.

Diagnostic Significance of BAL

When the cut-off levels of 30% for lymphocytosis and 3% for granulocytosis were set, 68 (92%) patients showed an absence of lymphocytosis in BAL (Figure 1). Among them, 63 (85%) patients showed a granulocytosis in BAL. All of these 68 patients were diagnosed as having IPF despite the presence or absence of BAL granulocytosis. Among the remaining six (8%) patients with a lymphocytosis in BAL, four (5%) patients also showed a granulocytosis in BAL (three patients [4%] with NSIP and one patient [1%] with EAA). The two (3%) patients with lymphocytosis and no granulocytosis were diagnosed as having EAA. The diagnosis of NSIP was confirmed by pathologic

TABLE 3. COMPARISON OF BRONCHOALVEOLAR LAVAGE FLUID ANALYSES IN IDIOPATHIC PULMONARY FIBROSIS AND NON-IPF GROUPS (N = 74)

	IPF (*n = 68*)	Non-IPF (*n = 6*)	*P* Value*
Total cell count, $\times 10^5$/ml BALF	1.58 ± 1.62	2.61 ±1.98	0.17
Macrophages, $\times 10^5$/ml BALF	1.21 ± 1.34	0.61 ± 0.53	0.28
Percentage	75 ± 17	27 ± 15	0.0001
Lymphocytes, $\times 10^5$/ml BALF	0.13 ± 0.16	1.67 ± 1.36	0.0007
Percentage	8 ± 6	57 ± 17	<0.0001
Granulocytes, $\times 10^5$/ml BALF	0.23 ± 0.31	0.26 ± 0.24	0.32
Percentage	16 ± 15	14 ± 10	0.90
Neutrophils, $\times 10^5$/ml BALF	0.17 ± 0.25	0.07 ± 0.04	0.80
Percentage	12 ± 13	8 ± 10	0.17
Eosinophils, $\times 10^5$/ml BALF	0.06 ± 0.13	0.18 ± 0.23	0.27
Percentage	4 ± 5	6 ± 5	0.20

Definition of abbreviations: BALF = bronchoalveolar lavage fluid; IPF = idiopathic pulmonary fibrosis.
Values are mean ± SD or *P* values.
* Mann-Whitney *U* test.

examination in two patients and a consistent clinical course after the administration of corticosteroids in one patient. The diagnosis of EAA was confirmed by histories of exposure to relevant environmental antigens, positive serum precipitins, and a favorable clinical course after avoidance of antigens and the administration of corticosteroids. Thus, BAL provided crucial new diagnostic information in 6 of 74 cases (95% confidence interval for prevalence, 0.03–0.17).

DISCUSSION

In the present study, we evaluated the clinical utility of BAL for the diagnosis of IPF. According to the 2002 ATS/ERS Consensus Classification (1), 74 patients of our series were diagnosed as having IPF with consistent HRCT, pulmonary function, and clinical findings. Among them, six (8%) patients demonstrated a lymphocytosis of 30% or greater in BAL cell differentials. Further examinations clarified the final diagnosis of idiopathic NSIP in three patients and of EAA in three patients. The patients with EAA had a history of exposure to birds and mold, humidifier water, and moldy hay, which became apparent only after the BAL results were known to the clinician, and the history was taken again with specific questions for potential sources of exposure. Thus, a BAL lymphocytosis changed the diagnostic perception in 6 of 74 cases, and the change in perception was validated by a surgical biopsy in two cases and by subsequent outcome in four cases.

Our study is important from a clinical point of view. Although clinical-radiologic-pathologic evaluation is considered to be the "gold standard" for the diagnosis of IIPs, there are certain limitations for the performance of a surgical biopsy in elderly patients with IPF, including severely impaired pulmonary function, the risk of acute exercerbation, and potential significant comorbidities. In clinical practice, less than 30% of patients are estimated to have had surgical lung biopsies (15). In addition, previous studies have demonstrated interlobar variability and/or interobserver variation, suggesting that the pathologic evaluation alone may result in an incorrect diagnosis (3, 6, 7, 16).

HRCT is important for the differential diagnosis and the assessment of prognosis in patients with IIPs (10, 17). Previous studies, however, have demonstrated that the sensitivity and the specificity of HRCT for the diagnosis of IPF were approximately 43 to 78% and 90 to 97%, respectively (8, 18–21). A significant interobserver variation for the interpretation of HRCT findings has also been reported (8–11). Flaherty and colleagues demonstrated that an HRCT pattern consistent with IPF can only be found in approximately half of patients with pathologically confirmed UIP and is associated with mid- to late-stage disease and a particularly poor prognosis (3). A UIP-like pattern on HRCT and on histopathology can also be seen in association with drug exposure, environmental factors, and collagen vascular diseases (22).

Our results suggest that the BAL analysis has an additional benefit for the diagnosis of IPF and that combined diagnostic procedures, including BAL, increase the diagnostic accuracy. Previous studies have demonstrated that the absence of a lymphocytosis in BAL is important for the diagnosis of IPF (22, 23). Our results are consistent with these previous studies. To the best of our knowledge, however, no exact cut-off level has been evaluated for the lymphocytosis in BAL. The 2002 ATS/ERS Consensus Classification suggested that lymphocyte counts above 15%, which is the upper limit of normal, should be indicative of an alternative diagnosis including NSIP, cryptogenic organizing pneumonia, EAA, or sarcoidosis (1). Our study demonstrated that the discriminating power between IPF and non-IPF was favorable, with a cut-off level of 30% for lymphocytosis in BAL. Previous studies have demonstrated that granulocytosis or neutrophilia in BAL is an important diagnostic and prognostic factor in IPF (24, 25). In our study, however, the indicator with the greatest impact in BAL for the diagnosis of IPF was the absence of a lymphocytosis.

Veeraraghavan and colleagues demonstrated that BAL findings do not discriminate between UIP and NSIP in patients presenting with clinical features of IPF (26). These authors analyzed 54 patients with pathologically confirmed IPF and fibrotic NSIP. Other fibrotic diseases, such as cellular NSIP or EAA, had been excluded. Veeraraghavan and colleagues (26) had selected their patients based on the histopathologic diagnosis. The current ATS/ERS Consensus Classification states, however, that a confident diagnosis of IPF can be made with consistent clinical findings and the typical features on UIP on HRCT in the absence of a surgical biopsy. Our study followed the diagnostic procedures recommended in the current ATS/ERS Consensus Classification and therefore is important from a practical aspect.

A potential limitation of our study is that the majority of our patients with IPF had not undergone surgical lung biopsy. Therefore, we did not evaluate the discriminative power of the BAL cell differentials as an independent test against a "gold standard," such as the clinico-radiologic-pathologic consensus. This would have led to a major verification bias in the setting of this study. Moreover, our study has not comprehensively evaluated the total spectrum of patients with IPF because we excluded patients with UIP on surgical biopsy but without typical features on IPF on HRCT, according to the design of the study. The current study, however, evaluated the additional diagnostic benefit of BAL analysis on the basis of the 2002 ATS/ERS Consensus Classification. Our results favor a multimodal diagnostic procedure, including BAL analysis.

In conclusion, this study demonstrates that the addition of BAL to the diagnostic procedures is useful in patients suspected of having IPF with a confident CT diagnosis and consistent clinical features in the absence of a surgical biopsy. BAL cell differentials are of additional diagnostic benefit in this clinical setting.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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