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BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia

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BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. S. Veeraraghavan, P.I. Latsi, A.U. Wells, P. Pantelidis, A.G. Nicholson, T.V. Colby, P.L. Haslam, E.A. Renzoni, R.M. du Bois. ©ERS Journals Ltd 2003.

ABSTRACT: Idiopathic pulmonary fibrosis (IPF), which has the histological pattern of usual interstitial pneumonia (UIP), is a progressive interstitial lung disease with a poor prognosis. Idiopathic interstitial pneumonias with a histological pattern of nonspecific interstitial pneumonia (NSIP) have a better prognosis than UIP, and may present with a clinical picture identical to IPF. The authors hypothesised that bronchoalveolar lavage (BAL) findings may distinguish between UIP and NSIP, and have prognostic value within disease subgroups.

BAL findings were studied retrospectively in 54 patients with histologically proven (surgical biopsy) idiopathic UIP (n=35) or fibrotic NSIP (n=19), all presenting clinically as IPF. These findings were also compared with the BAL profile of patients with other categories of idiopathic interstitial pneumonias.

BAL total and differential cell counts did not differ between the two groups. Survival was better in NSIP. In neither group were BAL findings predictive of survival or changes in lung function at 1 yr, even after adjustment for disease severity, smoking and treatment. BAL differential counts in fibrotic NSIP differed from respiratory bronchiolitis-associated interstitial lung disease, but not from desquamative interstitial pneumonia or cellular NSIP.

The authors conclude that bronchoalveolar lavage findings do not discriminate between usual interstitial pneumonia and nonspecific interstitial pneumonia in patients presenting with clinical features of idiopathic pulmonary fibrosis, and have no prognostic value, once the distinction between the two has been made histologically.
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Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease characterised by a poor prognosis and limited response to treatment. Considerable advances have recently been made in characterising the underlying histological appearances. KATZENSTEIN and MYERS [1, 2] propose that the term IPF should be reserved for cases with a histological appearance of usual interstitial pneumonia (UIP). Nonspecific interstitial pneumonia (NSIP) is a temporally uniform interstitial pneumonia, differing from the heterogeneous appearance of UIP [1, 2]. The recent American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement has concluded that UIP is the histological pattern associated with IPF and that the histological pattern of NSIP identifies an entity that should be viewed as distinct from IPF, although it can present clinically in an identical fashion to IPF [3, 4]. NSIP biopsies consisting primarily of mild-to-moderate chronic inflammation are classified as cellular NSIP, and biopsies consisting mainly of fibrosis as fibrotic NSIP [5, 6].

Overall, idiopathic NSIP has a better prognosis than UIP. However, although initial reports showed large differences in mortality between the two groups [7–9], later studies documented a high 5- and 10-yr mortality rate in fibrotic NSIP [5, 10]. Cellular NSIP, by contrast, has a 10-yr survival of 100% [5, 6]. Furthermore, when idiopathic NSIP presents with the clinical features of IPF (bilateral rales, restrictive lung function, bilateral reticular shadowing on chest radiograph and absence of connective tissue disease or occupational or environmental exposure), the prognosis is worse than in other patients with NSIP, with a 5-yr survival of only 45% [6].

Bronchoalveolar lavage (BAL) has been used as a marker of lower respiratory tract inflammation in pulmonary fibrosis. In studies performed in IPF, prior to the recent reclassification, a BAL neutrophilia and/or eosinophilia denoted a poor outcome, whereas a BAL lymphocytosis was associated with a more cellular biopsy, less honeycombing, and greater responsiveness to therapy [11–15]. In light of the new classification, it can be argued that a BAL lymphocytosis may be suggestive of NSIP, as indicated in the recent ATS statement [3]. In small groups of NSIP patients, not necessarily characterised by the clinical features of IPF, a BAL lymphocytosis has been observed [16–19]. By contrast DANIIL *et al.* [8] did not find a BAL lymphocytosis in a small cohort of NSIP patients.

BAL findings were compared between UIP and fibrotic NSIP in a large cohort of patients presenting with the clinical features of IPF. A second aim of the study was to determine the independent prognostic value of BAL findings, after taking the underlying histological diagnosis into account. In addition, these findings were compared with BAL findings in other idiopathic interstitial pneumonias subtypes, such as

For editorial comments see page 191.

cellular NSIP, desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-associated interstitial lung disease (RBILD), which may resemble the clinical and radiological features of NSIP or UIP.

Material and methods

Study subjects

A retrospective study (1978–2000) of BAL findings was conducted in patients with a histological diagnosis of UIP or NSIP, and a clinical diagnosis of IPF according to the following criteria [15]: 1) bilateral, predominantly basal rales; 2) restrictive functional defect or isolated reduction in the transfer factor of the lungs for carbon monoxide (DL,CO); 3) chest radiographic abnormalities of pulmonary fibrosis in a distribution compatible with IPF; and 4) absence of significant occupational or environmental exposure or connective tissue disease.

Seventy-four patients with a diagnosis of UIP or NSIP at open-lung biopsy presented with a clinical diagnosis of IPF and underwent BAL. Patients with an interval between BAL and biopsy of >4 months (n=17) were excluded. Patients with cellular NSIP (n=3) were analysed separately. In total, 54 patients (fibrotic NSIP=19, UIP=35) were included in the analysis; total cells·mL^{-1} (43 patients) and differential cell counts (54 patients) were compared. The median time interval between BAL and biopsy was 1 month. Demographic data are shown in table 1.

During the same period a further 29 patients with BAL and a histological diagnosis (open-lung biopsy) of cellular NSIP (n=3), DIP (n=11) or RBILD (n=15) were identified.

Histological examination

All patients had undergone a surgical biopsy procedure and histological sections had been routinely stained with haematoxylin-eosin with additional staining using elastin van-Gieson stains. The site of biopsy was determined by intraoperative inspection with a deliberate effort made to avoid areas of honeycombing on radiological examination. Two pulmonary pathologists reviewed the slides independently; discrepant observations were resolved by joint review. The histological diagnosis of UIP, NSIP, DIP or RBILD was made based on previously published criteria [1].

Pulmonary function tests

Pulmonary function tests performed before BAL were used for analysis (median interval 5 days, range 0–37 days). Pulmonary function tests were measured as described previously [20], with gas transfer levels corrected for haemoglobin levels. Forced vital capacity (FVC) was measured using a dry-rolling seal spirometer (PK Morgan Ltd, Gillingham, UK). The DL,CO was measured by means of a rebreathing manoeuvre, using modified transfer factor equipment (PK Morgan Ltd), and data amended to a 10-s single-breath result.

Brochoalveolar lavage

BAL was part of routine clinical evaluation. Bronchoscopy was performed and BAL fluid processed as described previously [20]. Aliquots of 60 mL of sterile normal saline were instilled through the bronchoscope and retrieved by mechanical suction. The standard volume used in most patients was 240 mL. Cells in the fluid were collected by low-speed centrifugation at 300×g for 5 min at 4°C and washed three-times with cold minimal essential medium (MEM) containing 25 mM N-2-hydroxyethylpiperazine-N-2-ethanesuphonic acid buffer (HEPES). Total cell counts were made using an improved Neubauer chamber (VWR International, Lutterworth, UK). Slide preparations for differential percentage counting of cells were made in a Shandon cytocentrifuge (Thermo Shandon Ltd, Runcorn, UK) using 100 μL aliquots of lavage cell suspensions adjusted to 1.25×10^6 cells·mL^{-1} in MEM. After fixation in methanol, the preparations were stained with May-Grünwald Giemsa stain. Differential counts were made from a total count of $\geqslant$300 cells.

Analysis

Group comparisons for normally distributed data were made using an unpaired t-test or, when appropriate, Chi-squared

Table 1. – Demographic characteristics, smoking history and lung function indices

	Fibrotic NSIP	UIP	p-value
Subjects n	19	35	
Age yrs	54.5±7.2	56.1±6.6	NS
F:M	5 (26):14 (74)	4 (14):31 (86)	NS
Smoking status			
Current	6 (32)	5 (14)	NS
Past	8 (42)	21 (60)	NS
Never	5 (26)	9 (26)	NS
Lung function			
FVC % at BAL	78.6±18.9	75.1±16.9	0.48
FVC % at 1-yr follow-up	83.9±24.8	69.9±22.2	0.04
DL,CO % at BAL	44.4±16.1	49.0±12.9	NS
DL,CO % at 1-yr follow-up	46.8±21.4	41.8±11.9	NS
Duration between BAL and biopsy months	0.50 (0–2.9)	0.79 (0–3.7)	NS
Treatment at BAL n			
Prednisolone only	3	5	NS
Prednisolone+azathioprine	1	1	
Prednisolone+cyclophosphamide	0	1	

Data are presented as mean±SD, n (%) or median (range) unless otherwise stated. NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; F: female; M: male; FVC: forced vital capacity; BAL: bronchoalveolar lavage; DL,CO: transfer factor of the lungs for carbon monoxide. NS: nonsignificant.

statistics. BAL cellularity was not normally distributed; the Mann-Whitney U-test was used for unadjusted comparisons of BAL cell counts. Spearman's rank correlation was used to evaluate univariate relationships between lavage cellularity and measures of disease severity. Multivariate linear regression models were constructed to identify independent determinants of BAL cellularity. The Kaplan-Meier analysis was used to compare survival between the groups.

Results

Demographics

As shown in table 1, there was no significant difference between NSIP and UIP patients in age, sex and smoking status.

Bronchoalveolar lavage

In the analysis of BAL, absolute numbers of individual cells·mL^{-1} and differential cell counts (percentage) were compared in order to detect any differences in cellular patterns between NSIP and UIP. Two patients had a normal BAL differential count (neutrophils $\leqslant$4%, eosinophils $\leqslant$3% and lymphocytes $\leqslant$14%); one UIP and one NSIP (table 2).

As shown in table 2, there were no significant or marginal differences in BAL data (total cells·mL^{-1} and differential counts) between UIP and fibrotic NSIP. Neutrophils were elevated in 17 of 19 (89%) patients with fibrotic NSIP and in 31 of 35 (89%) patients with UIP. One (5%) patient with fibrotic NSIP and eight (23%) patients with UIP had elevated lymphocytes and 15 (80%) patients with fibrotic NSIP and 25 (77%) patients with UIP had elevated eosinophils (fig. 1). There was a marginal trend towards greater prevalence of lymphocytosis in UIP (p=0.1, Fisher's exact test).

Multiple linear regression models were constructed to identify the independent determinants of lavage cellularity. No independent relationships were observed between histological pattern and BAL lymphocyte, neutrophil or eosinophil content.

To remove the confounding effect of histological misclassification (due to "sampling error" at lung biopsy), the comparison between the BAL cellular constituents was repeated in a cohort of 21 patients in whom the diagnosis was confirmed as either NSIP or UIP in biopsies from more than one lobe (fibrotic NSIP n=7, UIP n=14). The median (range) BAL differential counts were similar between NSIP (lymphocytes 5 (2–14), neutrophils 6 (2–20), eosinophils 5 (1–18)) and UIP patients (lymphocytes 6 (0–38), neutrophils 8.5 (1–20), eosinophils 5 (0–11)). There was no statistical difference in the total and differential cell counts between the two groups (Mann-Whitney test p=NS for all cell types; fig. 1d).

To compare these findings with other idiopathic interstitial pneumonia subtypes that could resemble the clinical features of NSIP or UIP, BAL differential cell counts were analysed in a further 11 DIP, 15 RBILD and three cellular NSIP patients. There was no difference in BAL differential cell counts between either fibrotic NSIP or UIP and cellular NSIP or DIP (fig 2). However, there was a significant difference in all the BAL cellular constituents between fibrotic NSIP or UIP and RBILD (fig. 2).

Table 2. – Bronchoalveolar lavage (BAL) fluid total cells·mL^{-1} and differential counts in patients with fibrotic nonspecific interstitial pneumonia (NSIP) compared with usual interstitial pneumonia (UIP)

	Fibrotic NSIP	UIP	p-value
Total subjects n	19	35	
Subjects with normal BAL	1	1	NS
Macrophages %	71 (25–92)	73 (24–89)	NS
Neutrophils %	9 (2–57)	9 (1–58)	NS
Lymphocytes %	5 (0–18)	4 (0–42)	NS
Eosinophils %	7 (1–28)	7 (0–32)	NS
Total cells$^{\#}$ $\times 10^5$ mL^{-1}	2.02 (0.40–11.43)	2.4 (0.4–11.6)	NS

Data are presented as median (range) unless otherwise stated. $^{\#}$: total cell counts were available in 15 fibrotic NSIP and 28 UIP patients. NS: nonsignificant.

Smoking

Since smoking can influence both BAL findings and lung function tests, smoking status was adjusted for in a multivariate comparison between the two groups. Lavage differential counts did not differ between UIP and NSIP even after controlling for smoking. Similarly, smoking did not affect the differences in lung function observed between the two groups.

Treatment

Seven patients with UIP and four patients with NSIP were on treatment at the time of BAL. All were receiving prednisolone; in addition, two patients with UIP and one patient with NSIP were receiving azathioprine or cyclophosphamide. On controlling for treatment, no difference in the BAL findings was found between UIP and NSIP patients. The analysis was also repeated after eliminating the patients on treatment; there was no difference in BAL cellular content between the groups. During follow-up, all except four patients with NSIP were on treatment.

Survival

Patients were followed until 1 January, 2001, unless they had died or were lost to follow-up. The median follow-up time was 3.4 yrs (NSIP 4.56, UIP 3.17). Twenty-nine (83%) of the UIP patients and 11 (58%) of the NSIP patients died during follow-up. Survival was linked to the histological pattern, with the NSIP patients surviving longer (p=0.004), and was higher in association with higher FVC levels at the time of lavage (p=0.04). None of the constituents of BAL cell counts predicted survival.

Pulmonary function tests

Lung function data was obtained at the time of lavage and at 1-yr follow-up. In the combined cohort, the per cent predicted FVC was 76.3±17.5 (mean±SD) and the per cent predicted *D*L,CO was 47.4±14.1. There was no significant difference in the FVC (% pred) and *D*L,CO between the two groups (FVC: NSIP *versus* UIP 78.6±18.9 *versus* 75.1±16.9, p=NS; *D*L,CO: 44.4±16.1 *versus* 49.0±12.9, p=NS). Follow-up lung function at 1 yr was available in 19 NSIP and 31 UIP patients. A higher percentage of patients with UIP deteriorated at 1-yr compared with NSIP. Four of the 19 patients with NSIP had a reduction (>10%) in FVC compared with 14 of 31 UIP patients (p=0.08). Similarly, *D*L,CO was reduced (>15%) in four of 19 NSIP patients compared with 18 of 31 UIP patients (p=0.01). Changes in lung function at 1 yr with BAL findings were then compared. On analysis, it was found

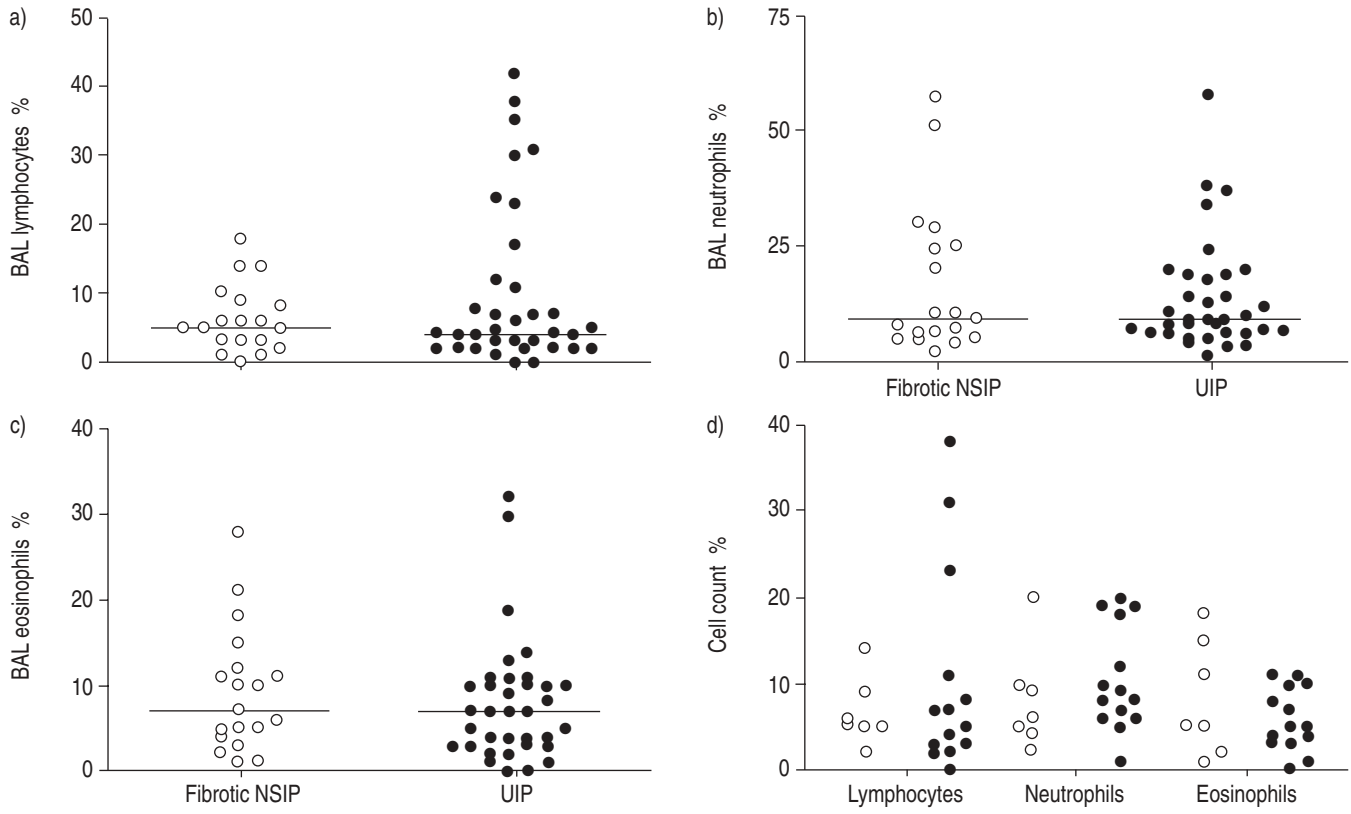

Fig. 1. – Histograms showing comparison of bronchoalveolar lavage (BAL) a) lymphocyte, b) neutrophil and c) eosinophil percentages between idiopathic fibrotic nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). The horizontal lines indicate the median values. d) Shows the BAL cellular percentages in patients with multiple concordant biopsies. ○: fibrotic NSIP; ●: UIP.

that BAL cell counts did not in any way predict the changes in lung function in both groups combined, as well as in the two groups individually.

Discussion

The aim of this study was to characterise and compare BAL findings in idiopathic NSIP and idiopathic UIP in patients presenting with the clinical features of IPF and to compare these findings with BAL findings in DIP and RBILD. To the best of the authors' knowledge, this is the first study in which BAL findings have been evaluated in a large group of patients presenting with a clinical picture of IPF and characterised histologically as UIP or fibrotic NSIP. This study differs from previous lavage studies in four key aspects: 1) the diagnosis was confirmed in all patients by surgical biopsy; 2) UIP and NSIP subtypes were defined using the new ATS/ERS criteria; 3) a group of patients with clinical and radiological features of IPF were identified specifically, and those with imaging features that would have precluded a diagnosis of IPF, such as consolidation, were excluded; and 4) the prognostic value of BAL was evaluated and compared separately in UIP and NSIP. This has not been reported before.

BAL absolute numbers of individual cells·mL^{-1} and differential counts had no prognostic value and did not differ between UIP and fibrotic NSIP, even after adjusting for smoking, therapeutic status and disease severity. The lavage findings of DIP and cellular NSIP were not significantly different from UIP or fibrotic NSIP though there were a very small number of patients in the cellular NSIP group (n=3). BAL findings in RBILD differed significantly from both UIP and fibrotic NSIP with a lower percentage of neutrophils, eosinophils and lymphocytes and an increased percentage of macrophages.

BAL findings in idiopathic NSIP have been reported in four recent studies [16–19]. In all four, the BAL lymphocyte count was strikingly elevated. NAGAI *et al.* [16] reported a 50% lymphocytosis in cellular NSIP (n=2) and 36% lymphocytosis in fibrotic NSIP (n=23). COTTIN *et al.* [17] reported a mean lymphocyte count of 47% in six patients with idiopathic NSIP, and PARK *et al.* [18] reported a mean lymphocyte count of 36% in six patients (cellular and fibrotic variant not distinguished). MUELLER *et al.* [19] reported a mean lymphocyte count of 34% in 14 patients with NSIP, however, the cellular and fibrotic variants of the disease were not analysed separately. In the current group of 19 patients with fibrotic NSIP, the mean lymphocyte count was <7% and only one patient had an increased BAL lymphocyte count.

The striking discrepancy between the present findings and earlier reports is likely to reflect the heterogeneous nature of clinical presentation of patients whose biopsy pattern is that of NSIP, and differences in the populations studied. A particular subset of patients with NSIP presenting with clinical features of IPF were evaluated. In earlier studies [16–19], cases were selected solely on the basis of a histological pattern of NSIP, without consideration of clinical features. This necessarily resulted in the inclusion of a spectrum of clinical disorders. NAGAI *et al.* [16] reported patients with striking BAL lymphocytosis and radiological features of organising pneumonia. COTTIN *et al.* [17] included patients with clinical features suggestive of extrinsic allergic alveolitis (EAA). Furthermore, cellular NSIP (a clinical entity characterised by BAL lymphocytosis [16] and a very good prognosis) patients were analysed separately. Combining cellular and fibrotic NSIP

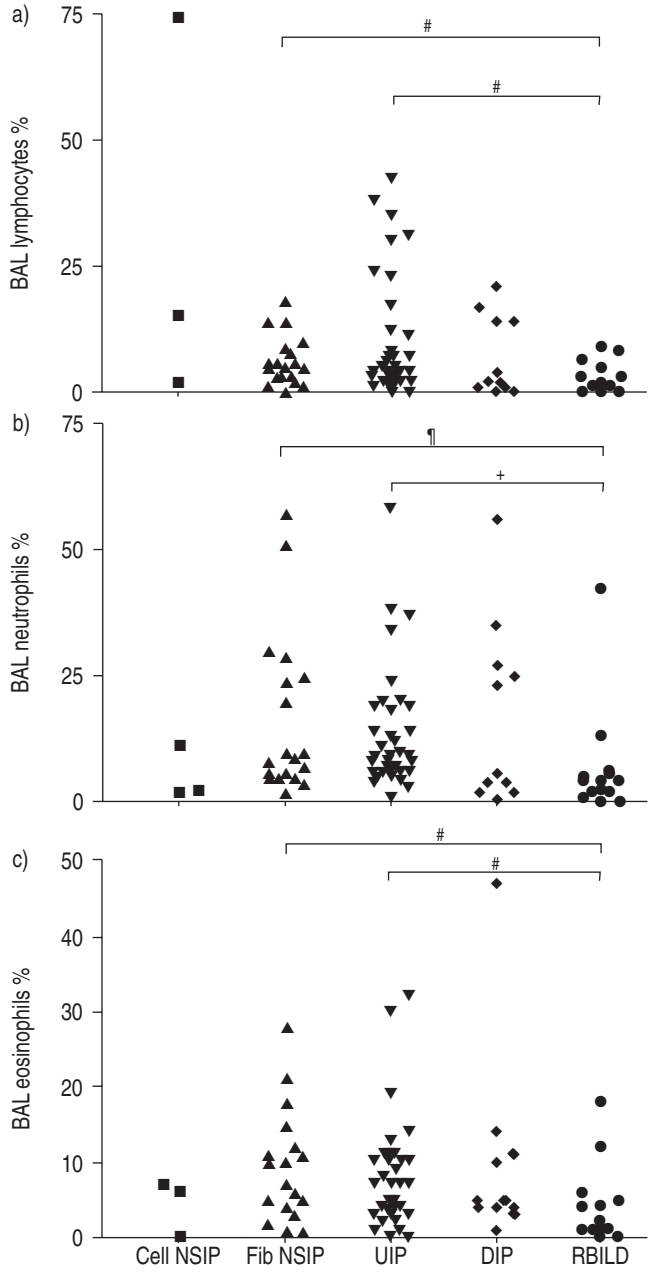

Fig. 2. – Histograms showing comparison of bronchoalveolar lavage (BAL) a) lymphocyte, b) neutrophil and c) eosinophil percentages, between idiopathic cellular nonspecific interstitial pneumonia (Cell NSIP), fibrotic nonspecific interstitial pneumonia (Fib NSIP), usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-associated interstitial lung disease (RBILD). #: p=0.01; ¶: p=0.001; +: p=0.0002 according to Mann-Whitney tests.

could have resulted in an elevated lymphocyte count in some studies [18, 19].

The importance of using strict clinical criteria to characterise subsets of NSIP is highlighted by the varied high-resolution computed tomography (HRCT) appearances in the NSIP spectrum of disease. In the study by HARTMAN *et al.* [21], where a histological appearance of NSIP was the sole inclusion criterion, 39 of the 50 patients studied had HRCT findings suggestive of alternative diagnoses including UIP, EAA or bronchiolitis obliterans-organising pneumonia. However, with the use of strict criteria to select idiopathic NSIP presenting with the clinical features of IPF, the HRCT findings consist of a spectrum of ground glass and reticular abnormalities, which are predominantly subpleural, similar in distribution to IPF, although lacking the honeycombing usually evident in that disease [22].

FLAHERTY *et al.* [23] have recently shown that the histological patterns of NSIP and UIP can be found in the same lung. To assess whether this occurrence could have confounded the current comparison, the analysis was repeated in a cohort of patients in whom the diagnosis was confirmed in biopsies from more than one lobe. The absence of significant or marginal differences in the BAL cellular constituents between UIP and NSIP in this cohort minimises the likelihood that histological misclassification due to sampling error at biopsy influenced the results.

A link between BAL cellularity and outcome was not found. A negative relationship between survival and BAL eosinophils was noted by BOOMARS *et al.* [12] in a large cohort of histologically proven IPF. However, SCHWARTZ *et al.* [24] did not find any relationship between BAL cellular constituents and survival. The good outcome in historical series of IPF, associated with a BAL lymphocytosis [11, 14, 15], cannot be ascribed to better survival in fibrotic NSIP, judging from these findings. Indeed, in the present study, a BAL lymphocytosis was marginally more prevalent in UIP. Not all patients in the earlier series were diagnosed histologically [14, 15], thus, some of the patients with a BAL lymphocytosis may have had sarcoidosis, EAA or cryptogenic-organising pneumonitis. Furthermore, even in biopsied patients [11], the appearances of cellular NSIP or DIP/RBILD would have been regarded as part of the spectrum of IPF. Thus, the current classification of idiopathic interstitial pneumonias has provided a new perspective on studies performed in the last two decades.

The terminology of NSIP, originally termed "nonclassifiable interstitial pneumonia", evolved as a "wastebasket" diagnosis of cases that did not satisfy criteria for acute interstitial pneumonia, DIP or UIP. KATZENSTEIN and FIORELLI [7] described the first large series using the descriptive term "nonspecific interstitial pneumonia" in 1994 and defined its histological features. Recently, it was suggested that NSIP should be viewed as a "holding pattern" rather than a waste basket [25]. Thus, the difficulty that still exists in defining NSIP characteristics is attributable to the association of a histological pattern of NSIP with a number of clinico-radiological syndromes, mostly readily characterised clinically and on computed tomography features, and clearly distinct from UIP. However, NSIP presenting clinically like IPF is not readily distinguished from UIP (IPF), and thus represents the only entity in which BAL may, in theory, have diagnostic utility, in the absence of a surgical biopsy. This study, designed to answer the simple, yet important, question of whether BAL differentiates these two entities has shown that BAL findings cannot be used as an aid in the diagnostic process of distinguishing between UIP and fibrotic NSIP in patients with an IPF-like presentation, despite recent recommendations [3].

Patients with nonspecific interstitial pneumonia are a heterogeneous group and should be subclassified according to clinical behaviour. The authors describe a distinct subgroup of patients with idiopathic nonspecific interstitial pneumonia who present clinically as idiopathic pulmonary fibrosis, have lavage characteristics similar to idiopathic pulmonary fibrosis, and can be viewed conceptually as an idiopathic nonspecific interstitial pneumonia variant of idiopathic pulmonary fibrosis. Nonspecific interstitial pneumonia patients with clinical characteristics suggestive of organising pneumonia or extrinsic allergic alveolitis may be more likely to have a bronchoalveolar lavage lymphocytosis and a better outcome, require different therapeutic approaches, and should be subclassified

according to clinical features. It is important to recognise distinct clinical subsets of nonspecific interstitial pneumonia and not to combine them indiscriminately in clinical studies and in the formulation of a management strategy.

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