

Bronchiolitis obliterans organizing pneumonia (BOOP): the cytological and immunocytological profile of bronchoalveolar lavage

U. Costabel, H. Teschler, J. Guzman

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ABSTRACT: The cytological and immunocytological profile of bronchoalveolar lavage (BAL) was studied in 10 patients with idiopathic bronchiolitis obliterans organizing pneumonia (BOOP) and compared with the data in idiopathic pulmonary fibrosis (IPF) (n=22), chronic eosinophilic pneumonia (CEP) (n=9), and extrinsic allergic alveolitis (EAA) (n=24). Lymphocyte subsets were enumerated using an immunoperoxidase slide assay.

The BAL pattern in BOOP patients was characterized by several features: 1) colourful cell differentials with an increase in all cell types, most markedly in lymphocytes, and more moderately in neutrophils, eosinophils and mast cells, as well as the presence of foamy macrophages and, occasionally, of plasma cells; 2) decreased CD4/CD8 ratio; 3) normal percentage of CD57+ cells; and 4) increase in activated T-cells in terms of human leucocyte antigen-DR (HLA-DR) expression, and occasionally also interleukin-2 receptor (CD25) expression. The findings were most similar to those in EAA except for the CD25 expression, which was always normal, and the CD57+ cells, which were increased in EAA. The increase in lymphocytes discriminated best between BOOP and IPF. The eosinophils were significantly higher in CEP than in BOOP with little overlap.

In conclusion, BAL may be of value to distinguish between BOOP and other interstitial lung disease.

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Bronchiolitis obliterans organizing pneumonia (BOOP) is a distinct clinicopathological entity characterized by the clinical presentation with a preceding flu-like illness and a short history of progressive dyspnoea, associated in most cases with patchy peripheral infiltrates on chest radiogram or computerized tomographic (CT) scan, and defined pathohistologically by the presence of organization tissue within the lumens of distal bronchioles, alveolar ducts, and neighbouring alveoli [1-7]. The vast majority of cases are idiopathic [1]. In the English literature, the term cryptogenic organizing pneumonia has been applied to this entity [8].

Before the association of the characteristic clinical and radiological signs with the pathological lesion was recognized [1, 8], BOOP was often misdiagnosed as idiopathic pulmonary fibrosis (IPF) [1]. The differential diagnosis also includes chronic eosinophilic pneumonia (CEP) and extrinsic allergic alveolitis (EAA).

Despite increasing interest in the clinical and pathological features of BOOP in recent years, there are no

detailed descriptions of the cytology and immunocytology of bronchoalveolar lavage (BAL). We undertook the present study to characterize the profile of BAL cell differentials and lymphocyte subpopulations in idiopathic BOOP and to determine its value in distinguishing BOOP from IPF, CEP and EAA.

Methods

Patients with BOOP

Ten consecutive patients (7 men, 3 women), with biopsy proven idiopathic BOOP (2 by transbronchial biopsy, 8 by open lung biopsy), were included in the study. Their mean age was 55 yrs, (range 27-74 yrs). Only one was a current smoker. All patients showed bilateral patchy infiltrates on chest radiographs. There was no evidence of an underlying disorder or known cause that may be associated with BOOP. The

symptoms, physical findings, and pulmonary function data are shown in table 1. The patients were studied at the time of diagnosis when none was being treated with corticosteroids.

Other study populations

For comparison with BOOP, three other patient groups and control subjects were studied. All patients were untreated at the time of BAL.

IPF. This group consisted of 22 patients (12 men, 10 women). Their mean age was 52 yrs (range 32–68 yrs). Four were current smokers. They all underwent open lung biopsy, which showed the histological features of usual interstitial pneumonitis (UIP). The diagnosis was based on a compatible history, physical examination, chest radiograph, pulmonary function tests, the results of open lung biopsy and the exclusion of known causes of pulmonary fibrosis (dust, drugs, animal exposure, collagen vascular disease).

CEP. This group included 9 patients (3 men, 6 women), mean age 44 yrs (range 28–58 yrs). Two were current smokers. The diagnosis was based on classic criteria [9, 10]. They all had a clinical picture consistent with the diagnosis of CEP, together with peripheral infiltrates on chest radiographs and biopsy evidence of infiltration of alveolar walls and spaces with eosinophils (3 transbronchial, 6 open lung biopsies).

Table 1. – Symptoms, physical findings and pulmonary function data in 10 patients with idiopathic BOOP

Symptoms and findings	Patients	
	n	
Dyspnoea	9	
Cough	9	
Flu-like symptoms, fever	10	
Weight loss	6	
Malaise	5	
Haemoptysis	0	
Duration of symptoms* months	3 (1–7)	
Crackles	7	
Clubbing	0	
Pulmonary function tests**	Patients with abnormal value	
TLC % pred	74±16	7
IVC % pred	55±10	9
FEV ₁ % pred	58±9	10
Pao ₂ rest kPa	9.3±0.9	8
Paco ₂ rest kPa	4.8±0.5	4
Pao ₂ exercise† kPa	9.1±0.8	6/6
Paco ₂ exercise† kPa	5.1±0.3	0/6

*: data given as mean (range); **: data given as mean±SD; †: only 6 patients performed exercise; BOOP: bronchiolitis obliterans organizing pneumonia; TLC: total lung capacity; IVC: inspiratory vital capacity; FEV₁: forced expiratory volume in one second; Pao₂: arterial oxygen tension; Paco₂: arterial carbon dioxide tension.

EAA. Twenty four patients had recently diagnosed EAA (11 men, 13 women), mean age 48 yrs (range 18–74 yrs). Only one was a smoker. The diagnosis was based on history, clinical and radiological features, and the functional pattern of interstitial lung disease. Twenty were bird fanciers and 4 had farmer's lung. All had precipitins against the relevant antigen.

Control subjects. Eleven healthy nonsmokers were studied (5 men, 6 women), mean age 37 yrs (range 17–61 yrs), to obtain the normal values of our laboratory as published previously [11].

Bronchoalveolar lavage

After informed consent was obtained from all persons, BAL was performed by instillation of 100 ml of 0.9% saline in five 20 ml aliquots, either into the involved segment, when the lesion was localized, or into the middle lobe, when the shadowing was diffuse. The recovered fluid was filtered through surgical gauze, and the volume was measured. The total cell counts were determined using a Neubauer chamber. Cell differentials were enumerated from smears stained with May-Grünwald-Giemsa stain by counting at least 600 cells.

The lymphocyte subpopulations were determined by surface marker analyses with the immunoperoxidase slide assay as described previously [11, 12]. Commercially available monoclonal antibodies were used to identify CD20 (B-cells), CD4 (helper/inducer T-cells), CD8 (suppressor/cytotoxic T-cells), CD57 (Leu7+ natural killer cells), CD25 (interleukin-2 (IL-2) receptors), and human leucocyte antigen-DR (HLA-DR) antigens (OKIa monoclonal antibody). HLA-DR+ T-cells were evaluated by subtracting the percentage of CD20+ B-cells from the percentage of lymphocytes staining positive for the monoclonal antibody OKIa, leaving the percentage of HLA-DR+ T-cells [12].

Briefly, 10 µl cell suspension (2×10⁶ cells·ml⁻¹) was added to each of the reaction areas of adhesive slides (Bio-Rad, Germany). After 10 min, the cells were settled and firmly attached to the glass surface. The cells were then fixed with 0.05% glutaraldehyde solution for 5 min. The staining was performed with the monoclonal antibodies using a sensitive four layer peroxidase-antiperoxidase technique, followed by postfixation with OsO₄. Cells were viewed under a light microscope and counted as positive when dark brown staining of the membrane was visible. At least 200 lymphocytes of each reaction area were counted, and the percentage of positive lymphocytes was noted.

Statistical analysis

Data are expressed as mean±standard deviation (SD). For comparison between groups, one way analysis of variance (ANOVA) was performed. Values of p<0.05 were considered significant.

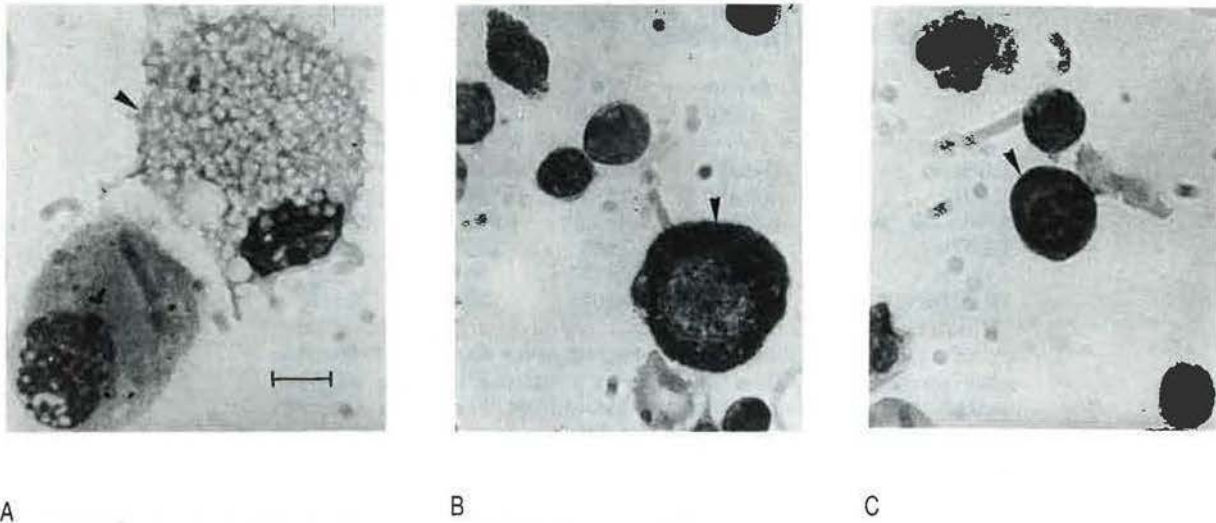


Fig. 1. - BAL cytology in a patient with idiopathic BOOP, showing a foamy macrophage (panel A, arrow), a mast cell (panel B, arrow) and a plasma cell (panel C, arrow) beside lymphocytes. May-Grünwald-Giemsa stain. Original magnification. $\times 400$, bar = $5\mu\text{m}$, BAL: bronchoalveolar lavage; BOOP: bronchiolitis obliterans organizing pneumonia.

Table 2. - Basic data and cell differentials in BAL*

	BOOP n=10	IPF n=22	CEP n=9	EAA n=24
BAL recovery %	47 \pm 9 ^A	56 \pm 17 ^A	50 \pm 16 ^A	55 \pm 13 ^A
Total cells $\times 10^6$	14 \pm 9 ^A	14 \pm 11 ^A	18 \pm 22 ^{AB}	34 \pm 22 ^B
Cell differentials % of total cells				
Macrophages	39 \pm 19 ^A	61 \pm 23 ^B	27 \pm 18 ^{AD}	18 \pm 10 ^{CD}
Lymphocytes	44 \pm 19 ^A	15 \pm 15 ^B	22 \pm 18 ^B	78 \pm 10 ^C
Neutrophils	10 \pm 13 ^{AB}	19 \pm 16 ^A	6 \pm 6 ^B	2 \pm 2 ^C
Eosinophils	6 \pm 8 ^A	5 \pm 5 ^A	46 \pm 22 ^B	1 \pm 1 ^C
Mast cells	1.0 \pm 0.4 ^A	0.3 \pm 0.7 ^B	1.0 \pm 0.9 ^{AB}	0.9 \pm 0.9 ^A
Plasma cells	0.1 \pm 0.1 ^A	0 \pm 0 ^B	0.7 \pm 0.4 ^{AC}	0.8 \pm 0.9 ^C
Foamy macrophages % of macrophages	25 \pm 10 ^A	14 \pm 13 ^B	6 \pm 11 ^B	22 \pm 17 ^{AC}

*: values are mean \pm SD and were compared using the analysis of variance (ANOVA) test. For each parameter the values identified by a different letter are significantly different, $p < 0.05$. For example regarding the total cells, BOOP is not significantly different from IPF and CEP, because all three show the superscript A, but is significantly different from EAA which has the superscript B; CEP is not significantly different from any of the others, because it shares the superscript A with BOOP and IPF, and the superscript B with EAA. BAL: bronchoalveolar lavage; BOOP: bronchiolitis obliterans organizing pneumonia; IPF: idiopathic pulmonary fibrosis; CEP: chronic eosinophilic pneumonia; EAA: extrinsic allergic alveolitis.

Results

BAL cell differentials in BOOP

BAL cytology in patients with BOOP showed a mixed cellularity (fig. 1), with a mean increase in all cell types, most markedly of lymphocytes, but also of neutrophils and eosinophils (table 2, fig. 2). Another feature was the frequent presence of foamy macrophages (>20% in 7 out of 10 cases), and plasma cells (4 out of 10 cases). As is evident from figure 2, all of our patients had an increase in the percentage of lymphocytes above 15%, the upper limit of normal in our laboratory. Neutrophils were elevated above 3% in 4 out of 10 patients. Eosinophils exceeded 1% in 8 out of 10 patients. Mast cells were increased above 1% in 6 out of 10 patients.

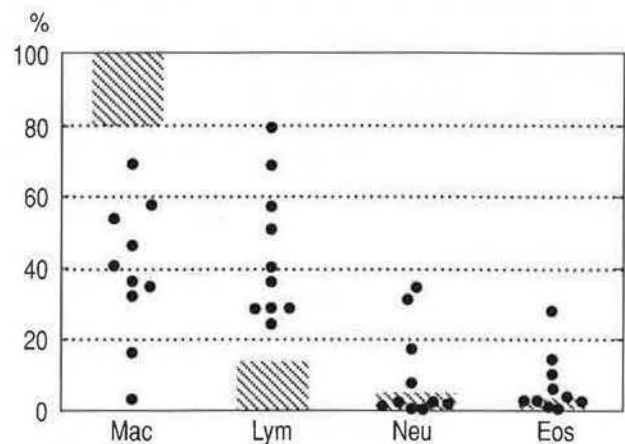


Fig. 2. - BAL cell differentials in BOOP. The hatched area represents the normal range. Mac: macrophages; Lym: lymphocytes; Neu: neutrophils; Eos: eosinophils. For further abbreviations see legend to figure 1.

Table 3. — Lymphocyte subpopulations in BAL shown as percentage of total lymphocytes*

	BOOP n=10	IPF n=12	CEP n=3	EAA n=24
CD4+	34±14 ^A	51±15 ^B	42±12 ^{AB}	46±16 ^B
CD8+	62±16 ^A	46±14 ^B	55±16 ^{AB}	53±14 ^{AB}
CD4/CD8 ratio	0.6±0.5 ^A	1.4±1.4 ^B	0.9±0.6 ^{AB}	1.0±0.7 ^{AB}
CD57+	6±4 ^A	7±8 ^A	6±7 ^{AB}	22±17 ^B
CD25+	7±12 ^{AB}	2±1 ^A	ND	3±2 ^B
HLA-DR+ T-cells	16±12 ^A	4±6 ^B	4±4 ^{AB}	20±16 ^A

*: values are mean±SD and were compared using the ANOVA test. For each parameter, the values identified by a different letter are different, $p < 0.05$. HLA-DR: human leucocyte antigen-DR. For further abbreviations and explanations see legend to table 2.

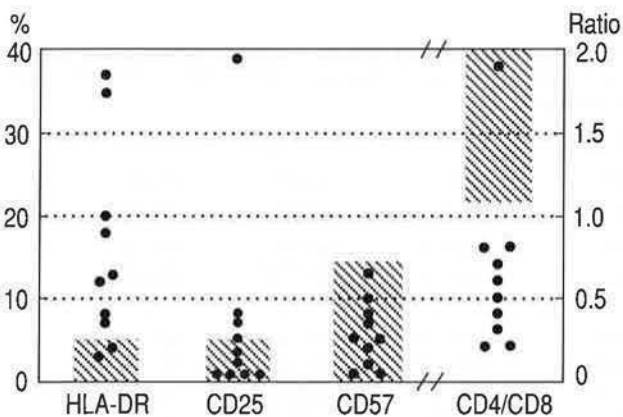


Fig. 3. — BAL lymphocyte surface marker expression shown as percentage of lymphocytes and CD4/CD8 ratio in BOOP. The hatched area represents the normal range. HLA-DR: MHC-Class II positive T-cells; CD25: interleukin-2 receptor positive T-cells; CD57: Leu 7 positive NK cells. HLA-DR: human leucocyte antigen-DR; MHC: major histocompatibility complex; NK: natural killer. For further abbreviations see legend to figure 1.

BAL lymphocyte subpopulations in BOOP

The most striking feature was the marked decrease in the CD4/CD8 ratio in the BAL of patients with BOOP (table 3, fig. 3). The ratio was below 1.0 in 9 out of 10 patients. Only one patient had a normal ratio. In the majority of patients, T-cells were activated in terms of increased expression of HLA-DR antigens, as was seen in 8 out of 10 patients, and to a lesser degree with respect to the expression of CD25, the IL-2 receptor, which was increased in only 3 out of 10 patients. CD57+ natural killer cells were within the normal range in all patients with BOOP. CD20+ B-cells were usually less than 1%, and rarely exceeded 3% of lymphocytes, and therefore were negligible.

Comparison of BOOP with other diseases

The differential diagnosis of BOOP includes IPF, CEP and EAA. Tables 2 and 3 show the mean values of the BAL cell differentials and lymphocyte subsets

in these diseases. The mean percentage of lymphocytes was highest in EAA, followed by BOOP, CEP and IPF. The mean CD4/CD8 ratio was lowest in BOOP, even lower than in EAA. But in contrast to EAA with elevated proportions of CD57+ natural killer cells, this cell type was normal in BOOP. Eosinophils were highest in CEP, and lowest in EAA. Plasma cells were never observed in IPF, but present in the other three diseases. Foamy macrophages were increased in BOOP and EAA to a similar degree.

When looking at the value of different BAL parameters to discriminate between BOOP and the other diseases, we found that the lymphocytes discriminated best between BOOP and IPF (fig. 4), $p < 0.001$, the eosinophils between BOOP and CEP (fig. 5), $p < 0.0001$, and the CD57+ natural killer cells between BOOP and EAA (fig. 6), $p < 0.005$. In every patient with BOOP, the BAL lymphocyte percentage was higher than the eosinophil percentage, whereas in 7 out of 9 patients with CEP the eosinophil percentage exceeded the lymphocyte percentage.

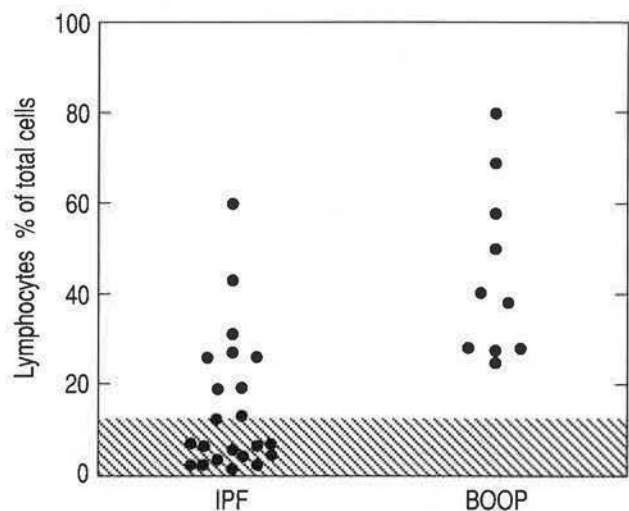


Fig. 4. — BAL lymphocytes shown as percentage of total cells in IPF and BOOP. The difference is significant, $p < 0.001$. The hatched area represents the normal range. IPF: idiopathic pulmonary fibrosis. For further abbreviations see legend to figure 1.

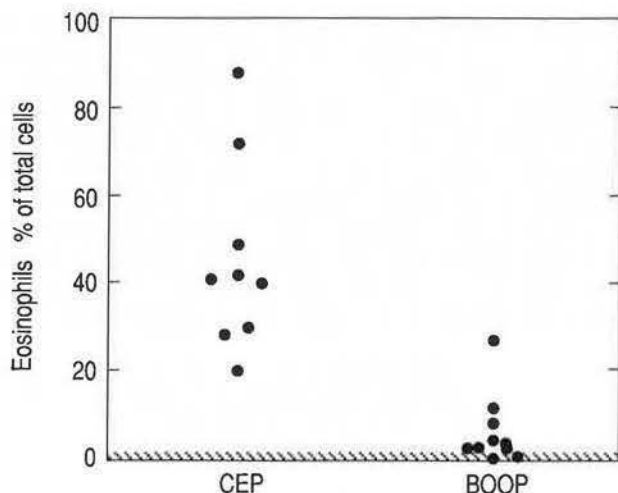


Fig. 5. - BAL eosinophils shown as percentage of total cells in CEP and BOOP. The difference is significant, $p < 0.0001$. The hatched area represents the normal range. CEP: chronic eosinophilic pneumonia. For further abbreviations see legend to figure 1.

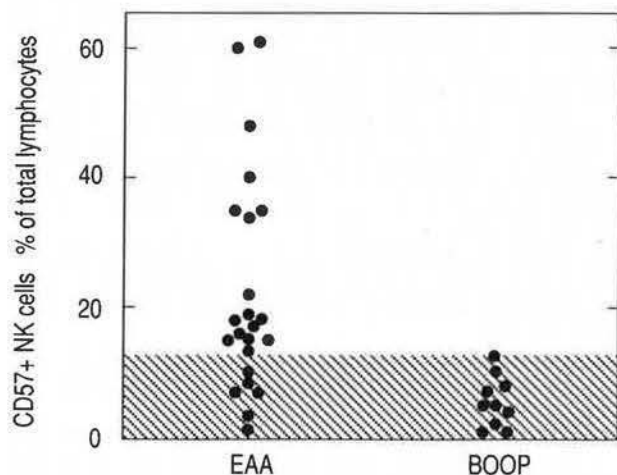


Fig. 6. - BAL CD57 positive NK cells shown as percentage of total lymphocytes in EAA and BOOP. The difference is significant, $p < 0.005$. The hatched area represents the normal range. NK: natural killer; EAA: extrinsic allergic alveolitis. For further abbreviations see legend to figure 1.

Discussion

This study delineated the cytological and immunocytological profile of BAL in a series of 10 patients with idiopathic BOOP. A well-defined group of patients was studied. They were all seen consecutively at our institution. Only patients with biopsy proven disease were included. All were studied at the time of diagnosis without being treated with corticosteroids. All showed the type of disease that is characterized by bilateral patchy peripheral infiltrates on chest radiogram. None of them presented with a solitary lesion or with the clinical profile of the diffuse interstitial lung disease type, which was recently identified as a special variant of BOOP [5]. Only patients with the idiopathic entity were included. None had

evidence of underlying conditions known to be associated with the BOOP pattern, such as collagen vascular disease, aspiration, irradiation, acquired immune deficiency syndrome (AIDS), organizing infections, or EAA. None had taken drugs that had been incriminated to induce BOOP [13].

Previously, BAL studies have been reported in only a few subjects with BOOP [5, 8, 14-17], and the analysis of BAL lymphocyte subsets was limited to the enumeration of CD4+ and CD8+ T-cells [14, 16]. According to our results, several characteristics seem to be present in BAL from this group of patients with idiopathic BOOP.

1. *Colourful cytology.* Regarding the cell differentials, all cell types were increased, most markedly the lymphocytes, but in many patients the neutrophils, eosinophils and mast cells were also moderately increased, in good agreement with other reports [5, 16-18]. Other features were the increased percentages of vacuolated foamy macrophages and, occasionally, the presence of plasma cells, both also known in EAA [19-20]. The BAL cytology seems to correlate well with histological and ultrastructural descriptions of the inflammatory cellular infiltrate in BOOP. The intra-alveolar plugs of the early stage were found to be composed of fibrinoid inflammatory cell clusters with numerous alveolar macrophages constantly associated with lymphocytes and plasma cells, in some cases also with neutrophils, eosinophils, and mast cells [6]. In the alveolar septa, the same inflammatory cells were present [4, 6]. Interestingly, finely vacuolated foamy macrophages, as seen in the BAL cytology, have been observed intraluminally in histological sections [4]. In ultrastructural tissue investigations, alveolar macrophages were found to engulf and degrade fibrin bundles intracellularly [4, 6], and to contain numerous phagolysosomes [4]. This finding may explain the light microscopical aspect of "foamy" macrophages in the BAL cytology.

2. *Decreased CD4/CD8.* This was a constant finding, consistent with a previous report (14). In our study, only one patient had a normal ratio. The mean value was even lower, although not significantly, than in the group of patients with EAA, a disease well-known for the reduced CD4/CD8 ratio [19, 20]. Other disorders characterized by a decreased CD4/CD8 ratio include silicosis, drug-induced pneumonitis, collagen vascular disease, and human immunodeficiency virus (HIV) infection [20]. That the smoking status may have influenced the results can be excluded, since only one of our BOOP patients was a smoker. Healthy cigarette smokers reportedly have a reduced BAL CD4/CD8 ratio compared to non-smokers [21, 22].

3. *Normal proportion of CD57+ lymphocytes.* This contrasts with EAA where the majority of patients have an increase in this cell type, paralleled by an enhanced natural killer (NK) activity [23]. However,

the CD57 antigen expression is known to be only loosely correlated with functional NK activity. Whether human lung T-cells in virus infections display the CD57 antigen is unclear. Hence, the lack of expression of this NK cell related marker on the BAL cells in patients with idiopathic BOOP cannot be used as an argument against a possible viral aetiology of this disease. Indeed, a recent report suggests that some cases of idiopathic BOOP may be due to adenoviral infection [24].

4. *Increase in activated T-cells.* Obviously, the BAL lymphocytes in BOOP are not only increased in proportion and number, but also activated, as evidenced by the increased expression of HLA-DR antigens, as occurs in EAA [12]. The expression on BAL T-cells of another activation and proliferation associated marker, the CD25 antigen (IL-2 receptor), was increased in only 3 of 10 patients with BOOP, but consistently normal in EAA [19, 20]. The mechanism leading to the expansion of activated, CD8+, CD57-lymphocytes in the airspaces of idiopathic BOOP remains to be elucidated.

Taken together, the above mentioned BAL findings in BOOP are most similar to those in EAA with the exception that the CD25+ cells were always normal in EAA, and that the CD57+ cells, characteristically elevated in EAA, were never increased in idiopathic BOOP. An increase in this cell type favours the diagnosis of EAA. One must be aware that the single characteristics described above are not specific for BOOP. The most useful aid to diagnosis is given by the full profile of BAL cell types in each patient.

One of the important diseases with peripheral infiltrates to be distinguished from BOOP is CEP [25]. In this regard, BAL may be extremely useful, since in our nine cases with CEP the percentage of BAL eosinophils always exceeded 20%. This was true for only one BOOP patient. In addition, 7 out of 9 patients with CEP showed higher eosinophil than lymphocyte percentages in BAL. This was not observed in any of the BOOP patients.

Another important differential diagnosis is IPF. In this respect, the percentage of BAL lymphocytes discriminated best between BOOP and IPF. A normal lymphocyte count and a lone increase in neutrophils and/or eosinophils was not seen in any of our BOOP patients but occurs frequently in IPF. On the other hand, given the type of BOOP with the clinical profile of the diffuse interstitial lung disease without patchy infiltrates [5], BAL is of little value for the differentiation against IPF, since in this variant the BAL profile has been reported to show a lone increase in neutrophils and eosinophils similar to IPF [5]. Most interestingly, the prognosis of this BOOP variant was also found to be worse than of those BOOP cases with patchy infiltrates [5] indicating that in BOOP, as in IPF, a high lymphocyte count may reflect a good chance of response to corticosteroid therapy, whereas a lone increase in neutrophils and eosinophils may indicate the opposite.

In conclusion, BAL may be of value in the clinical assessment of patients with BOOP. When the clinical picture is typical, patchy peripheral infiltrates on chest radiogram are present, and infection has been excluded by a sterile lavage fluid, a BAL cell profile showing the characteristic features as outlined above may support the diagnosis sufficiently to start a therapeutic trial of corticosteroids, thus obviating the need for an open lung biopsy. The pathophysiological meaning of these BAL changes and the kind of mediators involved remain to be elucidated in further studies.

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