Extrinsic allergic alveolitis

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Extrinsic allergic alveolitis (EAA) or hypersensitivity pneumonitis is an interstitial lung disease associated with repeated exposure to a wide range of inhaled organic dusts and related occupational allergens, especially bird and fungal proteins. We focus on the diagnostic and prognostic findings related to the use of BAL in the management of EAA patients.

The presentation of EAA varies from patient to patient and is mainly related to the frequency and intensity of exposure to the causative antigens. In addition, the different amounts of inhaled antigens and the timing of observation might be crucial. For this reason we will refer to the acute, subacute or chronic phases of the clinical picture rather than to the active and inactive forms of the disease.

Analysis of cellular constituents of BAL

As far as the evaluation of cellular constituents of BAL of patients with EAA performed more than one week after the acute episode is concerned, cellular recovery is approximately fivefold that observed in controls, with the cells accounting for this increase mostly represented by lymphocytes [112, 126, 127]. The increase of lymphocytes becomes evident several days after the acute episode and represents the most striking finding during the entire follow-up of the disease process.

Some authors focused their attention on the importance of an additional mild increase of neutrophils in the BAL of EAA patients [22, 128]. The number of neutrophils has been proved to be markedly increased in the acute phase of the disease, soon after the exposure to specific antigen or after the challenge with EAA causing antigens. This effect was only short-term since one week after challenge the neutrophils had fallen to pre-challenge values [128].

In the early phase of the disease mast cells have also been reported to increase in number [108–110]. This increase seems to be correlated to the phase of exposure, with a more than one hundredfold increase in the acute disease, and during recovery declining towards normal within a few months [128, 132]. A few plasma cells (0.1–2%) have also been observed in subacute stages of EAA [133].

Evaluation with monoclonal antibodies revealed that the most common finding in EAA patients is represented by the expansion of lymphocytes bearing the cytotoxic/suppressor phenotype. In fact, immunological evaluation of surface markers demonstrated that only a few BAL lymphocytes express B-cell related determinants, the majority of them being represented by T-lymphocytes [112, 126, 127].

The analysis of T-cell subsets revealed that in the majority of cases CD8+ lymphocytes are the predominant cells in the BAL of these patients. As a result, the CD4/CD8 ratio is low (usually less than 1.0). The number of cells bearing the proliferation associated markers (CD71 and CD25 antigens) is quite low; a statistically significant difference with respect to controls exists regarding their absolute numbers [127]. Also, the percentage and absolute number of T-cells expressing HLA-DR antigens is increased [134].

With regard to the frequency of cells bearing NK- related markers, notably the pattern of reactivity with MoAbs defining natural killer cells, only the positivity for CD57 MoAb is increased significantly with respect to controls [126, 117, 135]. The frequency of CD57 cells co-expressing T-cell markers is predominant over the number of cells that lack these antigens [117, 135].

Thus, the alveolitis in EAA patients is characteristically represented by cells with the CD3+/CD8+/CD57+/CD16- phenotype. In fact, at the present time, this phenotype has not been observed in other conditions, including HIV infection [136].

So far, phenotyping of alveolar macrophages cannot be recommended for the clinical use of BAL.

Diagnostic relevance of BAL findings in EAA

At present, we can only state that BAL can assist in achieving the diagnosis of EAA. Interestingly, in this disorder you can find the highest degrees of BAL lymphocytosis (an even higher average than in sarcoidosis). Therefore, the presence of a marked lymphocytosis characterized by the CD3+/CD8+/CD57+/CD16- phenotype is highly suggestive of EAA. In fact, no cases have been reported with normal BAL cytology. A "positive" BAL finding (*i.e.*, the characteristic profile) in a patient with interstitial lung disease of unknown origin should direct the clinician towards the probable diagnosis of EAA. A careful re-examination of the occupational environmental history and the screening of serum precipitins might then reveal previously unknown sources of relevant antigen exposure and confirm the diagnosis of EAA.

From the clinical point of view, BAL has the advantage of being the most sensitive tool in detecting signs of alveolitis in EAA patients, more sensitive than chest radiography, lung function testing and precipitins. We must, however, be careful to exclude, by history or other clinical tests, the disorders that are also characterized by an infiltrate bearing the suppressor/cytotoxic phenotype, including patients with interstitial pneumonia associated with collagen vascular disease, silicosis, bronchiolitis obliterans with organizing pneumonitis

(BOOP), human immune deficiency virus (HIV) infected patients and drug induced pneumonitis.

It is worth mentioning that the presence of very high percentages of lymphocytes in association with increases in mast cells >1% might represent a diagnostic indicator of EAA [22]. Of course, this combination is only of value in cases which are currently, or have been recently, exposed to antigen since mast cells return to the normal range within one to three months after removal from exposure.

The pattern of alveolitis in EAA during the follow-up

Although it is difficult to precisely separate patients on the basis of antigen exposure and, thus, correctly subdivide EAA cases into strictly defined groups, a distinction needs to be made between patients who continue to be exposed to antigens and patients who had been removed from the antigenic exposure.

Concerning those patients who continue to be exposed to antigens, several authors have shown a decrease (percentage or absolute) of lymphocytes during the follow-up [137, 138] while other authors have demonstrated that the increase of the total number of lymphocytes was a persistent feature in EAA patients still exposed to relevant antigens [139]. With regard to immunological surface markers, a recovery of the CD4/CD8 ratio has been evidenced during the follow-up only in those patients who had been removed from further antigen exposure [138, 140], thus suggesting that the immunological abnormalities in these patients progress towards normal. Note that the behaviour of the CD4/CD8 ratio is not consistent in all cases. A recovery of the CD4/CD8 ratio was not found in subjects still exposed to relevant antigens [141].

As far as clinical management is concerned, studies performed on this topic have indicated that there is no correlation between radiographic changes, pulmonary function, BAL findings or levels of precipitating antibodies and different phases of the disease [141–144].

Asymptomatic EAA patients

Although in asymptomatic EAA patients the increase of lymphocytes (mostly CD8+ cells) with respect to controls is less prominent, the data are qualitatively similar to those observed in symptomatic patients [112, 127, 143]. Data indicating that an alveolitis similar to that observed in EAA patients develops in asymptomatic patients raises the question of how, when and why clinical features become apparent. The answer, however, still remains inconclusive.

Analysis of humoral constituents of BAL

The analysis of humoral constituents of BAL does not significantly improve the diagnosis of patients with EAA, as compared to the great value of the BAL cytology and immunocytology in the clinical assessment of this disease. However, the evaluation of hyaluronate and type III procollagen peptide concentrations in BAL might be useful in monitoring the disease [60, 145].

Table 1. – Evolution of alveolitis in patients with extrinsic allergic alveolitis

Time from acute episode	Type of reaction	BAL findings
4–72 h	mediated by immune complexes	increase of neutrophils mast cells plasma cells
3rd day to weeks	mediated by suppressor/ cytotoxic lymphocytes	increase of CD8+ cells
Several months	delayed type hypersensitivity	increase of CD8+ cells CD4+ cells

Occupational lung diseases due to inhalation of inorganic dust

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This chapter aims to review the clinical use of BAL in patients with interstitial lung disease (ILD) associated with occupational or environmental exposure to inorganic dust and minerals. Excluded from this paper are occupational asthma and ILD due to inhalation of organic dusts (extrinsic allergic alveolitis).

Indications for performing a BAL in ILD associated with inorganic dust exposure are: 1) the exclusion of other causes of ILD, such as sarcoidosis, pulmonary haemorrhage syndromes, malignancies *etc.*, in patients additionally exposed to inorganic dust; 2) the documentation of mineral dust exposure in patients who may not be aware of being at increased risk of dust inhalation; 3) the documentation of the local immune and inflammatory reaction, *i.e.* the alveolitis.