Effects of oral steroids on immunoglobulins in bronchoalveolar lavage fluid in active sarcoidosis


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ABSTRACT: Immunoglobulin (Ig) levels increase in the lower respiratory tract of patients with pulmonary sarcoidosis. We evaluated the effects of prednisone therapy upon Ig concentrations in bronchoalveolar lavage (BAL) fluid of ten patients with active disease (> 30% T-lymphocytes in BAL and positive 67Ga lung scan). Therapy significantly lowered T-lymphocyte percentages in BAL and 67Ga lung scan indices and was followed by a slight improvement of the studied functional parameters. Biochemical analysis of BAL showed a significant decrease of both IgG/albumin (baseline 1.24±0.21; after therapy 0.40±0.12) and IgA/albumin (baseline 0.55±0.07; after therapy 0.14±0.03) ratios in all patients. Conversely, comparisons of IgM/albumin ratios did not show any change over the study period (baseline 0.05±0.01; after therapy 0.06±0.03). Thus oral steroid treatment suppresses the alveolitis of pulmonary sarcoidosis, as shown not only by the reduction of lung T-cells and 67Ga lung uptake, but also by the decreased Ig levels in the alveolar spaces.

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Patients and methods

A diagnosis of pulmonary sarcoidosis was established in ten non-smoking patients (four males, six females; aged 40.6±3.9 yr) according to previously described criteria [2]. Seven patients (three males, four females) had never been treated, whilst three (one male, two females), who had previously been treated, had not received steroids in the previous twelve months. Patients were considered to be affected by persistent active disease [14], as demonstrated by: 1) T-lymphocytes in BAL > 30% and 2) positive 67Ga lung scan in two consecutive assessments of alveolitis activity separated by therapy-free periods lasting 4-6 months. After demonstrating that spontaneous remission of the alveolitis had not occurred in any of the selected patients, the decision to start steroid therapy was taken.

Patients' evaluations were performed by chest X-rays, pulmonary function tests, 67Ga lung scans and BAL immediately before treatment (data hereafter referred to as ‘baseline’) (table 1) and after six months of oral prednisone therapy. 67Ga lung scans and BAL were typed according to conventional three stage classification [15].
Chemical analysis of BAL was carried out by centrifugation. Cells were then resuspended in lymphocytes, with respect to total cells recovered, determined by a rosette-forming method [2, 8], using neuraminidase-treated sheep erythrocytes. Biochemical analysis of BAL was carried out by nephelometric measurements (Immunochemistry Analyzer II, Beckman Instruments, Brea, CA, USA) of IgG, IgA, IgM and albumin concentrations on supernatants, as described previously [8]. The supernatants were concentrated ten times by using an Amicon 8MC ultrafiltration system and stored at \(-20^\circ\text{C}\). Loss of the investigated proteins, due to concentration procedures, was excluded by random comparisons of determinations performed on both concentrated and unconcentrated lavage fluids and by demonstrating lack of proteins in the filtrate fluids.

Analysis of data. All data are presented as mean±standard error of the means (SEM); comparisons were made by using the Student’s t-test for paired data.

Results

Chest roentgenograms performed at the beginning of the study allowed staging of the patients as follows: three patients (one male, two females) were considered to be affected by pulmonary sarcoidosis stage I, five patients (three males, two females) stage II and two patients (both females) stage III. After prednisone therapy a slight reduction in mediastinal node dimensions was observed in one of the three stage I patients and in three of the five stage II patients. No major changes in chest X-rays were seen in stage III patients.

Pulmonary function tests at the beginning of the study showed a moderate mean reduction in static and dynamic lung volumes (VC=84.8±6.4% of predicted; TLC=84±6.3% of predicted; FEV\(_1\)=86.4±7.4% of predicted), as well as a more marked impairment in diffusing capacity (DL\(_{\text{CO}}\)=73±4.5% of predicted). The same tests performed at the end of the study showed...
Fig. 1. Effects of oral prednisone therapy upon $^{67}$Ga lung uptake of patients with active pulmonary sarcoidosis. The data are expressed as $^{67}$Ga index Units (see reference [18] for details).

a significant mean increase of all the considered indices with respect to baseline mean values (VC= $+10.2 \pm 4.4\%$, $p<0.05$; TLC= $+9 \pm 3.5\%$, $p<0.05$; FEV$_1$= $+11.1 \pm 4.5\%$, $p<0.05$; DlC0= $+13 \pm 3.8\%$, $p<0.01$).

Evaluation of $^{67}$Ga lung scans showed a significant reduction of lung uptake after prednisone therapy with respect to baseline values (baseline $134 \pm 15.6$ Units, after therapy $91 \pm 11.5$ Units; $p<0.01$) (fig. 1); however, analysis of individual patients demonstrated no score modifications in two subjects and a slight elevation in one patient, whilst in two subjects scores dropped below the threshold value.

BAL was performed without difficulty in all patients. No bronchoscopic abnormalities were detected in the tracheobronchial tree and no differences were shown in terms of percentage of recovered fluid (baseline $57.3 \pm 4.5\%$, after therapy $55.2 \pm 5.8\%$; $p>0.2$). Comparative evaluation of cytological parameters showed that total cell counts (baseline $40.5 \pm 4.7 \times 10^6$ cells, after therapy $20.5 \pm 3.2 \times 10^6$ cells; $p<0.02$) and percentage of T-lymphocytes (baseline $40.6 \pm 2.8\%$, after therapy $20.6 \pm 4.5\%$; $p<0.01$) (fig. 2) were reduced after prednisone therapy. Biochemical analysis of BAL demonstrated a significant reduction of both IgG and IgA concentrations with respect to baseline values (IgG: baseline $6.99 \pm 1.27$ mg%, after therapy $1.78 \pm 0.37$ mg%; $p<0.005$) (IgA: baseline $2.9 \pm 0.31$ mg%, after therapy $0.64 \pm 0.13$ mg%; $p<0.001$); in contrast, IgM was detected at very low levels in all cases with no differences between the study groups (IgM: baseline $0.27 \pm 0.11$ mg%, after therapy $0.21 \pm 0.09$ mg%; $p>0.2$). In addition, although mean albumin concentrations were shown to be somewhat lower after steroid treatment, the difference was not significant (albumin: baseline $6.04 \pm 0.94$ mg%, after therapy $4.75 \pm 0.59$ mg%; $p>0.2$). In agreement with the previous data, comparisons of IgG/albumin and IgA/albumin ratios demonstrated a marked reduction of both ratios after prednisone therapy (IgG/albumin: baseline $1.24 \pm 0.21$, after therapy $0.40 \pm 0.12$; $p<0.001$) (IgA/albumin: baseline $0.55 \pm 0.07$, after therapy $0.14 \pm 0.03$; $p<0.001$) (figs 3 and 4), whilst comparisons of IgM/albumin ratios did not show any change over the study period (IgM/albumin: baseline $0.05 \pm 0.01$, after therapy $0.06 \pm 0.03$; $p>0.2$).

Fig. 2. Effects of oral prednisone therapy upon T-lymphocyte component of the alveolitis in patients with active pulmonary sarcoidosis. The data are expressed as percentages of BAL recovered cells (see Methods for details).

Fig. 3. Effects of oral prednisone therapy upon local IgG production, as assessed by comparisons of IgG/albumin ratios in BAL before and after six months treatment in patients with active pulmonary sarcoidosis.
Bronchoalveolar lavage in sarcoidosis.

consequence of the suppression provided by corticosteroids on transcription of both lymphokines' genes [25] and was confirmed by recent studies performed on the lung T-cells isolated from sarcoid patients [26].

Modulation of macrophages and T-lymphocyte activities after steroid therapy may be responsible for reduction of IgG and IgA levels in BAL, as demonstrated in the present study. However, it must still be determined whether steroid therapy can directly reduce activation of B-cells and the proportion of Ig-secreting cells in the lungs of sarcoid patients.

The role played by increased local Ig production and immune complex formation in the pathogenesis of pulmonary sarcoidosis is still unclear. However, since immune complex deposition can result in the formation of granulomata in some tissue [27] and Ig's and immune complexes are present in sarcoid granulomata within the lungs [28], it is possible that Ig synthesized at sites of disease activity may be important in modulating at least some of the sarcoid lesions.

Therefore, reduction of local Ig levels after steroid therapy, as suggested by the results of the present study, may not simply mirror suppression of cell-mediated immune processes in the lower respiratory tract, but possibly reflects the inhibition of a process that might be relevant to the derangement of lung parenchyma in this disorder.

References


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IMMUNOGLOBULINS IN SARCOIDOSIS


RÉSUMÉ: Les niveaux d’immunoglobulines augmentent dans l’arbre respiratoire inférieur des patients atteints de sarcoïdose pulmonaire. Nous avons évalué les effets d’une corticothérapie à la prédiction sur les concentrations d’immunoglobulines dans le lavage alvéolo-alvéolaire de 10 patients atteints de maladie active (T lymphocytes supérieurs à 30% dans le BAL et scan positif au Gallium 67). Les pourcentages de T lymphocytes dans le BAL sont significativement abaissés et les index du scan pulmonaire au Gallium également. De plus, on a noté une légère amélioration des paramètres fonctionnels étudiés. L’analyse biochimique du lavage alvéolo-alvéolaire a montré une diminution significative, à la fois du rapport IgG/albumine (1.24 ± 0.21 au début; 0.40 ± 0.12 après traitement). On a trouvé également un abaissement du rapport IgA/albumine (0.35 ± 0.07 au début; 0.14 ± 0.03 après traitement) chez tous les patients. De plus, les comparaisons des rapports IgM/albumine n’ont pas montré de modification pendant toute l’étude (valeur de base 0.05 ± 0.01; valeur après traitement 0.06 ± 0.03; p > 0.2). Une corticothérapie orale diminue l’alvéolite de la sarcoïdose pulmonaire, ainsi que le démontrent, aussi bien la réduction du pourcentage de cellules T pulmonaires et la captation pulmonaire de Gallium, que par ailleurs la diminution des taux d’immunoglobulines dans les espaces alvéolaires.