CASE STUDY

Nongranulomatous interstitial lung disease in Crohn's disease

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ABSTRACT: Crohn's disease is a granulomatous systemic disorder of unknown aetiology. Obvious pulmonary involvement is exceptional. We report the case of a 33 year old woman treated with mesalazine for Crohn's disease and presenting with dyspnoea.

Pulmonary function tests showed a restrictive ventilatory pattern with hypoxaemia on exertion. Chest radiography disclosed an interstitial pattern with ground glass on high resolution computer tomography. Clinical and radiological abnormalities progressed after withdrawal of mesalazine. Corticosteroids led to a partial regression but were stopped because of severe side-effects.

Because of worsening of the clinical situation, open lung biopsy was performed and showed a histopathological aspect of nongranulomatous interstitial diffuse lung disease with an inflammatory lymphoid infiltration associated to some mild interstitial collagen fibrosis. Addition of cyclophosphamide to high-dose pulse steroid therapy induced a significant and sustained improvement.


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Pulmonary involvement is rare in Crohn's disease and was evaluated as 0.4% in a study concerning 1,400 patients [1]. Previous cases of bronchopulmonary associated disease have been described, such as granulomatous interstitial lung disease (ILD) [2, 3]. We report the case of a patient with Crohn's disease, who developed a fibrosing nongranulomatous ILD.

Case report

A 33 years old woman was admitted in October 1991 for chronic cough and dyspnoea on exertion. Since 1988, she had been treated with mesalazine (Pentasa®) for Crohn's disease. Clinical examination revealed disseminated crackles. Chest radiography and high resolution computed tomography (HRCT) showed diffuse ground-glass opacities (fig. 1). Pulmonary function tests (PFT) showed a restrictive pattern (vital capacity (VC) 47% of predicted value, total lung capacity (TLC) 66% pred). Blood gas showed a moderate hypoxaemia (arterial oxygen tension (P_{a,O_2}) 10.5 kPa (79 mmHg)). On exertion, P_{a,O_2} fell (table 1). Blood tests showed a moderate increase of the inflammatory markers: erythrocyte sedimentation rate (ESR) 33 mm·h^{-1}; C reactive protein 16 mg·L^{-1}; anti deoxyribonucleic acid (DNA) antibodies, circulating immune complexes, antinuclear antibodies, and complement were all normal. Serodiagnoses

for Aspergillus, Candida, and bird breeders' lung were negative. Angiotensin converting enzyme (ACE) was increased to 53 nmol·mL^{-1}. The only abnormality was an increased immunoglobulin (IgE) level of 693 KIU·L^{-1}.

Bronchoalveolar lavage (BAL) showed 705,000 cells·mL^{-1} in 78 mL, with 54% macrophages, 23% lymphocytes, 14% neutrophils and 9% eosinophils [4]. Transbronchial biopsies revealed an inflammatory mononuclear cell infiltrate. Biopsy of minor salivary glands was normal.

Mesalazine was withdrawn in November 1991 without any improvement, and corticotherapy 0.5 mg·kg^{-1} q.d.

Fig. 1. – High resolution computed tomography (HRCT) scan, showing diffuse ground-glass opacities in both lungs.
was initiated in January 1992. Four months later, the patient was feeling better. Oximetry on exertion had improved (table 1), the ventilatory defect was less marked (fig. 2), and tomodensitometry showed a mild regression of the ground-glass opacities. BAL was repeated and showed 527,000 cells·mL⁻¹ in 74 mL, with 56% macrophages, 29% lymphocytes, 5% neutrophils and 10% eosinophils. However, despite the respiratory improvement, the patient wished to stop the corticotherapy in May 1992 because of uncomfortable side-effects, such as extensive acne and excessive facial hair. The dyspnoea rapidly increased, with asthenia, extension of the ground-glass opacities to the whole parenchyma, and worsening of the ventilatory tests.

Open lung biopsy was performed and showed an inflammatory lymphoid infiltration, essentially in the interalveolar walls and irregularly within the airspaces, with eosinophils and macrophages but without any granulomatous lesions (fig. 3). There was some interstitial collagen fibrosis and bronchioles contained some mucoid retention but the pleura and the vessels had a normal aspect.

Because of these histological appearances, corticotherapy was restarted, this time as high-dose pulse (30 mg·kg⁻¹ once a week for 6 weeks), in order not to induce a recurrence of the side-effects. Long-term therapy was then added with cyclophosphamide (100 mg·day⁻¹). The evolution was favourable with progressive clinical and functional improvement (table 1). Immunosuppressive therapy was stopped in February 1994. A new clinical and functional evaluation was performed in November 1994, showing a sustained improvement without significant radiological changes.

Table 1. – Sequential evaluation of clinical exercise testing

<table>
<thead>
<tr>
<th>Date</th>
<th>At rest</th>
<th>Effort</th>
<th>On exertion</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$P_{a,O_2}$</td>
<td>$S_{a,O_2}$</td>
<td>$P_{(A-a,O_2)}$</td>
</tr>
<tr>
<td></td>
<td>kPa</td>
<td>%</td>
<td>kPa</td>
</tr>
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<td>96</td>
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<tr>
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<td>98</td>
<td>ND</td>
</tr>
<tr>
<td>11/92</td>
<td>12.9</td>
<td>98</td>
<td>ND</td>
</tr>
<tr>
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<tr>
<td>11/94</td>
<td>11.2</td>
<td>94</td>
<td>1.9</td>
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</tbody>
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$P_{a,O_2}$: arterial oxygen tension; $S_{a,O_2}$: arterial oxygen saturation; $P_{(A-a,O_2)}$: alveolar to arterial difference in oxygen tension; $V'O_2$: oxygen consumption; ND: not determined.
Discussion

This case may be considered as pulmonary fibrosing alveolitis occurring in Crohn's disease. Although one cannot exclude that previous steroid therapy had altered the histological pattern of the lung parenchyma, the pathological characteristics of this observation were a thickening of the alveolar wall by collagen fibrosis and an inflammatory lymphoid infiltration without any granulomatous lesion. This observation clearly differs from granulomatous pulmonary involvement occurring in Crohn's disease, consisting of noncaseating epithelioid granuloma with multinucleated giant cells in the interstitium and in the peribronchiolar and perivascular regions. These granulomatous, sarcoid-like lesions are not specific and may be considered either as pulmonary involvement in Crohn's disease or as an unknown sarcoidosis with intestinal involvement [5–10]. A few cases of pulmonary parenchymal involvement in Crohn's disease have been reported, including seven cases of interstitial lung fibrosis [11–13], one case of alveolar consolidation [14], one case of bronchiolitis obliterans organizing pneumonia (BOOP) [2] and one case of lung infiltrates with peripheral eosinophilia [2]. Among the seven patients suffering from Crohn's disease with radiological and clinical signs of ILD, open lung biopsies were performed in only two cases. The alterations were similar, showing acute alveolitis, granulomatous lymphocytic infiltration of the interstitium and of the walls of small arteries, with slight interstitial fibrosis. In four patients, no biopsy was performed, and in the last one, bronchial biopsy did not reveal any specific lesion. In the case of alveolar consolidation of the left lower lobe, the open lung biopsy showed multiple focal areas of noncaseating epithelioid granuloma containing multinucleated giant cells in the interstitium. Lastly, in the case of pulmonary infiltrates and eosinophilia, the open lung biopsy revealed interstitial and airspace infiltration by eosinophils and an oedematous thickening of the septa. These aspects were all different from the lesions observed in our observation. The main problem when interstitial lung disease occurs in the course of systemic disorders is to exclude drug-induced lung disease, in our case mesalazine-associated pneumonitis. Only two cases of mesalazine-induced lung disease have previously been reported [15, 16], with a rapid improvement after mesalazine withdrawal. In our case, ILD worsened after withdrawal of the drug and PFT deteriorated after steroid withdrawal.

Interestingly, the outcome of interstitial lung disease was favourable using a combination of steroids and cyclophosphamide. Pulmonary manifestations of inflammatory bowel disease usually respond dramatically to inhaled and/or systemic steroids [2] The addition of cyclophosphamide in our case allowed a sustained beneficial effect, as was recently demonstrated in the course of patients with idiopathic pulmonary fibrosis [17]. Taken together, these findings suggest that nongranulomatous interstitial lung disease mimicking idiopathic pulmonary fibrosis may occur during the course of Crohn's disease.

References