Case Report

Bronchoalveolar lavage cytology in pulmonary fibrosis associated with neurofibromatosis

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Introduction

Neurofibromatosis (von Recklinghausen's disease) is an autosomal-dominant, inherited disorder. Both sexes are affected equally (1,2). The disease is characterized by multiple neurofibromas which can arise in any organ system. Most of the patients belong to the more common type I (formerly called classical or peripheral form with 'cafe-au-lait' spots, multiple neurofibromas, Lisch nodules found in the iris, and other changes of the skeletal or neural system), less patients are grouped under the rare type II (formerly called central or acoustic form), and a few patients cannot be separated clearly into one of the two types (2,3).

Co-existing pulmonary fibrosis and/or cystic lung disease and neurofibromatosis have been noted since 1928 (4,5). Sporadic reports on pulmonary changes have been published in about 50 patients with neurofibromatosis (4-16). Three larger studies showed diffuse pulmonary fibrosis in 10-30% of adults with the disorder (5,7,9). Although neurofibromatosis is congenital, pulmonary fibrosis does not appear until adulthood.

To the best of the authors' knowledge, bronchoalveolar lavage (BAL) cellular findings have not been reported previously in this disorder.

Case Report

A 48-year-old woman was hospitalized with mildly progressive dyspnoea on exertion, and sporadic cough with moderate sputum production for 2 yr. She had been smoking 40 cigarettes day⁻¹ for 30 yr. There was no exposure to dusts.

Physical examination revealed at least seven 'café au lait' patches, axillary freckling, and multiple typical neurofibromas over the trunk. Fine, late inspiratory crackles were audible over the right lung base. The chest radiograph showed micronodular infiltrates involving mainly the lower zones on both sides. The computerized tomographic (CT) scans showed reticular shadowing with some ground glass densities in the upper zones, and more extensive opacities with subpleural bullous lesions in the lower zones. Laboratory studies disclosed a mildly elevated sedimentation rate of 16 mm h⁻¹, and a γ-GT of 48 U l⁻¹ (normal range 4-18 U l⁻¹). Other values were within normal limits. Skin prick tests for the most common allergens and precipitins against bird, aspergillus and farmer's lung antigens were negative. Lung function tests showed mild obstruction with a vital capacity (VC) of 2-91 (73% predicted), total lung capacity 6.5 l (114% predicted), residual volume 3.6 l (211% predicted) and FEV₁/VC 52% (70% predicted). Airways resistance was normal. After β-agonist inhalation, there was no significant increase in FEV₁. Measurements of arterial blood bases at rest revealed a PaO₂ of 66 mmHg (8.8 kPa) and a PaCO₂ of 34 mmHg (4.4 kPa). PaO₂ at exercise (30 W) dropped to 59 mmHg (7.8 kPa); PaCO₂ remained at 34 mmHg (4.4 kPa).

Fibre-optic bronchoscopy disclosed no abnormalities. Bronchoalveolar lavage was performed with 5 x 20 ml saline in the lateral segment of the middle lobe, and fractions were pooled before analysis. Cell smears were stained with May–Grunwald–Giemsa stain and revealed an elevated fraction of 7% eosinophils and a mild increase in mast cells (see Table 1). Open lung biopsy was performed in the anterobasal segment of the lower lobe. The
Table I Bronchoalveolar lavage fluid cytology

<table>
<thead>
<tr>
<th>Patient</th>
<th>Normal smokers (n=15)</th>
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<tbody>
<tr>
<td>Fluid recovery (ml)</td>
<td>40</td>
</tr>
<tr>
<td>Total cells (×10⁶)</td>
<td>25</td>
</tr>
<tr>
<td>Cell differentials</td>
<td></td>
</tr>
<tr>
<td>Macrophages (%) (×10³ ml⁻¹)</td>
<td>83.4</td>
</tr>
<tr>
<td>Lymphocytes (%) (×10³ ml⁻¹)</td>
<td>520.0</td>
</tr>
<tr>
<td>Neutrophils (%) (×10³ ml⁻¹)</td>
<td>6.6</td>
</tr>
<tr>
<td>Eosinophils (%) (×10³ ml⁻¹)</td>
<td>41.3</td>
</tr>
<tr>
<td>Mast cells (%) (×10³ ml⁻¹)</td>
<td>12.5</td>
</tr>
<tr>
<td>Values are means ± sd.</td>
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</tbody>
</table>

histological features were consistent with pulmonary fibrosis with subpleural predominance. The alveolar walls were thickened due to fibrous tissue proliferation. There was only mild interstitial inflammation with scattered lymphocytic accumulation and minimal irregular emphysema. Eosinophils and mast cells were not predominant. Pneumocytes showed cubic transformation. There were no honeycomb transformation, vascular changes or abnormal neural proliferations.

Despite treatment with prednisone for 3 months, and combined prednisone/azathioprine for another 3 months, the disease was progressive. The patient, who had continued smoking, was next placed on prednisone 20 mg and cyclophosphamide 125 mg daily. Ten months later, her lung function showed a slight improvement.

Discussion

To the authors’ knowledge, this is the first study on BAL findings in pulmonary fibrosis associated with neurofibromatosis. Interestingly, the BAL cell differential showed a mild eosinophilic alveolitis, as may be seen in some patients with idiopathic pulmonary fibrosis. In addition, the mast cells were increased slightly. These cells were not predominant in the lung biopsy. However, discrepancies between BAL and histology regarding the profile of inflammatory cells are not unusual. However, although it has been pointed out that there are no specific histological changes in pulmonary fibrosis in neurofibromatosis type I, most investigators describe large apical bullae with interstitial changes (6,7,15), or comparable findings to those seen in diffuse fibrosing alveolitis (6,7,9).

The pathogenesis of the disorder remains unknown. One possible explanation would be an inherited mesenchymal defect resulting in the immediate deposition of collagen (8). This view is supported by the observation of fibrous tissue proliferation in other mesenchymal tissues, e.g. bone or blood vessels, in neurofibromatosis (17–19). More recently, the role of mast cells for the manifestation of skin lesions in neurofibromatosis has been emphasized (20). As neurofibromas contain a large number of mast cells able to release heparin and histamine, mast cell stabilization has been suggested as a therapeutic possibility to reduce neurofibroma growth and pruritus (20). In this respect, it is of interest that the BAL fluid of the present patient contained an increased proportion of mast cells. Whether these mast cells are protagonists in the pathogenesis of pulmonary fibrosis in neurofibromatosis should be subject of future studies.

In conclusion, the BAL fluid of this patient with pulmonary fibrosis and neurofibromatosis revealed a mild increase in eosinophils and mast cells. Both cell types may play a role in the pathogenesis of the disorder.

References


