Serial Bronchoalveolar Lavage Studies in a Patient with Intra-Alveolar Fibrosis Following Legionnaires’ Disease

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A 48-year-old male developed acute respiratory failure owing to Legionnaires’ disease (LD). Antibiotic treatment including erythromycin and rifampicin was not effective, thus transbronchial lung biopsy was performed. The histological examination of the lung showed intra-alveolar fibrosis. Corticosteroid therapy was begun and he responded well with definite clinical improvement. Bronchoalveolar lavage (BAL) was performed three times in the following year. The first BAL showed an increase of lymphocytes which then decreased significantly in the following studies. This case report thus demonstrates the importance of lung biopsy of protracted LD and the usefulness of BAL in the assessment of corticosteroid therapy.


Key words: transbronchial lung biopsy, corticosteroid therapy, T-lymphocyte

Introduction

Since the epidemic outbreak in 1976, Legionella infection has emerged as an important cause of both community acquired and nosocomial pneumonia. Prospective clinical studies have reported the incidence of pneumonia caused by Legionella to vary from 2 to 27% (1). The clinical features of Legionnaires’ disease (LD) range from an asymptomatic course to fatal pneumonia. Although there have been no properly controlled studies of prolonged sequelae, a few case reports have noted a permanent pulmonary sequelae including pulmonary fibrosis following LD (2–9).

In this report, we demonstrate a case of intra-alveolar fibrosis caused by fulminant LD, which responded well to corticosteroid therapy, and we discuss the findings of three bronchoalveolar lavages performed in the following year.

Case Report

A 48-year-old man was admitted to our hospital on October 1, 1991 because of fever, productive cough and left flank pain for three days before admission. He had no history of pulmonary disease but had smoked a pack of cigarettes per day for 25 years.

Physical examination revealed blood pressure of 120/60 mmHg, heart rate of 90 beats/minute, temperature of 38.5°C, no cyanosis, and coarse crackles over the right lower chest. A chest X-ray (Fig. 1) demonstrated a dense infiltration in the right lower lung field. Laboratory findings showed a white blood cell count of 8,100/mm³ with 4% metamyelocytes, 84% band forms, 5% polymorphonuclear leukocytes, 4% lymphocytes, and 3% monocytes. Erythrocyte sedimentation rate (104 mm/h) and C-reactive protein (42.6 mg/dl) which are parameters of inflammation were elevated; mild liver and renal dysfunction were also noted (alkaline phosphatase 356 IU/l, aspartate aminotransferase 51 IU/l, alanine aminotransferase 38 IU/l, lactic acid dehydrogenase 486 IU/l, leucine aminopeptidase 75 IU/l, gamma-glutamyl transpeptidase 170 IU/l, blood urea nitrogen 4.1 mg/dl, creatinine 1.3 mg/dl). Lung function test showed mild restrictive ventilatory impairment [FVC 2,980 ml (%VC 77.4%); FEV₁ 1.0 2,300 ml (FEV₁% 76.2%)].

While antibodies for Legionella species were not detected on the third hospital day, a diagnosis of LD was made since the indirect immunofluorescence study done on the 21th hospital day revealed a rise in the titers for Legionella pneumophila serogroup 6 and 7 to 1:512 and 1:1,024, respectively.

Along with the abnormal laboratory findings the patient took an undesirable clinical course. On the second hospital day, his body temperature rose to 40.1°C and dyspnea worsened. Specimens of arterial blood revealed that the PaO₂ was 35 Torr, the
PaCO₂ 35 Torr, and the pH 7.36. Therefore, mechanical ventilation and antibiotic therapy including erythromycin and rifampicin were started. However, these were not effective upon hyperthermia and hypoxemia. Since pneumonia was still progressive as determined by chest roentgenogram (Fig. 2), transbronchial lung biopsy was performed on the 21st hospital day to define the pathological change in the lung tissue. Histological analysis demonstrated marked intra-alveolar fibrosis (Fig. 3), while stains for acid-fast bacilli, fungi, pneumocystis carinii and gram-staining bacteria were all negative. The patient was consequently treated intravenously with 60 mg of prednisolone per day from the 26th hospital day, then his symptoms and chest roentgenogram started to improve gradually. PaO₂ was normalized and lung infiltrations were found to be cleared two months after prednisolone therapy was started.

BAL study was performed 4 weeks, 13 weeks and 12 months after the start of prednisolone in order to assess the degree of inflammation and determine the dose of prednisolone (Table 1). The first BAL showed a marked increase of lymphocytes and we continued the oral prednisolone therapy (30 mg) for the subsequent 9 weeks. Since the second BAL showed normalization of the proportion of lymphocytes, we reduced the dose of prednisolone. Although there had been no clinical evidence of a recurrence of pulmonary fibrosis, the third BAL, performed during oral prednisolone therapy of 5 mg, revealed an increased proportion of lymphocytes again. We accordingly continued the same dose of prednisolone and have found no signs of a recurrence to date (December 1992).

Discussion

We diagnosed an infection of Legionella pneumophila on the basis of an indirect immunofluorescence test, and intra-alveolar fibrosis by transbronchial lung biopsy specimen. Immunohistochemical analysis with a monoclonal antibody for Legionella pneumophila (Chemicon Inc, CA, USA) of his lung tissue, however, showed no LD bacteria. These findings suggest that a pulmonary structural alteration in the form of intra-alveolar fibrosis followed Legionella infection, although we could not rule out an influence of oxygen therapy on intra-alveolar fibrosis.

Since the first report from the Massachusetts General Hos-
Lung Fibrosis after Legionella Infection

Table 1. Bronchoalveolar Lavage Analysis

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<thead>
<tr>
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<tbody>
<tr>
<td>Total cell counts</td>
<td>4.5x10^5/ml</td>
<td>2.1x10^5/ml</td>
<td>4.8x10^5/ml</td>
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<tr>
<td>Macrophage</td>
<td>48.0%</td>
<td>89.5%</td>
<td>75.0%</td>
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<tr>
<td>Lymphocyte</td>
<td>46.0%</td>
<td>8.5%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>6.0%</td>
<td>2.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Lymphocyte subset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OKT3</td>
<td>78.6%</td>
<td>44.4%</td>
<td>77.7%</td>
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<tr>
<td>OKT4</td>
<td>36.7%</td>
<td>36.1%</td>
<td>59.2%</td>
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<tr>
<td>OKT8</td>
<td>28.6%</td>
<td>11.4%</td>
<td>21.8%</td>
</tr>
<tr>
<td>OKT4/OKT8</td>
<td>1.28</td>
<td>3.17</td>
<td>2.72</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>43.5 Torr</td>
<td>39.7 Torr</td>
<td>36.9 Torr</td>
</tr>
<tr>
<td>PaO₂</td>
<td>66.6 Torr</td>
<td>85.9 Torr</td>
<td>84.3 Torr</td>
</tr>
</tbody>
</table>

pital (2), several cases of pulmonary fibrosis following LD have been reported (3–9). Blackmon et al (4) reported three cases of pulmonary fibrosis which developed after LD in patients who died in respiratory failure. Chastre et al (6) studied 20 critically ill patients with acute LD. Of the 20 patients, five developed pulmonary fibrosis, including four who died of this complication and one who survived but was left with pulmonary sequelae. In contrast, there have been two case reports of patients with pulmonary fibrosis following LD, who responded to corticosteroid therapy and improved without pulmonary sequelae (7, 8). We believe that intra-alveolar fibrosis was the direct cause of death in some cases of LD which led to death in spite of appropriate antibiotic therapy. Therefore, in such cases, it is important to examine the lung tissue histopathologically in an early phase and to determine an indication of corticosteroid therapy.

Intra-alveolar fibrosis probably represents a type of response to injury. The alveolar epithelial lining and the basement membranes are often disrupted in LD patients (6). Thus, it is likely that exudation of protein and migration of inflammatory cells and fibroblasts to the intra-alveolar space occur through gaps in the epithelial basement membranes and that organization of this exudation leads to intra-alveolar fibrosis.

In the present study, BAL was performed three times in the following year to monitor changes occurring under corticosteroid therapy. There are some reports that BAL lymphocytosis in idiopathic pulmonary fibrosis patients is associated with responsiveness to corticosteroid therapy (10–12). Turner-Warwick and Haslam (10) reported that the serial lavage cell counts of patients with cryptogenic fibrosing alveolitis responding to corticosteroid therapy tend to return toward normal. In the present case, the first BAL performed four weeks after the start of corticosteroid therapy, showed a marked BAL lymphocytosis, although the patient’s symptoms and chest X-ray findings were improved. We continued the same dose of prednisolone, as we thought BAL lymphocytosis may be indicative that the suppression of inflammation was not sufficient. Then, the second BAL showed a significant decrease in the percentages of lymphocytes in accordance with complete clinical improvement. It is interesting that the first and second BAL findings of this case were similar to those of a subset in idiopathic pulmonary fibrosis patients who respond favorably to corticosteroid therapy.

The relationship between T lymphocytes and intra-alveolar fibrosis has not been clear, although some observations suggest that T lymphocytes may have a role in fibrogenesis regulation (13–14). Soluble mediators released by inflammatory cells, mainly macrophages, including fibronectin, alveolar macrophage-derived growth factor and platelet-derived growth factor (15–17), probably play a role in inducing septal fibroblasts to migrate through the epithelial defect, to replicate and to produce connective tissue components. Although the time course of inflammatory cell accumulation in lung fibrogenesis has not been evaluated, the markedly increased lymphocytes in this BAL study may represent one of the characteristic findings of the early phase of intra-alveolar fibrosis, and the degree of adhesion of the inflammatory cells to alveolar walls may be one of the causes of BAL lymphocytosis.

Here, the third BAL however, revealed a re-increase of the proportion of lymphocytes. Hürter et al (8) reported a case of recurrence of fibrosing alveolitis following LD after the end of an eight-month period of corticosteroid therapy. In the present case, there has been no evidence of recurrence, but we consider the re-increase of lymphocytes as a predictive sign of the recurrence and thus observe the patient more carefully. Serial BAL studies were useful for this patient in the assessment of suppression of inflammation and determination of the dose of corticosteroid. These methods were valuable in preventing a recurrence of pulmonary fibrosis and respiratory failure caused by a premature discontinuation of corticosteroid therapy.

This case report demonstrates the importance of lung biopsy for patients with LD who had a protracted course, and suggests the usefulness of serial BAL studies in following intra-alveolar fibrosis associated with LD.

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References


