Bronchoalveolar Lavage as a Possible Cause of Acute Exacerbation in Idiopathic Pulmonary Fibrosis Patients

NANAKO HIWATARI, SANAЕ SHIMURA, TAMOTSU TAKISHIMA and KUNIO SHIRATO

The First Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980-77

HIWATARI, N., SHIMURA, S., TAKISHIMA, T. and SHIRATO, K. Bronchoalveolar Lavage as a Possible Cause of Acute Exacerbation in Idiopathic Pulmonary Fibrosis Patients. Tohoku J. Exp. Med., 1994, 174 (4), 379-386 — In the past 13 years (1980 to 1992), bronchoalveolar lavage (BAL) was performed on 124 idiopathic pulmonary fibrosis (IPF) patients (29 F and 95 M, 60±1 years, mean±s.e.) at Tohoku University Clinic and Hospital. Among them, three patients showed acute exacerbation immediately after BAL and died of progressive respiratory failure after 2.5 weeks, 2 months and 3.5 months, respectively, despite intensive care. They were all older patients (79, 74 and 66 years old) and we failed to find any evidence of viral, bacterial or fungus infections either before or after BAL in blood, sputum or BAL fluid samples. Further, all autopsied lungs showed interstitial pneumonia and fibrosis and no evidence of infectious diseases. In contrast, no progressive deteriorations after BAL were observed in 282 patients (122 F and 160 M, 48±1 years old) with other pulmonary diseases (sarcoidosis, bronchial asthma, collagen diseases and other interstitial lung diseases), who received BAL during the same period. This suggests that BAL itself sometimes induces a progressive degeneration in IPF patients, especially in older patients.

bronchoalveolar lavage; complications; exacerbation; idiopathic pulmonary fibrosis

Bronchoalveolar lavage (BAL) is widely used both for the management of patients with pulmonary diseases and for clinical research. Although cough, slight fever, alveolar infiltration in lavaged area and some deterioration of lung functions including hypoxia are seen during and/or after BAL, these have been reported to be transient, with or without any specific treatment (Klech and Hutter 1990). Thus, to date, BAL has been regarded as a safe procedure and no lethal complications directly attributable to BAL have been reported (Klech and Hutter 1990) and no definite criteria for the indication of BAL have been proposed.
From our experience, however, BAL induces a progressive degeneration in a few patients with pulmonary diseases. We report here three patients with idiopathic pulmonary fibrosis (IPF) who showed acute exacerbation after BAL, resulting in progressive degeneration and death.

**Case Reports**

*Case T.H.* 74 years old, male, height 165 cm, bodyweight 51 kg, nonsmoker

There was nothing noteworthy in his family or past history. Since winter 1978, he had complained of persistent cough and since February, 1981, of an exertional dyspnea. In June, 1981, he visited a clinic and was diagnosed as having pulmonary fibrosis based mainly on the findings of a chest roentgenogram. In November 1981, he was referred to our clinic for further examination. Chest roentgenogram showed diffuse reticulonodular, linear shadows in both lung fields. Pulmonary function tests showed moderate restrictive impairment (VC, 1.66 liter; %VC, 52%; FEV\textsubscript{1.0}, 1.37 liter; FEV\textsubscript{1.0}, 83%), severe hypoxia (PaO\textsubscript{2}, 57 mmHg; PaCO\textsubscript{2}, 43 mmHg, pH 7.47), decreased diffusing capacity (DLco, 5.17 ml/min/mmHg; %DLco, 24%) and decreased lung compliance (Cst, 0.063 liter/cmH\textsubscript{2}O). Under local anesthesia with lidocaine, he received transbronchial biopsy (TBLB) via a bronchoscope on December 2, 1981, with the administration of supplemental oxygen during and after TBLB. After the TBLB, there were no significant alterations in symptoms or laboratory findings. Histologic findings of biopsy samples showed increased collagen deposits and mononuclear cell infiltration in alveolar septa, without any other specific findings, suggesting usual interstitial pneumonia (UIP) (Carrington et al. 1978). Based on clinical and other laboratory and histological findings, his final diagnosis was idiopathic pulmonary fibrosis (IPF). Prednisolone (40 mg/day) was orally administered for one month, and dyspnea, diffuse shadows in chest roentgenogram, VC (1.66 to 1.91 liter) and PaO\textsubscript{2} (57 to 86 mmHg) all improved to some degree. To determine the degree of alveolar inflammation, he received BAL under local anesthesia with lidocaine on January 27, 1982. BAL was performed at the right middle subsegmental lobe with a warmed sterile isotonic saline of 20 ml×5=100 ml, and the recovery rate and total cell recovery were 63% and 9.6×10\textsuperscript{6}, respectively. Immediately after BAL, he complained of progressive degeneration in dyspnea, and chest roentgenogram and arterial blood gas analysis showed increased diffuse shadows in both lung fields and increased hypoxia (Table 1). Laboratory data also indicated a worsening of inflammation (Table 1). However, he had no fever and laboratory findings did not indicate bacterial or fungus infections either before or after BAL. In spite of intensive care with large amounts of glucocorticoids (Table 1) in addition to various antibiotics including antifungus drugs, he showed progressive worsening both in symptoms and laboratory findings, and died of progressive respiratory failure on February 14, 1982. Autopsied lungs showed advanced pulmonary fibrosis with honeycomb changes, especially marked in both
lower lobes, but we could not find any specific cause for interstitial fibrosis, including granulomatous or infectious diseases.

Case K.K. 66 years old, male, height 157 cm, bodyweight 64 kg, ex-smoker (20 pack-years)

His history included an operation for gall stones, and thereafter acute hepatitis at 49 years old. Since 1979, he had complained of cough and exertional dyspnea and had been diagnosed as having pulmonary fibrosis of undetermined cause, based mainly on chest roentgenogram findings. In October, 1986, he was referred to our clinic for further examination because of increased dyspnea. On November 17, 1986, BAL was performed at the right middle subsegmental lobe (warmed saline, 20 ml x 5 = 100 ml) with a 38% recovery rate and simultaneous TBLB via a bronchoscope on the left lung. BAL fluid showed slight increases in both neutrophils and eosinophils (recovery total cells, 3 x 10^6; macrophage, 92%; lymphocyte, 3%; neutrophil, 3%; eosinophil, 2%) and the tissue samples from TBLB showed diffuse nonspecific alveolar septal fibrosis. Due to the chronic state, no glucocorticoids nor immunosuppressants were administered. Although he did not have any significant alteration in symptoms soon after the first BAL with TBLB, laboratory or chest roentgenogram findings, cough and dyspnea gradually increased and he again visited our clinic. Chest roentgenogram on the second visit showed diffuse linear reticulonodular shadows in both lung fields and small ring shadows (honeycomb appearance) in the right lower lung field. Pulmonary function tests showed moderate restrictive impairment (VC, 2.06 liter; %VC, 65%; FEV1, 1.81 liter/sec; FEV1/VC, 88%), moderate hypoxia (65 mmHg; PaCO2, 41 mmHg), decreased diffusion capacity (DLco, 8.4 ml/min/mmHg; %DLco, 41%) and decreased lung compliance (Cst, 0.057 liter/cm H2O).

To determine the inflammatory change of the alveolar region, BAL was performed at the right middle subsegmental lobe (warmed saline, 50 ml x 3 = 150 ml) on July 1, 1988, and the recovery rate and total cell recovery were 67% and 3 x 10^6, respectively, showing a prominent increased in neutrophils (30%) (Table 1). Immediately after the second BAL, he complained of fever (37-38°C) and increased dyspnea, with increased diffuse shadows in chest roentgenogram. Laboratory data also showed severe hypoxia and a worsening in inflammation (Table 1). Administrations of various antibiotics including antifungus drugs, followed by large amounts of glucocorticoids (Table 1), could not stop the progression of the disease. Sputum, blood and BAL fluid all failed to disclose any evidence of viral, bacterial and fungus infections. He died of progressive respiratory failure on October 12, 1988. Autopsied lungs showed interstitial pneumonia in various stages from an exudative appearance (hyaline membrane formation) to fibrous thickening of alveolar walls and a honeycomb appearance, mostly in the lower lobes of both lungs. However, there was no evidence of bronchopneumonia, bacterial, viral, pneumocystis carinii, or fungus infection.

Case K.S. 79 years old, female, height 140 cm, bodyweight 38 kg, non-
There was nothing of note in her past or family history. Since the winter of 1986, she had complained of cough and, in addition, slight dyspnea on exertion since 1989. In September, 1989, she was referred to our clinic for further examination. Chest roentgenogram on admission showed slight reticular and linear shadows mainly in peripheral regions of both lung fields. Pulmonary function tests showed normal values in %VC (93%), FEV₁ 0% (82%) and arterial gas analysis (Table 1). However, there was decreased diffusion capacity (DLco, 8.8 ml/min/mmHg) and decreased lung compliance (Cst, 0.023 l/cmH₂O). On October 27, 1989, TBLB was performed, without complications, and the tissue samples showed alveolar septal thickening with both fibrosis and mononuclear cell infiltration without any specific findings. To determine the degree of alveolar inflammation, BAL was performed on December 1, 1989, and the recovery rate and total cell recovery were 54% and 3 x 10⁷, respectively. Immediately after BAL, she complained of worsening dyspnea with fever (37-38°C) and laboratory data indicated progressing inflammation (Table 1). Both chest roentgenogram and arterial blood gas analysis showed progressive degeneration. Although blood and sputum samples failed to detect significant bacterial or fungus infections, various antibiotics were administrated in addition to prednisolone (Table 1). However, she died of progressive respiratory failure on January 26, 1990. Autopsied lungs showed diffuse interstitial pneumonia and fibrosis and slight right cardiac hypertrophy, with no evidence of viral, bacterial or fungus infections nor known causes of interstitial lung disease.

**DISCUSSION**

In the past 13 years (1980 to 1992), bronchoalveolar lavage (BAL) was performed by us on 124 IPF patients including 48 patients aged 65 years or older at Tohoku University Clinic and Hospital (Table 2). Under local anesthesia with lidocaine, a right middle or left lingual subsegmental lobe was lavaged with warmed sterilized isotonic saline (20 ml x 50 = 100 ml during 1980 to 1987 and 50 ml x 3 = 150 ml during 1988 to 1992). When the initial arterial oxygen tension (PaO₂) on room air was less than 70 mmHg, supplemental oxygen was administrated during BAL for 2 to 4 hr thereafter. Diagnosis of IPF was made from a combination of medical records, clinical and laboratory data, and histologic findings of autopsied lungs and lung biopsy according to previously described criteria (Crystal et al. 1976). Among them, as described above and summarized in Table 1, three IPF (chronic type, not Hamman Rich syndrome) patients who were all older than 65 years showed an exacerbation immediately after BAL, and died of progressive respiratory failure after 2.5 weeks to 3.5 months despite intensive care, including the administration of large amounts of glucocorticoids and artificial respiration. Medical records and autopsied lungs failed to find any evidence of viral, bacterial, pneumocystis carinii, or fungus infections before or
Table 1. Physical, laboratory and BAL data of three IPF patients who showed acute exacerbation after BAL

<table>
<thead>
<tr>
<th>Case Age (years /sex)</th>
<th>Duration of symptoms (years)</th>
<th>%VC (%)</th>
<th>%Dl,co (%)</th>
<th>PaO₂ (mmHg)</th>
<th>PaCO₂ (mmHg)</th>
<th>BAL cell population</th>
<th>CRP (µg/ml)</th>
<th>LDH (IU/ml)</th>
<th>Steroid treatment after BAL</th>
<th>Survival after BAL (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.H. (74/M)</td>
<td>3</td>
<td>60</td>
<td>–</td>
<td>82 (51)</td>
<td>38 (39)</td>
<td>86 10 4 0</td>
<td>–</td>
<td>457</td>
<td>MP 1 g x 9 days,</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P 100 mg x 3 days, 80 mg x 6 days</td>
<td></td>
</tr>
<tr>
<td>K.K. (66/M)</td>
<td>10</td>
<td>65</td>
<td>41</td>
<td>65 (48)</td>
<td>41 (48)</td>
<td>67 2 30 1</td>
<td>+</td>
<td>578</td>
<td>MP 1 g x 3 days, P 100 mg x 2 weeks, 80 mg x 1 month, 60 mg x 2 months</td>
<td>3.5</td>
</tr>
<tr>
<td>K.S. (79/F)</td>
<td>3</td>
<td>99</td>
<td>58</td>
<td>80 (58)</td>
<td>47 (44)</td>
<td>92 3 2 3</td>
<td>1.0</td>
<td>414</td>
<td>P 100 g x 2 weeks, 80 mg x 1 month, 60 mg x 2 weeks</td>
<td>2.0</td>
</tr>
</tbody>
</table>

All pulmonary function data were obtained at room air within 2 weeks before BAL and ( ) : data 24 hr after BAL at room air.
CRP and LDH in serum were obtained within one week before BAL and ( ) : data 3 to 5 days after BAL.
Mφ, macrophage; Ly, lymphocyte; N, neutrophil; Eo, eosinophil; MP, methylprednisone; P, prednisolone.

Table 2. Patients who received bronchoalveolar lavage (BAL) at Tohoku University Clinic and Hospital during 1980 to 1992

<table>
<thead>
<tr>
<th>Group</th>
<th>Number (sex)</th>
<th>Age (years)</th>
<th>Disease Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>124 (62 F and 62 M)</td>
<td>60±1 years old</td>
<td>60±1 years old</td>
</tr>
<tr>
<td>IPF patients older than 65 years</td>
<td>48 (23 F and 25 M)</td>
<td>69±3 years old</td>
<td>69±3 years old</td>
</tr>
<tr>
<td>B</td>
<td>282 (122 F and 160 M)</td>
<td>48±1 years old</td>
<td>48±1 years old</td>
</tr>
<tr>
<td>Other pulmonary disease patients*</td>
<td>23 (11 F and 12 M)</td>
<td>68±2 years old</td>
<td>68±2 years old</td>
</tr>
</tbody>
</table>

Mean ± S.D.
*Sarcoidosis, bronchial asthma, collagen disease and other interstitial disease patients.
after BAL. Twelve of 124 IPF patients (6 F and 6 M, 60±5 years old) died of progressive respiratory failure within 1 year of the onset of disease. It is possible that BAL also had induced an acute exacerbation in these patients since it was difficult to distinguish the BAL-induced exacerbation from the natural course in their medical records because of their rapid degeneration.

Bronchoscopy or TBLB itself does not seem to be responsible for the exacerbation of IPF. In our experience, as well as previous reports (Dhillon et al. 1986; Klech and Hutter 1990), such an exacerbation by bronchoscopy or TBLB has not been reported. Although pneumothorax and significant bleeding was seen in 14 of 307 patients (5%) who received TBLB during the same period, they completely recovered within 3 weeks with adequate treatment. In fact, TBLB itself which was performed prior to BAL did not produce any exacerbation in the two patients (case T.H. and case K.S. in Table 1). Further, 43 IPF patients (24 F and 19 M, 59±2 years old) who received TBLB alone because of severe hypoxia (PaO₂, 52±2 mmHg) did not show any significant alteration in symptoms, pulmonary functions, or chest roentgenogram 48 hr or more after the bronchoscopy with TBLB. In addition, no progressive deteriorations in the disease after BAL during the same period were observed in 282 patients with other pulmonary diseases (sarcoidosis, bronchial asthma, collagen diseases and other interstitial lung diseases), including 23 patients aged 65 years or older (Table 2). Therefore, acute exacerbation after BAL seems to be peculiar to IPF patients.

It is possible that the death of these three patients had been due to the terminal phase of the illness or severely impaired lung functions. However, these patients include an IPF patient with well preserved lung functions (case K.S. in Table 1). Further, the two other IPF patients did not produce much lower data in pulmonary function tests than the total IPF patients who received BAL during the same period; i.e., PaO₂, 73±1 mmHg; %VC, 80±2% (n = 124). In addition, there were about 35 other patients who showed lung function impairment similar to the two other IPF patients before BAL and did not show such a progressive deterioration after BAL. In addition, in case K.K. in Table 1, the first BAL presumably induced a slow progressive deterioration since the second BAL fluid showed a prominent increase in neutrophils, compared to that in the first BAL. Based on these findings, the possibility that the disease was in the terminal phase or that lung function was severely impaired seems remote. All three patients were older than 65 years, suggesting that aging may be a risk factor for the exacerbation after BAL in IPF patients. For example, IPF patients in the present study are significantly older than those reported by Dhillon et al. (1986) who have reported no such an exacerbation or progressive deterioration (60±1 years old, n = 124 vs. 52±1 years old, n = 62).

Increased neutrophils in BALF are known to be characteristic of IPF and have been suggested to play a role in the pathogenesis (Reynolds et al. 1977), and it also has been shown that BAL itself causes the migration of a large number of
neutrophils to nonlavaged areas as well as lavaged areas of the lung (Kazmierowski et al. 1977; Von Essen et al. 1991). Therefore, in these three patients, the increase and/or activation of neutrophils in alveolar regions due to BAL may be related to the exacerbation. Meanwhile, a major role for tumor necrosis factor (TNF) in pulmonary fibrosis has been suggested by animal experiments (Piguet et al. 1989), and serum levels of TNF$\alpha$ after BAL were elevated in human (Standiford et al. 1991). Thus, we can speculate some possibilities concerning IPF exacerbation after BAL, but the mechanism remains unclear. Further, our idea that BAL itself induced the exacerbation in these IPF patients may not be conclusive and requires further epidemiologic studies.

The findings from BAL, especially BAL cell counts alone, did not produce significant information for the diagnosis because of an overlap within diseases, and provided little information for the management of IPF patients, while that from TBLB did provide some clues for the diagnosis. This suggests that BAL is not diagnostic although it may be of some benefit in the staging and monitoring of the prognosis in IPF patients (Crystal et al. 1976; Walters et al. 1987). However, based on our present findings, BAL should not be considered in IPF patients older than 65 years. In conclusion, our patient history suggests that BAL should be more carefully considered and/or limited in older IPF patients.

References
