Bronchiolitis Obliterans Organizing Pneumonia*

Diagnosis by Transbronchial Biopsy

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Transbronchial biopsy (TBB) has been considered to be inadequate for the diagnosis of bronchiolitis obliterans organizing pneumonia (BOOP). We describe herein two patients with interstitial pulmonary disease in whom the diagnosis of BOOP was achieved by TBB. The two patients presented with progressive dyspnea, cough, tachypnea, and fine end-inspiratory crackles. The radiologic findings disclosed patchy alveolar infiltrates. Pulmonary function tests showed a restrictive pattern and decreased diffusing capacity. The pathologic findings disclosed bronchioles, alveolar ducts, and alveoli infiltrated with mononuclear cells. The lumina were obliterated with fibroblasts and loose granulation tissue. Corticosteroid treatment resulted in significant improvement. Transbronchial biopsy should be considered as a useful diagnostic tool for BOOP.

(Ches t 1993; 104:1899-1901)

AST = aspartate aminotransferase; BOOP = bronchiolitis obliterans organizing pneumonia; CMV = cytomegalovirus; Dco = diffusing capacity of carbon monoxide; EBV = Epstein-Barr virus; ESR = erythrocyte sedimentation rate

**Bronchiolitis obliterans organizing pneumonia (BOOP)** is a clinicopathologic entity characterized by a subacute illness with shortness of breath, fever, malaise, and weight loss present for a period ranging from 3 to 6 months.1 Spirometric studies show a restrictive pattern and impairment of gas exchange. The radiologic findings are variable, ranging from few alveolar opacities to diffuse reticulonodular densities.2,3 The bronchioles and the surrounding alveolar ducts and alveoli are infiltrated with mononuclear cells, lymphocytes, and plasma cells; with the progression of the disease, the air spaces become obliterated with fibroblasts and granulation tissue.3 Pathologic confirmation of BOOP is important, as it implies a benign course and therapeutic response to corticosteroid therapy. Performing an open lung biopsy is usually recommended.4 In this article, we describe two patients in whom the diagnosis of BOOP was achieved by transbronchial biopsy (TBB).

**Case Reports**

**Case 1**

A 17-year-old patient was admitted with a nonproductive cough, progressive dyspnea, and weight loss of 3 months' duration. In the past, she had been in good health, and she denied smoking. Physical examination revealed tachycardia (120 beats per minute), tachypnea (24 breaths per minute), and end-inspiratory crackles in the lower lungs. The chest x-ray film and computed tomographic scan (Fig 1) showed bilateral alveolar infiltrates. Pulmonary function studies disclosed a restrictive pattern, with evidence of air trapping and decreased diffusing capacity for carbon monoxide (Dco). Arterial blood gas levels showed hypoxemia, with an increased alveolar-arterial gradient (Table 1).

Laboratory findings disclosed the following values: erythrocyte sedimentation rate (ESR), 20 mm/h; hemoglobin level, 13.8 g/dl; leukocyte count, 8,200/mm³, with a normal differential cell count; platelet count, 397,000/mm³; BUN, 10 mg/dl (normal range, 5 to 25 mg/dl); creatinine, 1 mg/dl (normal range, 0.5 to 1.5 mg/dl); potassium, 4.1 mEq/L (normal range, 3.5 to 5.3 mEq/L); sodium, 140 mEq/L (normal range, 136 to 147 mEq/L); lactate dehydrogenase, 268 IU/L (normal range, 60 to 225 IU/L); alkaline phosphatase, 113 IU/L (normal range, 30 to 115 IU/L); serum aspartate aminotransferase (AST), 724 IU/L (normal, 5-45 IU/L); angiotensin-converting enzyme, 62 IU/L (normal, 8 to 52 IU/L); and IgG, 2,463 mg/dl (normal, 640 to 1,350 mg/dl). Levels of IgM and IgA were normal. Levels of antinuclear antibody, anti-DNA antibody, rheumatoid factor, and anticardiolipin antibody were all normal; and complement levels were normal. Serologic assays for viral antibodies revealed no diagnostic rise for the Epstein-Barr virus (EBV), cytomegalovirus (CMV), adenovirus, influenza, or parainfluenza titers.

Transbronchial biopsy (Fig 2) disclosed the characteristic polypoid fibrous-tissue plugs filling air spaces. In the surrounding air spaces, numerous foamy macrophages were evident. The interstitium showed thickened walls infiltrated by chronic inflammatory cells. With higher magnification (Fig 2), the air-space plug was composed of loose connective tissue with scattered spindle fibroblasts, a few plasma cells, and lymphocytes. The alveolar septa contained lymphocytes, macrophages, plasma cells, and type 2 pneumocytes. These pathologic findings were consistent with the diagnosis of BOOP.

Treatment with prednisone (60 mg/day) was initiated and resulted in significant clinical, physiologic, and radiologic improvement within 1 month; complete recovery was observed after 3 months (Table 1). The dose of prednisone was gradually tapered, and therapy was stopped after 1 year.

**Case 2**

A 66-year-old woman was admitted for progressive dyspnea accompanied by a nonproductive cough and weight loss of 4 kg over several days. The patient had had a preceding episode of influenza. Until then, she had been healthy except for mild osteoporosis. The physical examination revealed only tachycardia (108 beats per minute), tachypnea (26 breaths per minute), and diffuse bilateral end-inspiratory crackles. The chest x-ray film (Fig 3) showed bilateral patchy infiltrates in the lower lungs and linear opacities in the midlungs. Pulmonary function tests disclosed a mild restrictive...
Table 1—Pulmonary Function and Arterial Blood Gas Levels Before and After 3 Months of Treatment*

<table>
<thead>
<tr>
<th>Data</th>
<th>Patient 1 Before</th>
<th>Patient 1 After</th>
<th>Patient 2 Before</th>
<th>Patient 2 After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>O</td>
<td>O/P %</td>
<td>O</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.54</td>
<td>1.57</td>
<td>44</td>
<td>3.56</td>
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<tr>
<td>FEV1, L</td>
<td>2.97</td>
<td>1.64</td>
<td>55</td>
<td>3.16</td>
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<tr>
<td>FEV1/FVC%</td>
<td>84.5</td>
<td>96.8</td>
<td>115</td>
<td>88.8</td>
</tr>
<tr>
<td>RV, L</td>
<td>1.12</td>
<td>1.30</td>
<td>116</td>
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<tr>
<td>TLC, L</td>
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<td>2.97</td>
<td>61</td>
<td>4.66</td>
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<tr>
<td>BV/TLC, %</td>
<td>23.5</td>
<td>45.4</td>
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<td>26.6</td>
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<tr>
<td>Dco, mmol/min/kPa/L</td>
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<td>1.18</td>
<td>58</td>
<td>1.83</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>...</td>
<td>54</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
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<td>36</td>
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<td>pH</td>
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<tr>
<td>HCO3, mEq/L</td>
<td>...</td>
<td>24</td>
<td>...</td>
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</tr>
</tbody>
</table>

*P, predicted; O, observed; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

pattern with decreased diffusing capacity. Arterial blood gas levels showed mild hypoxemia (Table 1).

Laboratory findings disclosed the following values: ESR, 90 mm/h; normal complete blood cell count; hemoglobin level, 11.9 g/dl; leucocyte count, 11,700/mm³, with a normal differential cell count; platelet count, 254,000/mm³; BUN, 14 mg/dl; creatinine, 0.9 mg/dl; potassium, 3.5 mEq/L; sodium, 136 mEq/L; lactate dehydrogenase, 313 IU/L; alkaline phosphatase, 241 IU/L; and AST, 331 IU/L. Serum levels of immunoglobulin, antinuclear antibody, antinuclear antibody, rheumatoid factor, and anticardiolipin antibody were normal, and complement levels were normal. Viral titers for EBV, CMV, adenovirus, influenza, and parainfluenza were negative for IgM and weakly positive (1/16) for IgG. Transbronchial biopsy was performed and disclosed BOOP. Therapy with prednisone (60 mg) was initiated, and improvement was noticed within a month. After 3 months of treatment, the alveolar infiltrates resolved; however, linear opacities in the midlines persisted, and pulmonary function tests showed mild reduction in Dco (Table 1).

### DISCUSSION

Bronchiolitis obliterans organizing pneumonia is a clinicopathologic entity first described by Epler and his colleagues in 1985. Fifty patients were described; in all of them, diagnosis was made by open lung biopsy.

The distinguishing histopathologic feature of BOOP is the filling of the alveolar and bronchiolar lumina by buds of loose connective tissue containing inflammatory cells and fibroblasts; most patients have associated interstitial inflammation. It is important to distinguish bronchiolitis obliterans, the airflow disorder, from BOOP, the interstitial disorder. The former is occasionally idiopathic but generally occurs after inhalation of toxic fumes (SO₂ or NO₂) or after a viral or mycoplasmal infection or is associated with connective tissue diseases. It has been associated with penicillamine only in patients with rheumatoid arthritis.

The latter disorder, BOOP, is generally idiopathic but may be associated with connective tissue disorders (lupus of the lung), some types of viral infections, and a variety of miscellaneous causes, such as amiodarone, bleomycin, or human immunodeficiency viral infection. Pathologic confirmation is important, as it implies a favorable prognosis and response to corticosteroid therapy. More than 65 percent of the patients have complete resolution; some may have resolution without therapy, some require low-dose maintenance therapy with prednisone for several years, and others may have stabilization with chronic symptoms and pulmonary dysfunction.

The benefit of cytotoxic agents in these cases has not yet been established. Death in idiopathic BOOP occurs in 5 percent of the cases. Since the description by Epler et al.

![Figure 2. Air space with BOOP (hematoxylin-eosin, original magnification ×300).](https://example.com/figure2.jpg)

![Figure 3. Chest x-ray film showing diffuse interstitial opacities (case 2).](https://example.com/figure3.jpg)
of 50 patients diagnosed by open lung biopsy, it has been cited repeatedly that TBB is not recommended because of the small specimens and patchy nature of the disease. Our own experience, as well as that of others, differs, since the diagnosis of BOOP was made by TBB; however two criteria must be met: (1) the biopsy must contain both bronchiolar airway elements (proliferative bronchiolitis obliterans) and alveolar elements (organizing pneumonia); and (2) the clinical findings must be consistent with idiopathic BOOP, ie, influenza-like illness, crackles, patchy infiltrates on the x-ray film, and physiologic studies showing a decreased vital capacity and abnormal DCO. If these broad criteria are fulfilled, then TBB may be sufficient. In this article, we describe two patients with clinicophysiologic evidence of subacute interstitial pulmonary disease. It is interesting to note that patient 1 had transient abnormal results on hepatic function tests; recently, biochemical cholestasis was described in patients with BOOP. In our two patients, TBB yielded sufficient specimens for the diagnosis of BOOP. The two patients responded dramatically to corticosteroid therapy. Therefore, it is concluded that TBB is a useful diagnostic tool in BOOP. Open lung biopsy should be reserved for those times when the specimen from TBB is inadequate for diagnosis.

REFERENCES


Persistent Bronchopleural Fistula in a Patient With Adult Respiratory Distress Syndrome

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Bronchopleural fistula (BPF) continues to present a treatment problem in mechanically ventilated patients. We report a patient with a traumatic BPF, pneumonia, and adult respiratory distress syndrome (ARDS) who was successfully ventilated with pressure-controlled ventilation (PCV). This mode, by allowing the use of lower inspiratory airway pressures, may promote closure of the fistula.

(CHEST 1993; 104:1901-02)

Pressure-controlled ventilation (PCV) used with inverse ratio ventilation may be a beneficial mode of ventilation in patients with adult respiratory distress syndrome (ARDS). It has been reported to improve oxygenation, ventilation, and allow decreased peak airway pressure (PAP) and lower positive end-expiratory pressure (PEEP). Conventional ventilation modalities known to reduce airway pressures and promote closure of the BPF are often not viable alternatives if ARDS coexists, as high fractional inspired oxygen (FiO2) and airway pressures may be required to maintain adequate oxygenation and ventilation. Surgery may not be possible due to the impact of severe lung disease on gas exchange.

CASE REPORT

A 39-year-old black man weighing 75 kg, with no known history of cardiovascular or respiratory disease, was admitted to the hospital with multiple stab wounds, involving the left upper chest and the axillary area. A left hemopneumothorax was drained and emergency surgery was performed, where the axillary vein was ligated and the axillary artery repaired. A combination of hypothermia, hemodynamic instability, and the presence of a BPF necessitated postoperative ventilation and the patient was transferred to the ICU. At the time of admission, the patient was hemodynamically stable and was ventilated with a ventilator (Bird 8400) on synchronized intermittent mandatory

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