Bronchoalveolar Lavage, Serum Angiotensin-converting Enzyme, and Gallium-67 Scanning in Extrathoracic Sarcoidosis*

Benoit Wallaert, M.D.; Philippe Ramon, M.D.; Eric Fournier, M.D.; André Bernard Tonnel, M.D.; and Cyr Voisin, M.D., F.C.C.P.

Results of bronchoalveolar lavage (BAL), 67Ga scanning, and serum angiotensin-converting enzyme (SACE) assay are compared in the assessment of pulmonary involvement in ten cases of extrathoracic sarcoidosis. Standard clinical, radiologic, and pulmonary function tests detected no pulmonary changes in these patients, but BAL demonstrated an increased alveolar lymphocytosis in eight of ten cases. SACE levels were increased in two cases, and the thoracic gallium uptake was normal in all cases. BAL appears to be the best technique for diagnosing latent pulmonary involvement in extrathoracic sarcoidosis.

Recent progress in the knowledge of the mechanisms implicated in pulmonary sarcoidosis permits a better approach to the physiopathology of this disease. It is now recognized that the earliest manifestation of pulmonary sarcoidosis is alveolitis, ie, the accumulation of inflammatory and immune cells within the alveolar structures. The alveolitis precedes and is responsible for granuloma formation in the lung, which is the hallmark of the disease. Staging of pulmonary sarcoidosis using pulmonary function testing and chest x-ray examination shows a poor relationship to the intensity of alveolitis as assessed by histopathologic studies.

Three new techniques—bronchoalveolar lavage (BAL), 67Ga scanning, and serum angiotensin-converting enzyme (SACE)—provide sensitive and specific means of assessing the activity of the disease. BAL shows that the sarcoid lung, whatever the radiologic stage, is characterized by an increased number of helper T-lymphocytes. These T-lymphocytes release lymphokines, which are implicated in granuloma formation. 67Ga scanning gives an estimate of the extent and the intensity of inflammation in the lung. SACE levels have been reported elevated in active sarcoidosis. These methods permit a repetitive and quantitative evaluation of the activity of pulmonary sarcoidosis.

The aim of this work is to compare the usefulness of BAL, SACE, and 67Ga scanning in evaluating the pulmonary involvement in ten cases of extrathoracic sarcoidosis, without any clinical or radiologic mediastinopulmonary changes (stage 0).

Materials and Methods

Ten patients with extrathoracic sarcoidosis were included in the study. Four patients (cases 4, 6, 7, and 9) had splenectomy for idiopathic thrombocytopenic purpura. The diagnosis of sarcoidosis was confirmed by the histologic study of the spleen. One patient (case 8) had ulcer of the stomach. Gastrectomy was performed after a six-month trial of cimetidine therapy had proved inefficient. Histology of the stomach and adenopathy confirmed the diagnosis of sarcoidosis. The Kveim test was positive. One patient (case 10) had interstitial nephritis, hypercalcemia (125 mg/L), cervical adenopathy, and ocular changes. Diagnosis of sarcoidosis was made by minor salivary gland biopsy examination. Two patients had lesions easily accessible for biopsy: superficial adenopathy (case 5) and skin sarcoid (case 1). Two patients had a clinical history and ocular changes compatible with sarcoidosis. The Kveim test was positive in one patient (case 2) and it was not done in the second (case 3).

The standard examinations for evaluation of pulmonary involvement of sarcoid disease were carried out in all ten patients, including chest x-ray examination and pulmonary function tests.

Informed consent was obtained from all patients. BAL was performed using a wedged fiberoptic bronchoscope (Olympus BF-B3) and 250 ml of sterile saline solution in 5×50-ml aliquots with immediate gentle vacuum aspiration after each aliquot injection. The cells were separated from the lavage fluid by centrifugation, resuspended in Hank's solution, and evaluated for total number and differential count.

The assay for SACE was performed according to the method of Lieberman. Activity was expressed in units per milliliter, and the normal value was 25.2 ± 4.7 units/ml in healthy controls.

Each patient received, before the BAL, 35 μCi/kg of

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 Bronchoalveolar lymphocytes (BAL) were studied in ten patients with extrathoracic sarcoidosis. The diagnosis of sarcoidosis was made by the presence of noncaseating epithelioid granulomas in tissue biopsy specimens. The results of this study are presented in Table 1.

**Table 1**—Bronchoalveolar Lymphocytosis, SACE, and Gallium Scan Results in 10 Cases of Extrathoracic Sarcoidosis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Extrathoracic Sarcoidosis</th>
<th>% Lymphocytes in BAL</th>
<th>SACE, Unit/ml</th>
<th><strong>9Ga Scan</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cutaneous</td>
<td>36</td>
<td>25</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Ocular</td>
<td>12</td>
<td>32</td>
<td>Not done</td>
</tr>
<tr>
<td>3</td>
<td>Ocular</td>
<td>21</td>
<td>19</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>Spleen*</td>
<td>19</td>
<td>27</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>Cervical adenopathy</td>
<td>19</td>
<td>26</td>
<td>Lymph node uptake</td>
</tr>
<tr>
<td>6</td>
<td>Spleen*</td>
<td>3</td>
<td>29</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>Spleen*</td>
<td>35</td>
<td>48</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>Stomach†</td>
<td>87</td>
<td>37</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>Spleen*</td>
<td>19</td>
<td>27</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>Kidney + salivary gland</td>
<td>45</td>
<td>15</td>
<td>Salivary gland uptake</td>
</tr>
</tbody>
</table>

*Investigations performed after splenectomy.
†Investigations performed after gastrectomy.

**Results**

All patients had normal chest x-ray film findings without any mediastinal or pulmonary changes. No alteration of FEV₁, vital capacity, P0₂, and single-breath carbon monoxide diffusing capacity was found in these ten patients.

In eight of ten cases, an abnormal percentage of lymphocytes (>18 percent) was noted (19 percent to 87 percent). No mediastinopulmonary galium uptake was observed; the SACE levels were normal in eight cases but significantly increased (>2 SD) in two cases (37 and 48 units/ml) (Table 1). A transbronchial biopsy performed on one (patient 1) with a BAL lymphocytosis of 36 percent did not show granuloma in the lung but an accumulation of mononuclear cells.

The evolution of these parameters was studied in five cases. In two untreated patients (cases 6 and 7) the favorable evolution of hematologic disease correlated with normal lymphocytosis. Gallium scan of the lungs was negative. SACE was normal in case 6 but increased (40 units/ml) in case 7.

In two untreated patients (cases 8 and 9) a persistent or increased abnormal lymphocyte percentage was noted, respectively, 12 and 9 months later. In case 9, the lymphocyte increase was correlated with secondary bilateral hilar lymph node enlargement, mediastinal gallium uptake, and significantly increased SACE.

In case 10, given corticosteroids for 12 months, we noted a favorable course of the disease: regression of cervical adenopathy and ocular changes and standardization of calcemia (101 mg/L). The clinical amelioration was associated with a decrease of the BAL lymphocytosis (from 45 percent to nine percent). SACE was 26 units/ml.

**Discussion**

Lymphocyte alveolitis is a usual but not pathognomonic feature of pulmonary sarcoidosis. In our observations, eight of ten patients had increased alveolar lymphocytosis. Although such alveolar lymphocytosis does not allow us to affirm the presence of pulmonary granulomatosis, it is the first step in the formation of granulomas. In addition, Rosen et al. have demonstrated that if sufficient lung tissue is obtained from open lung biopsy, granulomas are found in 100 percent of the patients with stage 1 sarcoidosis. The lack of clinical and radiologic manifestations did not ethically allow us to perform any open lung biopsies in this series of patients. One transbronchial biopsy in a patient with a BAL lymphocytosis of 36 percent did demonstrate an accumulation of mononuclear cells. The absence of granulomas may be related to the small size of the tissue sample studied.

Study of bronchoalveolar cells in patients with extrathoracic sarcoidosis without any clinical or ra-
diologic evidence of thoracic involvement provides an interesting and noninvasive criterion for diagnosis and survey of latent pulmonary involvement. In such cases, BAL is more sensitive than gallium scanning and SACE in assessing the activity of the disease and staging the latent alveolitis. Although the lungs may be secondarily involved by extrathoracic sarcoidosis, these data suggest that the pulmonary involvement occurs earlier than was previously thought, and, in fact, that the initial event in the pathogenesis of extrathoracic sarcoidosis may be the aggression of the respiratory tract. These possibilities need to be studied in depth.

REFERENCES

4 Reynolds HJ, Newball HH. Analysis of proteins and respiratory cells obtained from human lung by bronchial lavage. J Lab Clin Med 1974; 84:559-73

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