Limited Role of Auxiliary Endobronchial Biopsy in the Diagnosis of Japanese Patients with Sarcoidosis

Hiroshi Ishii, Satoshi Otani, Atsuko Iwata, Hiroaki Oka, Kosaku Komiya, Daisuke Yoshioka, Kazuhiko Hashinaga and Jun-ichi Kadota

1Internal Medicine 2, Oita University Faculty of Medicine, Yufu, Japan

The diagnosis of sarcoidosis, a multisystem granulomatous disease of unknown etiology, is established when clinicoradiological findings are supported by histological evidence of non-caseating epithelioid cell granulomas. For pathological diagnosis, an endobronchial biopsy of normal-appearing bronchial mucosa in combination with transbronchial lung biopsy (TBLB) has been reported to be useful for sarcoidosis patients in Europe or the U.S. This is the first report assessing the utility of endobronchial biopsy for diagnosis of Japanese patients with sarcoidosis. Eighteen consecutive patients with strongly suspected sarcoidosis were evaluated by endobronchial biopsy of normal-appearing bronchial mucosa, together with TBLB and bronchoalveolar lavage. The TBLB specimens demonstrated non-caseating epithelioid cell granulomas in the lungs of 11 patients (61.1%), but not any specific findings in those of other 7 patients. In contrast, endobronchial biopsy specimens confirmed a diagnosis of sarcoidosis in only one patient that required steroid therapy for deterioration of pulmonary sarcoidosis. All 18 patients of this study, including 5 patients with pathological findings obtained from extrapulmonary sites, met the pathological or clinical diagnostic criteria. In conclusion, endobronchial biopsy of normal-appearing bronchial mucosa in combination with TBLB does not improve the diagnostic capacity for detecting sarcoidosis in Japanese patients, despite earlier reports. Thus, this method is of limited usefulness as a conventional diagnostic modality for Japanese patients with suspicious sarcoidosis. The present study also suggests the racial difference in the endobronchial involvement in pulmonary sarcoidosis.

Keywords: endobronchial biopsy; epithelioid cell granuloma; normal bronchial mucosa; racial differences; sarcoidosis

Tohoku J. Exp. Med., 2011, 223 (2), 119-123. © 2011 Tohoku University Medical Press

The diagnosis of sarcoidosis requires both compatible clinical features and pathologic findings as a means to exclude other differential diagnoses. It is crucial to prove the presence of non-caseating epithelioid cell granulomas in order to make a definitive diagnosis of sarcoidosis. Currently, fiberoptic bronchoscopy with transbronchial lung biopsy (TBLB) and transbronchial needle aspiration (TBNA) for mediastinal lymphadenopathy are the diagnostic procedures that are most frequently used to pathologically diagnose pulmonary sarcoidosis. Recently, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) (Fritscher-Ravens et al. 2000; Annema et al. 2005) and real-time endobronchial ultrasound (EBUS)-guided TBNA (Garwood et al. 2007; Wong et al. 2007; Oki et al. 2007; Nakajima et al. 2009; Tremblay et al. 2009) for mediastinal lymphadenopathy have been reported to be high-yield, safe modalities for diagnosing this disease. However, these methods have not so far been commonly used or become widespread. On the other hand, lymphocytosis and increased levels of the CD4+ lymphocyte subset in bronchoalveolar lavage (BAL) fluid are well-known findings in patients with sarcoidosis (Costabel et al. 1986a; Danila et al. 2009).

In Japan, a combination of TBLB and BAL is the “gold standard” method for diagnosing pulmonary sarcoidosis. However, the results of TBLB are affected by radiographic evidence of parenchymal diseases, and its diagnostic accuracy for pulmonary sarcoidosis is far from perfect. In addition, TBLB occasionally induces serious complications, such as bleeding and pneumothorax. A prospective study of endobronchial biopsy (EBB) for sarcoidosis in Europe and the U.S. indicated that EBB had a diagnostic accuracy comparable to TBLB, and safely increased the diagnostic value of fiberoptic bronchoscopy (Armstrong et al. 1981; Bjørmer et al. 1991; Bilaceroglu et al. 1999; Shorr et al. 2001). In addition, EBB specimens, even if they are obtained from normal-appearing airways, have shown the presence of granulomas in approximately one-third of all
sarcoidosis patients (Armstrong et al. 1981; Shorr et al. 2001). However, racial differences in the endobronchial involvement in pulmonary sarcoidosis have been reported (Torrington et al. 1997), and there has been so far no data reported about the usefulness of EBB in Japanese patients with sarcoidosis.

In this study, to assess the utility of EBB for pathological diagnosis of Japanese patients with sarcoidosis, consecutive patients with suspected sarcoidosis were evaluated using TBLB and BAL, in combination with EBB.

**Subjects and Methods**

**Subjects**

This study was a case-series evaluating consecutive patients during a limited period of time. Eighteen patients referred to Oita University Hospital between October 2007 and January 2010 with strongly-suspected sarcoidosis were enrolled in this study. None of these patients had received steroid or antibiotic therapy at the time of clinical sample collection. Patients with suspected or known malignancies or a prior established diagnosis of sarcoidosis were excluded from the study. The study was approved by the Human Ethics Review Committees of Oita University Faculty of Medicine and a signed consent form was obtained from each patient. The median duration of follow-up was 21 (range; 6-28) months.

**Evaluation**

All subjects underwent a standard evaluation for sarcoidosis that included taking a medical history, a physical examination, a chest roentgenogram, pulmonary function tests, chest and abdominal computed tomographic scans, Gallium-67 scintigraphy, and fiberoptic bronchoscopy. In addition, the serum levels of angiotensin-converting enzyme (ACE: normal value < 21.4 IU/L), lysozyme (< 10.2 μg/mL), and soluble interleukin-2 receptor (< 519 U/mL) were measured.

**Bronchoscopy**

All bronchoscopic procedures were performed on an inpatient basis under local anesthesia with 1-4% lidocaine and mild sedation with intravenous pethidine hydrochloride (25-50 mg). All patients received three diagnostic modalities during the same examination (BAL, TBLB and EBB), using a conventional flexible bronchoscope. First, BAL was performed mainly from the right middle lobe in a standard fashion (50 ml of sterile saline, repeated three times). Then, at least five biopsied specimens were obtained from parenchymal fields of the lung by TBLB under X-ray fluoroscopy. If there was evidence of a pulmonary lesion by chest roentgenogram (indicating stage II or III disease), TBLB specimens were obtained from these regions. If there were no radiological findings in the lung field (stage 0 and I disease), the specimens were randomly obtained from the upper and lower lobes. Finally, three to five (at least three) EBB specimens of normal-appearing bronchial mucosa were obtained mainly from the right secondary carina. If any endoscopically abnormal lesions were observed on the secondary carina, then EBB was performed on the normal-appearing mucosa either on the main carina or other bifurcation areas.

**Diagnostic criteria**

The diagnostic criteria (Diagnostic standard and guideline for sarcoidosis. 2006) established by the Japan Society of Sarcoidosis and other Granulomatous Disorders is outlined below. In the tissue diagnosis group, non-caseating epithelioid cell granulomas are detected on biopsy specimens obtained from one organ. Additionally, at least one of the following three items is seen: (1) There are non-caseating epithelioid cell granulomas in other organs, (2) There are highly-suggestive clinical findings of sarcoidosis in other organs, (3) There are more than one item out of six items as follows: bilateral hilar lymphadenopathy, an elevated level of serum ACE, a negative tuberculin skin test, findings of a markedly-increased uptake in Gallium-67 scintigraphy, lymphocytosis or an elevated CD4/CD8 ratio in BAL fluid, and elevated levels of serum or urinary calcium. In the clinical diagnosis group, no non-caseating epithelioid cell granulomas were pathologically identified. However, there were highly-suggestive clinical findings of sarcoidosis in more than one organ, and there was more than one item out of the six items described above.

**Results**

**Patient characteristics**

During the study period, 18 consecutive patients referred for suspected sarcoidosis because of uveitis and/or
abnormal chest findings with/without respiratory symptoms, such as a non-productive cough and breathlessness, were enrolled in our study. As shown in Table 1, there were 8 Japanese males and 10 Japanese females (median age: 60 yrs) included in this study. Although the majority of patients (15/18; 83.3% of patients) were classified as having stage II and III disease based on a chest roentgenogram, there were more than a little findings from high resolution computed tomography of the lungs, such as small nodules or thickening of the interlobular septum or broncho-vascular bundles, in all of the patients. Ten patients (55.6%) had extrapulmonary sarcoidosis at the time of bronchoscopy (Table 1).

Findings obtained during bronchoscopic procedures
As shown in Table 2, endoscopic findings included hypervascularity (13/18; 72.2%), mucosal edema (2/18; 11.1%), and mucosal irregularity due to complicated amyloidosis (Case No. 10 in Table 2, previously reported by Oka et al. 2009). No mucosal nodularity or bronchial stenosis was observed in any of the patients in this study. The BAL fluid of the majority of patients revealed lymphocytosis with a relative increase in CD4+ cells. TBLB specimens demonstrated non-caseating epithelioid cell granulomas in the lungs of 11 patients (61.1%). EBB specimens of normal-appearing bronchial mucosa confirmed a diagnosis of sarcoidosis in one patient, who was only patient that needed steroid therapy for deterioration of pulmonary sarcoidosis (Case No. 7 in Table 2). None of the patients suffered from a complication during any of the bronchoscopic procedures. All of the patients in this study, including 5 cases with pathological findings obtained from extrapulmonary sites, met the above-mentioned diagnostic criteria. Therefore, based on the findings of chest computed tomography and BAL fluid analysis, we concluded that all of the patients had lung involvement of sarcoidosis (Table 1).

Discussion
According to reports from the U.S. (Armstrong et al. 1981; Shorr et al. 2001), EBB specimens of normal-appearing airways have shown non-caseating epithelioid cell granulomas in 30-37% of patients with sarcoidosis. These reports suggest that routinely performing EBB can easily provide high diagnostic value for use in combination with TBLB and BAL. However, 64.7% of the subjects in the report by Shorr et al. (2001) were African-Americans, and it has been reported that abnormal endobronchial mucosal findings occur more often in African-Americans (Torrington et al. 1997). In addition, it has been reported that the utility of EBB for African-American patients was significantly greater than for Caucasians in the U.S. (Torrington et al. 1997). The main reason for this racial difference was that there is a greater granuloma density in bronchial and lung tissues of African-American sarcoidosis patients compared with Caucasian patients (Burke et al. 2009). However, there have so far been no reports showing positive identification of the presence of epithelioid granulomas in EBB specimens of normal-appearing bronchial mucosa in Asian sarcoidosis patients. Thus, this is the first report describing the usefulness of EBB from normal-appearing airways for

<table>
<thead>
<tr>
<th>No.</th>
<th>Endoscopic findings</th>
<th>Lymphocyte rate (CD4/8 ratio*) in BAL fluid</th>
<th>Non-caseating granuloma in TBLB</th>
<th>Non-caseating granuloma in EBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypervascularity (mild)</td>
<td>45.6% (1.27)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Mucosal edema</td>
<td>20.9% (0.9)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>Hypervascularity</td>
<td>34.0% (20.8)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>Mucosal edema (mild)</td>
<td>22.3% (3.4)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>Hypervascularity</td>
<td>38.9% (4.1)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>Hypervascularity (mild)</td>
<td>17.0% (2.3)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>No abnormality</td>
<td>30.0% (2.5)</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>8</td>
<td>No abnormality</td>
<td>51.3% (2.4)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>9</td>
<td>Hypervascularity (mild)</td>
<td>40.0% (3.5)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>10</td>
<td>Irregular mucosa (amyloidosis)</td>
<td>10.2% (4.3)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>11</td>
<td>Hypervascularity (mild)</td>
<td>43.3% (2.6)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>12</td>
<td>Hypervascularity</td>
<td>7.0% (2.4)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>13</td>
<td>Hypervascularity</td>
<td>13.0% (5.6)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>14</td>
<td>Hypervascularity</td>
<td>40.0% (7.3)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>15</td>
<td>Hypervascularity</td>
<td>52.2% (11.6)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>16</td>
<td>Hypervascularity</td>
<td>17.3% (0.8)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>17</td>
<td>Hypervascularity</td>
<td>18.7% (2.6)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>18</td>
<td>Hypervascularity</td>
<td>10.0% (5.1)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*normal value: 1.1-3.5 in non-smokers, 0.5-1.5 in smokers (Costabel U et al. 1986b)
diagnosing sarcoidosis in Japanese patients.

In the report by Shorr et al. (2001), four specimens were obtained from a secondary carina and two specimens were obtained from the main carina, in patients with normal-appearing airways. As a result, positive findings were seen in three of ten individuals. However, there was no information available about the differences in the pathological findings due to the different biopsy sites used in this report. Our previously experienced patients tended to exhibit hypervascularity in the main carina. Therefore, the EBB specimens in our study were obtained mainly from the right secondary carina, and we could not clarify whether or not there was a different occurrence of granulomatous change in EBB specimens due to the differences in the biopsy locations. In addition, Takemura et al. (2003) reported that bronchial involvement of granulomas in the proximal bronchi and medium-sized bronchi were found in 33% and 56% of Japanese autopsy cases with sarcoidosis. Therefore, it is important to keep in mind the fact that the frequency of bronchial involvement may be relatively high in Japanese patients with sarcoidosis. However, it is not appropriate to make a simple comparison of the results between the biopsy specimens obtained from the normal-appearing mucosa and autopsy specimens.

A report by Armstrong et al. (1981) about patients in the U.S. demonstrated that, in 101 patients with sarcoidosis, endoscopic findings included mucosal nodularity (64% of patients), mucosal edema (55%), hypervascularity (38%), and bronchostenosis (26%), and indicated that these findings do not necessarily vary with the radiographic disease stage. They also indicated that EBB improved the overall diagnostic yield when it was obtained in conjunction with TBLB (Armstrong et al. 1981). In Japan, there have been a small number of reports regarding endoscopic mucosal findings in patients with sarcoidosis (Matsuoka et al. 1988; Ishii et al. 2002; Yamada et al. 2005). For example, Matsuoka et al. (1988) reported that, in 114 Japanese patients with sarcoidosis, hypervascularity was observed in 69-91% (including all roentgenographic stages) and endobronchial nodules were observed in 0-33%, and that these endoscopic findings did not correlate with disease activity, such as serum ACE levels or BAL lymphocyte counts. These reports indicate that there seems to be a racial difference in endobronchial findings, demonstrating that these findings are not related to chest radiographic findings or disease activity.

On the other hand, Bjørner et al. (1991) reported that signs of more intense inflammatory activity in European patients with bronchial sarcoidosis were found compared to those without, and that bronchial involvement might influence the clinical course of sarcoidosis, thus leading to a more severe impairment of pulmonary function and a greater use of systemic steroids. Interestingly, only one patient who needed steroids in this study was considered to be pathologically positive based on the EBB specimens of normal-appearing airway. This is of significance, because the number of patients with pulmonary sarcoidosis who need treatment with systemic steroids is relatively small in Japan. However, according to the previous reports, from one-third to two-thirds of all patients with sarcoidosis were treated with oral corticosteroids, and many of them in Europe and the U.S. were treated due to worsening of pulmonary involvement (Gibson et al. 1996; Baughman et al. 2006). In contrast, a mean 3% of Japanese patients needed oral corticosteroid therapy due to worsening of their pulmonary sarcoidosis (Shijubo et al. 2007).

In conclusion, auxiliary EBB of normal-appearing bronchial mucosa does not appear to improve the diagnostic capacity in combination with TBLB and BAL, at least in Japanese patients with sarcoidosis. Thus, it is not recommended that this method is added to the conventional diagnostic modalities for Japanese patients with suspicious sarcoidosis. However, it is hoped that a large multi-center survey can be accomplished in Japan in the near future.

**Conflicts of Interest**

No conflicts of interest in connection with this article.

**References**


