The Significance of Bronchoscopy for the Diagnosis of Mycobacterium avium complex (MAC) Pulmonary Disease

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Summary: To investigate the usefulness of bronchoscopy for the diagnosis of Mycobacterium avium complex (MAC) pulmonary disease, we retrospectively reviewed the clinical charts, and radiographic and bacteriologic findings of all patients who were admitted to our hospital between 1994 and 2000, and who fulfilled the 1997 American Thoracic Society (ATS) criteria for MAC pulmonary infection. A total of 132 patients were diagnosed as affected by MAC pulmonary disease during that period. Of these, bronchoscopic examination was performed in those patients who showed negative sputum smear for mycobacteria on three consecutive days (n=43) or who could not expectorate sputum (n=2). Of 42 patients, sputum culture was positive for MAC in 34 patients (81.0%). Bronchial washing sample was smear-positive for MAC in 17 of 39 patients (43.6%), and culture-positive for MAC in 33 of the 39 patients (84.6%). Transbronchial lung biopsy (TBLB) specimens revealed specific findings (epithelioid cell granuloma and/or acid-fast bacilli) in 14 of 38 patients (36.9%). Bronchial washing of all patients who showed specific histology in TBLB grew MAC in culture. Based on the bronchoscopic examination, we could diagnose MAC pulmonary disease in 36 patients. In addition, smear and polymerase chain reaction (PCR) results of bronchial washing made possible an early diagnosis of MAC pulmonary disease in 15 patients. We examined the relation of CT findings to bronchial washing results. Isolation of MAC in bronchial washing is significantly related to small nodular opacity around the ectatic bronchi on the CT scan (p=0.016). In our retrospective study, in sputum smear-negative patients with MAC pulmonary disease, MAC isolation by culture of bronchial washing was no more frequent than that with sputum culture. However, bronchial washing is useful to differentiate infection from casual isolation of MAC. In addition, we could make early diagnosis of MAC pulmonary disease based on smear and PCR results of bronchial washing. To make a diagnosis of MAC, bronchial washing is superior to TBLB, and should be done in the bronchus which drains the area revealing small nodular opacity around ectatic bronchi.

Key words bronchial washing, mycobacterium avium-intracellulare complex, small nodular opacity, CT finding

INTRODUCTION

Recently the incidence of pulmonary mycobacterium avium complex (MAC) infection without predisposing lung disease has reportedly increased [1-3]. In 1997, the American Thoracic Society (ATS) reported criteria for diagnosis and treatment of disease caused by nontuberculous mycobacteria, which included clinical and radiographic findings, and bacteriologic outcome using bronchoscopy [4]. Several authors reported the usefulness of bronchoscopy and CT in the diagnosis of MAC pulmonary disease. Huang et al. [3] reported the usefulness of bronchoscopy in patients who have MAC pulmonary disease, but
reveal negative sputum culture. Tanaka et al. [5] reported that bronchoscopic examination was more sensitive than the routine examination of expectorated sputum for MAC isolation in some patients who had clusters of small nodules in the periphery of the lung associated with ectatic changes of the draining bronchi on CT scan. However, the yield of positive results of bronchoscopy material (bronchial washing, transbronchial lung biopsy (TBLB)) in patient with negative sputum results is unclear. Furthermore, there have been few studies regarding what kind of CT abnormalities are related to positive bronchoscopy results.

In the present study, we investigate how useful is bronchoscopy in the diagnosis of MAC. We also elucidated what part of the lung we should examine in order to obtain positive results with bronchoscopy.

**PATIENTS AND METHODS**

We reviewed the clinical charts, CT, results of bacteriology of sputum and bronchial washing samples, and TBLB of patients diagnosed as MAC pulmonary disease who had been admitted to our hospital between January, 1994 and January, 2000. The diagnosis of MAC pulmonary disease was based on the 1997 ATS criteria for diagnosis of diseases caused by nontuberculous mycobacteria. A total of 132 patients were diagnosed with MAC pulmonary disease during that period. Of these, bronchoscopic examination was performed in those who showed negative sputum smear for mycobacteria on three consecutive days (n=43) or who could not expectorate sputum (n=2). Two patients were excluded from the study, because they showed only solitary nodule on chest CT. Accordingly, 43 patient (sputum smear negative 42, not expectorate sputum 1) were involved in the present study.

Bronchial washing was done as follows. We injected 20 ml sterile normal saline via a bronchoscope wedged into the segmental or subsegmental bronchus of the most heavily involved lobe, as seen on the chest CT, and aspirated the fluid with a vacuum. The aspirated fluid was examined using the same procedures used to process the expectorated sputum samples.

TBLB was performed from the same segment where bronchial washing was done. At least 4 specimens were obtained. The culture of biopsy specimen homogenate was not performed.

Fisher and chi square tests were used for comparison between groups. A P value <0.05 was considered significant.

**RESULTS**

**Clinical features**

The patients complained of cough, sputum, and/or bloody sputum. Twelve of the 43 patients were men, and 31 were women. The age of the patients ranged from 40 to 87 years, with a mean of 64 years. Chest CT scans were performed in all patients. Of the 43 patients with MAC infection, 42 had bronchiectasis, 3 had cavity and 28 had small nodular opacity.

Though sputum culture grew MAC in 34 patients of 42 (81.0%), only 15 patients (35.7%) satisfied the 1997 ATS criteria when using the result of sputum bacteriology alone.

**Bronchial washing**

Bronchial washing was performed in 39 of the 43 patients. Smear of bronchial washing was positive for acid-fast bacilli in 17 patients (43.6%). Culture of bronchial washing revealed growth for MAC in 33 patients (84.6%). Either the smear or the culture was positive in 33 of the 39 patients (84.6%) (Fig. 1). Polymerase chain reaction (PCR) examination of bronchial washing was done in 15 of the 17 patients with positive smear of bronchial washing. All 15 patients showed a positive PCR result for MAC (M. avium=5, M. intracellulare=7, M. avium + M. intracellular=3).

**TBLB**

TBLB was performed in 38 of the 43 patients. Epithelioid cell granuloma with multinucleated giant cells was found in 12 patients (31.6%) and acid-fast bacilli were positive in 2 (5.3%) of the biopsy speci-
mens. Either of them was positive in 14 of the 38 patients (36.9%).

In addition to these specific findings, a dense chronic inflammatory infiltrate was seen in the bronchiolar mucosa in 13 patients (59.1%) of 22 patients in whom a bronchiole was obtained in the section. Of these, epithelioid cell granuloma was also found in the same bronchiole in 8 patients. There were no granulomatous lesions in the remaining 5 patients.

Of 14 patients who had positive results (that is, epithelioid cell granuloma or acid-fast bacilli) in TBLB specimens, bronchial washing was performed in 10 patients, and all of them showed positive acid-fast bacilli in smear (n=3) or culture (n=10).

Usefulness of bronchoscopic examination for the diagnosis of MAC pulmonary disease

When using the results of sputum culture alone, only 15 patients among 42 patients (35.7%) satisfied the 1997 ATS criteria. The bronchoscopic examination made the diagnosis of MAC pulmonary disease possible in the remaining 27 patients (64.3%). In addition, smear results of bronchial washing made an early diagnosis of MAC pulmonary disease possible in 17 patients of 39 (43.6%) with the aid of PCR result.

Relation of CT findings to bronchial washing results

Several features such as small nodules, ectasis of bronchioles and bronchi, and pleural thickening were observed on the chest CT of patients with MAC pulmonary disease.

In cases in whom bronchoscopy showed positive results, mild, moderate and severe bronchiectasis was noted in 19, 8 and 6 cases, respectively. On the other hand, in those with negative bronchoscopy results, mild, moderate and severe bronchiectasis was observed in 4, 1, and 1 cases, respectively (Table 1). These was no significant difference in the degree of bronchiectasis between these groups.

In 33 patients with positive bronchoscopy results, small nodular opacity was seen in 24 cases (72.7%), while such opacity was observed in only one case (16.7%) in 6 patients with negative bronchoscopy results (Table 2). There was a significant difference (p=0.016) in the incidence of small nodular opacity on CT between patients with positive and negative bronchoscopy results.

We also compared the incidence of consolidation around ectasic bronchi in the two groups. Consolidation was found in 13 cases (39.4%) of the patients with positive bronchoscopy results, and in one (16.7%) of the patients with negative bronchoscopy results (Table 3). Though the incidence was not statistically significant, there was a tendency for consolidation around ectasic bronchi to be frequently observed in cases with positive bronchoscopy results.

In 33 patients with positive bronchoscopy results, cavitary formation was seen in 3 cases, whereas such abnormality was found in one case in 6 patients with negative bronchoscopy results.

| TABLE 1. | Bronchial washing results in patients with various degrees of bronchiectasis |
|------------------|------------------|------------------|
| Degree (n) | MAC (+) | MAC (−) |
| Mild (n=23) | 19 | 4 |
| Moderate (n=9) | 8 | 1 |
| Severe (n=7) | 6 | 1 |

MAC: Mycobacterium avium complex

| TABLE 2. | MAC isolation from bronchial washing in patients with (+) and without (−) small nodular opacity on chest CT |
|------------------|------------------|------------------|
| Small nodular opacity | MAC (+) (%) | MAC (−) (%) |
| (+) (n=33) | 24 (72.7) | 9 (27.3) |
| (−) (n=6) | 1 (16.7) | 5 (83.3) |

| TABLE 3. | MAC isolation from bronchial washing in patients with (+) and without (−) consolidation around ectasic bronchi on chest CT |
|------------------|------------------|------------------|
| Consolidation | MAC (+) (%) | MAC (−) (%) |
| (+) (n=33) | 13 (39.4) | 20 (60.6) |
| (−) (n=6) | 1 (16.7) | 5 (83.3) |
DISCUSSION

The incidence of MAC pulmonary disease in patients without predisposing lung disease and with no evidence of immunodeficiency has increased, but a number of patients cannot be diagnosed by sputum culture alone [2,3,6].

In 1997, the ATS reported guidelines for diagnosis and treatment of disease caused by nontuberculous mycobacteria, and showed that the diagnosis of active infection is possible using bronchoscopic specimen in conjunction with the appropriate clinical and radiographic findings [4]. However the ATS statement does not clearly show the role of bronchoscopy in the diagnosis of active MAC infection. In clinical practice, we usually perform bronchoscopic examination when sputum examination in patients suspected of MAC pulmonary disease does not show acid-fast bacilli or when patients cannot expectorate sputum. A few studies have evaluated the utility of bronchial washing and/or TBLB for the diagnosis of MAC pulmonary disease. Tanaka et al. [5] reported that 50% and 38.5% of patients who were suspected of having MAC pulmonary disease on chest CT had positive culture for MAC in the bronchial washing, and epithelioid granuloma in TBLB, respectively. Huang et al. [3] showed that 100% and 85.7% of patients who fulfilled the 1997 ATS criteria and had negative sputum culture, had positive culture for MAC in bronchoalveolar lavage (BAL), and granuloma in TBLB, respectively. In the present study, positive yield of MAC isolation in bronchial washing was 43.6% in smear and 84.6% in culture, and that of specific histology in TBLB was 36.9% (Table 4). It is possible that the study of Tanaka et al. included diseases other than MAC pulmonary disease. This may explain why the positive yield of MAC isolation in bronchial washing was lower than in Huang et al. and in our study. The patients in the study of Huang et al. and in our study fulfilled the 1997 ATS criteria. However, the patients in the study of Huang et al. were sputum culture-negative, while the patients in the present study included sputum smear-negative patients as well as sputum culture-negative ones. The 100% positive yield of bronchial washing in Huang et al. study is probably attributable to the fact that bronchial washing of these patients with negative sputum culture must be culture-positive to obtain the diagnosis of MAC pulmonary disease. In the present study, there were 6 patients with negative sputum culture, and all of them showed MAC in the bronchial washing. The most striking difference between the two studies is the positive yield of TBLB. Our patients are considered to have more severe MAC lesion than those of Huang et al., because our patients included sputum smear-negative, but culture-positive patients. Nevertheless, the positive yield of TBLB in our study is about half of that in Huang et al. study. It is possible that this difference is due to the fact that the patients characteristic is different between these two studies.

In patients with MAC pulmonary disease with negative sputum smear, the positive yield of MAC isolation with bronchial washing culture was no greater than with sputum culture (84.6% v.s. 81.0%). However, in this situation, bronchial washing is useful for the diagnosis of MAC pulmonary disease, because we cannot necessarily differentiate infection from casual isolation of MAC based on the sputum examination alone. In addition, positive smear and PCR results of bronchial washing made an early

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Diagnostic criteria</th>
<th>Positive yield of bronchial washing</th>
<th>Positive yield of TBLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanaka et al.</td>
<td>26</td>
<td>CT *</td>
<td>50%</td>
<td>38.5%</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>13</td>
<td>1997 ATS criteria **</td>
<td>100%****</td>
<td>85.7% (n=7)</td>
</tr>
<tr>
<td>Present study</td>
<td>43</td>
<td>1997 ATS criteria ***</td>
<td>84.6%</td>
<td>36.9%</td>
</tr>
</tbody>
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N: patient number
* Patients who had cluster of nodular consolidation with ecticat changes on CT scan.
** Sputum culture negative or unable to product sputum
*** Sputum smear negative or unable to product sputum
**** BAL.

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diagnosis of MAC pulmonary disease possible in 38.5% of cases.

In Huang et al. and our studies, all the patients who revealed specific histology in TBLB also showed positive result in BAL or bronchial washing [3]. Conversely, only a fraction of the patients who showed positive result in BAL or bronchial washing revealed specific histology in TBLB. Therefore, for the diagnosis of MAC pulmonary disease, bronchial washing is considered to be superior to TBLB.

The reported CT findings in MAC pulmonary disease have been predominantly of small nodular infiltrates and bronchiectasis involving mainly the right middle lobe and lingula [7-10]. We examined the relationship of CT findings to bronchial washing results. Positive bronchial washing results were significantly correlated with the presence of small nodular opacity around ectatic bronchi. Accordingly, to isolate MAC, bronchial washing should be done in the segmental or subsegmental bronchus which drains the area revealing small nodular opacity around ectatic bronchi on the CT scan. The small nodular opacity around ectatic bronchi on the CT scan has been reported to represent peribronchial epithelioid granuloma [11]. The density of MAC-induced lesion such as granuloma is considered to be high in such area. Therefore, to wash such area may result in high yield of MAC isolation. The degree of bronchiectasis did not have a significant relationship to the bronchial washing results. There were reportedly granulomas in the wall of ectatic bronchi. The severity of bronchiectasis may be related to the degree of bronchial wall remodeling resulting from granulomatous inflammation, and not to the density of the granuloma itself. Some authors reported that cavitary formation on the CT scan is related to high yield of MAC isolation [5,12]. In our study, only 3 cases showed cavitary change on the CT scan, so we could not ascertain the relationship of such change on the CT scan to the yield of MAC isolation in the bronchial washing.

In summary, in sputum smear-negative patients with MAC pulmonary disease, positive yield of MAC isolation with culture of bronchial washing was no greater than with sputum culture. However, bronchial washing is useful to differentiate infection from casual isolation of MAC. In addition, we could make early diagnosis of MAC pulmonary disease based on smear and PCR results of bronchial washing. To make a diagnosis of MAC, bronchial washing is superior to TBLB, and should be done in the bronchus which drains the area revealing small nodular opacity around ectatic bronchi.

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REFERENCES