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Mycobacterium avium Complex Disease: Prognostic Implication of High-Resolution CT findings

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Keywords

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Running Title: HRCT for pulmonary MAC disease

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Abstract

To evaluate the prognostic implications of computed tomography (CT) findings in assessing responses to treatment in *Mycobacterium avium* complex (MAC) pulmonary disease without underlying lung disease, we correlated high-resolution CT (HRCT) findings based on the results of sputum conversion after anti-MAC therapy. Fifty-nine patients underwent HRCT before treatment and the therapeutic efficacy was evaluated by the results of sputum conversion. Atelectasis, cavities, and pleural thickening at HRCT findings were significantly more frequent ($p = 0.03$, 0.02, and <0.0001, respectively) and extensive ($p = 0.02$, 0.02, and 0.0002, respectively) among patients in the sputum non-converted group than those in the converted group. Furthermore, bronchiectasis was also significantly more extensive among patients in the non-converted group ($p = 0.006$), even though there was no significant difference in frequency between these two groups. These results suggest that HRCT findings are good predictors of response to treatment in MAC pulmonary disease.

Introduction

Nontuberculous mycobacteria (NTM), especially *Mycobacterium avium* complex (MAC), are being recognized with increasing frequency as clinical pathogens of chronic lung disease in immunocompetent patients [1]. These infections have traditionally been difficult and frustrating to treat. Although there are some reports demonstrating the efficacy of clarithromycin (CAM) - containing regimens, current drugs are not as effective as they are in treating pulmonary tuberculosis [2-5].

Several investigators reported radiological findings of patients with MAC pulmonary disease. Moore reviewed the computed tomography (CT) and high-resolution CT (HRCT) findings of patients who had cultures positive for NTM [6]. In their study, bronchiectasis was one of the most common findings in combination with nodules. Swensen et al found that CT findings of small lung nodules in association with bronchiectasis had a high level of sensitivity, specificity, and accuracy in predicting positive cultures for MAC [7]. Hence, HRCT findings are useful for making a diagnosis of MAC pulmonary disease. However, there are few reports describing CT findings in relation to therapeutic outcome in MAC pulmonary disease. We assessed the prognostic implication of HRCT findings based on the results of sputum conversion after anti-MAC treatment. Furthermore, we also evaluated the changes in CT findings on follow-up examinations.

Material and Methods

Patient Selection

We reviewed the medical records of patients who received an initial diagnosis of MAC in our facilities from August 1995 to December 2001. All patients fulfilled the American Thoracic Society criteria for the diagnosis of NTM infection [8].

In this study, patients, who were basically immunocompetent, who had other lung diseases such as chronic obstructive pulmonary disease, interstitial lung disease, lung cancer, or healed tuberculosis were

excluded. Patients who had a history of treatment for MAC infection or pulmonary surgery were also excluded. All patients were treated with a CAM-containing regimen for at least 12 months. Patients who discontinued therapy because of adverse effects were excluded.

Data collection

Clinical data, including causative organism of MAC infection, gender, age, performance status, body mass index, laboratory data (white blood cell count, erythrocyte sedimentation rate, total protein, albumin, C-reactive protein, PaO_2), and dose of clarithromycin were obtained from the patient's medical records.

Specimen Preparation

At least three adequate sputum cultures were obtained from all patients. Specimens stained with Ziel-Neelsen and Gram's stains were reviewed from all cases and cultured for mycobacteria with other bacteria and fungi. Mycobacteria were cultured with 3% Ogawa egg medium (Nissui Pharmaceutical, Tokyo, Japan). An identification of *Mycobacterium avium* and *Mycobacterium intracellulare* was made using the Cobas Amplicor Mycobacterium test (Roche Diagnostics Japan, Tokyo, Japan). All patients were diagnosed from sputum specimens.

CT scans

CT scans were performed with X-Vigor (single-slice helical CT, Toshiba, Tokyo, Japan), X-vision (single-slice helical CT, Toshiba, Tokyo, Japan), Hi-speed Advantages (single-slice helical CT, GE Yokokawa Medical Systems, Tokyo, Japan), or Light-Speed QX/i (multi-slice helical CT, GE Yokokawa Medical Systems, Tokyo, Japan) scanners. The radiographic factors were as follows; X-Vigor (2-mm slice thickness, 20-mm gaps), X-Vision (2-mm slice thickness, 10-mm gaps), HiSpeed Advantage (3-mm slice

thickness, 10-mm gaps), and LightSpeed QX/i (1.25-mm × 4 collimation, 2.5-mm slice thickness, 15-mm gaps). Image data of HRCT were reconstructed with 512 × 512 matrix and 20-25 cm field of view using a high-resolution algorithm. The presence of small nodule (=< 5 mm), nodule (> 5 mm), mass (> 3 cm), bronchiectasis, air space consolidation, atelectasis (lobar atelectasis and segmental atelectasis), cavity formation, hilar or mediastinal nodes >1 cm in diameter, and pleural thickening was evaluated in each lung lobe. In all patients, the number of lung lobes that contained lesions was counted (right upper lobe, right middle lobe, right lower lobe, left upper lobe, lingula, left lower lobe). The finding of bronchiolectasis was also included in bronchiectasis.

In 23 patients, follow-up CT scans were obtained 12 to 47 months (mean 25 months) after the initial scan. The CT findings on the follow-up scan were compared with those on the initial CT scan. In this follow-up CT scan, we assessed the improvement of CT findings, which was defined as disappearance or decrease of each finding. The initial and follow-up CT scan findings were reviewed by two observers (M.S and Y.N) who had no knowledge of the patients' clinical data, and consensus was obtained.

Treatment

All patients were initially treated with a CAM-containing regimen according to the recommendation by the American Thoracic Society [8]. All patients were treated with rifampin (0.3-0.45 g/day), ethambutol (0.5-0.75 g/day), and CAM (0.4-0.8 g/day) with or without the addition of streptomycin for the first two months (SM; 0.4-0.6 g three times weekly). These regimens were subsequently modified individually due to adverse reactions. Treatment was continued for at least 12 months.

Estimation of outcome

Sputum conversion was defined as consecutive negative sputum cultures over a 3 mo period, with the time of conversion defined as the date of the first negative culture. When the patient's condition

improved and excretion of sputum disappeared completely, sputum induction with sterilized 3% NaCl was performed. If the patient could not expectorate sputum even after the sputum induction, it was considered that sputum had converted to negative. Eventually, all patients were divided into two groups. The first group consisted of the patients who converted their sputum to negative (converted group). The other group consisted of the patients who could not convert their sputum to negative (non-converted group).

Statistical analysis

Values were expressed as the mean ± SD in the text and in the Tables. For the statistical evaluation of differences between the two groups, we used Student's t-test and the Mann-Whitney U test for parametric data and non-parametric data, respectively. Fisher's direct way was used for comparison between the two groups. Analysis was completed with a statistical software package (Stat View version 5.0; SAS Institute Japan Inc; Tokyo, Japan), and P-values of less than 0.05 were considered to indicate statistical significance.

Results

Patients/Disease

The total number of patients who satisfied the ATS criteria in our institutions during the study period was 190. Seventy-two patients were excluded because of having underlying lung disease (60 patients) or previous history of treatment for MAC lung disease (12 patients). Forty-five patients were excluded because they were not examined the initial CT scan. A further 14 patients were withdrawn from the study because one of the following occurred: a request for withdrawal from the treatment was made by the patient, lost to follow-up, or adverse events that required the discontinuation of treatment. Fifty-four patients had a positive sputum sample on smear with at least two positive sputum samples on culture. The remaining

5 patients had at least three positive sputum samples on culture with a negative sputum sample on smear. The mean time to sputum conversion was 10.5 ± 9.0 months in the sputum converted group.

Clinical characteristics

The clinical characteristics of patients with MAC pulmonary disease are summarized in Table 1. Although 74% were female, there was no difference in gender between the sputum converted and the non-converted group. Patients in the non-converted group had a significantly higher erythrocyte sedimentation rate (ESR) ($p=0.006$), and higher serum level of C-reactive protein (CRP) ($p=0.01$). No significant difference in the dose of clarithromycin (CAM) per day was observed between the sputum non-converted group and the converted group. In addition, only 5 patients initially received streptomycin (SM); however, there was no significant difference in the result of sputum conversion.

HRCT findings

1. Table 2 outlines the HRCT findings of the patients in the non-converted and converted groups. Atelectasis, cavities, and pleural thickening in HRCT findings were significantly more frequent among patients in the non-converted group than those in the converted group ($p=0.03$, $p=0.02$, $p<0.0001$, respectively). Although a few combinations of more than one HRCT findings were also significantly different in the non-converted group compared to the converted group (all combinations including at least one HRCT finding that was significantly more frequent in the non-converted group by itself, see Table 2), no combination of findings could predict with certainty conversion in the individual patient.
2. Next, we compared the extent of the HRCT findings between the two groups. The findings related to the number of lobes involved, bronchiectasis, as well as atelectasis, cavities, and

pleural thickening were significantly more extensive in patients in the non-converted group than in those in the converted group (Table 3).

3. To investigate the improvements in HRCT findings, we assessed the changes in HRCT findings between the initial and follow-up examination in the available cases. There were no significant differences in improvements in HRCT findings between the non-converted and converted groups. However, in all available cases, improvements of micronodules and nodules were higher than those of bronchiectasis and pleural thickening on follow-up examinations (Table ~~5~~ 4).

Discussion

It is not clear that CT findings could predict the therapeutic outcome in patients with MAC pulmonary disease. Tanaka et al showed that the extent of the disease in chest X-ray did not correlate with the results of sputum conversion in MAC patients treated with CAM-containing regimens [2]. In contrast, Kobashi et al reported the sputum conversion rates were significantly poorer in patients with advanced disease throughout the unilateral lung field [3]. In the present study, we reviewed a consecutive group of MAC patients, and examined the CT findings in relation to the results of sputum conversion. We found atelectasis, cavities, and pleural thickening at HRCT were significantly more frequent findings in patients with therapeutically poor response group. Furthermore, those findings in patients with therapeutically poor response group were significantly more extensive than those in patients with therapeutically good response group. Additionally, the bronchiectasis was also significantly more extensive in patients with therapeutically poor response group. These results suggest HRCT findings might be good predictors of response to treatment in MAC pulmonary disease.

Several investigators reported CT findings of NTM patients without underlying lung disease [6,7,9-15]. In these communications, micronodules (95-100%), bronchiectasis (65-94%), cavity formation (13-43%), air space consolidation (26-62%), and pleural thickening (17-52%) were frequently observed.

Consistent with these reports, in our study, micronodules (100%) and bronchiectasis (76%) were the most frequent findings followed by cavity formation (37%), air space consolidation (22%), and pleural thickening (27%).

Intriguingly, in our study, bronchiectasis was significantly more extensive in the sputum non-converted group than in the converted group, even though there was no significant difference in frequency between these two groups. Fujita et al demonstrated on pathology peribronchiolar lesions, including bronchiolitis and bronchiectasis with granuloma formation, were caused by MAC infection [16]. These findings suggest extensive bronchial lesions represent the progression of NTM disease, while Koh et al. reported CT findings of bronchiectasis involving more than five lobes are highly suggestive of NTM pulmonary disease in patients with bilateral bronchiectasis and bronchiolitis in chest CT [17]. Collectively, extensive bronchiectasis might be an important diagnostic indicator as well as having prognostic implications for NTM.

There are some reports describing changes in CT findings with therapy in NTM patients. Obayashi et al reported that the finding of bronchiectasis worsened in about 2 years in a follow-up study; however, centrilobular nodules did not deteriorate [18]. Kim JS et al reported that improvement of cavitary lesion (24%) and bronchiectasis (32%) was much less than that of nodular shadow (51%) [10]. Furthermore Kim TS et al suggested bronchial nodules evolve into focal bronchiectasis [11]. In our study, consistent with these studies, the findings of pleural thickening or bronchiectasis did not improve. On the other hand, micronodules or nodules improved in 70% of cases. These results suggest that each finding evolved separately. Furthermore, these results indicate small nodules are reversible in response to drug therapy. In contrast, once bronchiectasis is completed, there is little prospect for radiographic improvement.

In our study, patients in the sputum non-converted group had extensive lesions including ‘irreversible’ bronchiectasis in CT findings. In addition, the levels of CRP or ESR in patients in the

non-converted group were significantly higher than those in the converted group. These findings indicate that patients in the non-converted group have active, advanced disease. Although it is not clear when therapy should be started, our findings suggest that early treatment may contribute to a cure of NTM.

It is clear that this retrospective study is bound by several limitations. Although all the patients in this study were treated with a CAM-containing regimen, treatment dose was individually tailored. We recognized two major differences which seemed not to follow ATS criteria in daily practice. The first was a lower dose of clarithromycin, and the second was the choice of rifampin instead of rifabutin. In several studies, a high dose of CAM was significantly more effective than low dose CAM with other companion drugs. However, at present high dose CAM (1000 mg/day) has not been approved for clinical use by the Ministry of Health and Welfare in Japan. A controlled trial will be necessary to determine the appropriate dose of clarithromycin. Although the difference was not significant, the rate of successful treatment was 22 of 26 (85%) in the rifabutin-containing regimen, and 10 of 13 (77%) in the rifampin regimen in the study by Wallace and colleagues [4]. However, the disadvantage of rifabutin is that it causes adverse events, including uveitis and leukopenia, which are infrequent with rifampin. Furthermore, currently rifabutin is not available in Japan. It was not possible to determine whether alternate treatment regimens might have had a differential effect on outcome. Our study contains selection bias. In this retrospective study, some patients were followed by only chest X-ray, but not HRCT. In addition, the percentage of patients with exclusion from this study is relatively high. In order to eliminate those biases and to understand the longitudinal course of HRCT findings, a prospective study will be needed. Since our institutions (Tenryu Hospital, Seirei Mikatahara Hospital) are regional referral centers for mycobacterial diseases, the extent of the CT scan abnormalities reported here may differ substantially from those found in the community. Referral bias might have led us to see patients with more severe disease. Finally a variety of previous CT techniques have superseded by new developments [19]. In the future, the use of more increased resolution of images by

reducing the slice thickness or applying a higher spatial resolution reconstruction algorithm technique may allow us to better understand the outcome of MAC pulmonary disease.

We conclude that HRCT may eventually play a role in clinical evaluation and follow-up of patients with MAC pulmonary disease. A prospective study, with lower drop-out rate and data more complete may provide a stronger evidence of prognostic implication of HRCT in clinical evaluation and follow-up of patients with MAC pulmonary disease.

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Figure Legends

Fig.1. - HRCT findings of MAC pulmonary disease. (a) Pretreatment HRCT scan in a 50-year-old woman demonstrates multiple micronodules in the right middle and lower lobes. (b) Pretreatment HRCT scan in a 75-year-old woman demonstrates mass (33 mm) and pleural thickening in the right upper lobe. Bronchiectasis and nodules are also seen. (c) Pretreatment HRCT scan in a 64-year-old man demonstrates cavity formation with air space consolidation. (d) Pretreatment HRCT scan in a 69-year-old man demonstrates bronchiectasis and atelectasis in right middle lobe. Multiple micronodules are also seen in the right lower lobes.

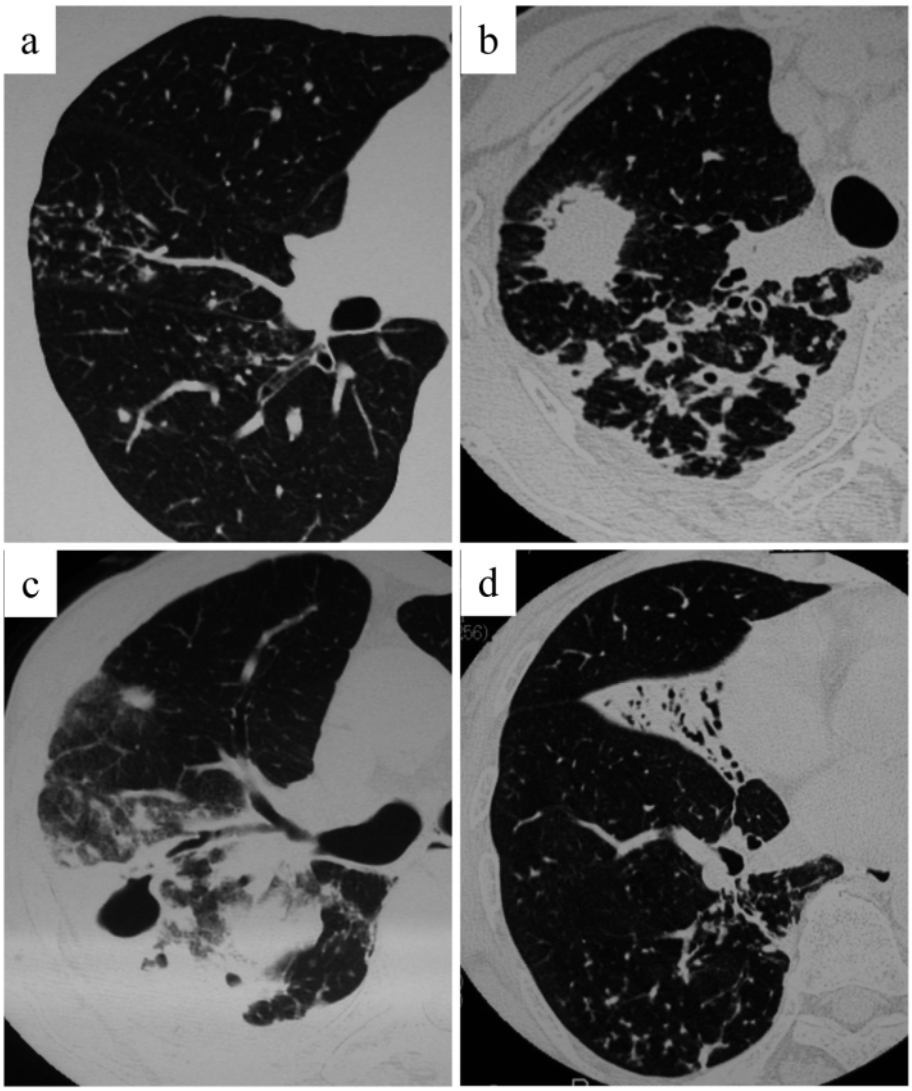

Figure.1

Table 1. – Patients characteristics in patients with MAC pulmonary disease

	Overall (n=59)	Non-converted group (n = 20)	Converted group (n = 39)	*p* Value*
Organism, *M.avium* / *M.intracellulare*	35 / 24	12 / 8	23 / 16	NS
Gender, female / male	44 / 15	13 / 7	31 / 8	NS
Age, yr	67.7 ±15.2	70.9 ± 8.8	66.1 ± 17.6	NS
Symptom				
Cough	28 (47.6%)	9 (45.0%)	19 (48.7%)	NS
Hemoptysis	13 (22.0%)	5 (25.0%)	8 (20.5%)	NS
Fever	10 (16.9%)	2 (10.0%)	8 (20.5%)	NS
Length of symptoms before diagnosis, month	3.5 ± 4.8	2.1 ± 1.7	4.2 ± 5.7	NS
Performance status	1.5 ± 0.9	1.7 ± 0.9	1.4 ± 1.0	NS
BMI, kg/m^2	18.5 ± 2.8	17.3 ± 1.3	19.1 ± 3.21	NS
White Blood Cell, /μl	5,900 ± 2,300	6,300 ± 2,900	5,700 ± 1,800	NS
Erythrocyte sedimentation rate, mm/h	41.2 ± 29.6	56.2 ± 30.9	34.1 ± 28.6	0.006
Total protein, g/dl	7.2 ± 0.5	7.2 ± 0.5	7.1 ± 0.6	NS
Albumin, g/dl	4.0 ± 0.5	3.9 ± 0.6	4.1 ± 0.5	NS
C-reactive protein, mg/dl	1.4 ± 3.0	2.7 ± 4.2	0.8 ± 2.0	0.01
PaO_2, torr	79.3 ± 11.1	80.7 ± 12.3	77.8 ± 9.5	NS
Dose of CAM, mg/day	622 ± 160	569 ± 160	644 ± 158	NS
Initial use of SM, number of patients	5	3	2	NS
Duration of observation period (month)	38.7 ± 17.2	36.3 ± 13.0	39.9 ± 20.8	NS

*: Non-converted group versus converted group, BMI: body mass index, CAM: clarithromycin, SM: streptomycin

Table 2. – Frequencies of HRCT findings in patients with MAC pulmonary disease

	Overall (n=59)	Non-converted group (n=20)	Converted group (n=39)	*p* Value*
Micronodules	59 (100%)	20 (100%)	39 (100%)	NS
Nodules	48 (81.3%)	15 (75%)	32 (82.1%)	NS
Mass	5 (8.5%)	2 (10%)	3 (7.7%)	NS
Consolidation	13 (22.0%)	6 (30%)	7 (17.9%)	NS
Bronchiectasis	45 (76.2%)	18 (90%)	27 (69.2%)	NS
Atelectasis	35 (59.3%)	16 (80%)	19 (48.7%)	0.03
Cavity formation	22 (37.3%)	12 (70%)	10 (25.6%)	0.02
Pleural thickening	16 (27.1%)	12 (70%)	4 (10.2%)	<0.0001
Pleural effusion	5 (8.5%)	2 (10%)	3 (7.7%)	NS
Lymphadenopathy	21 (35.6%)	8 (40%)	13 (33.3%)	NS

*: Non-converted group versus converted group

Table 3. – The numbers of lung lobes involved by the disease in patients with MAC pulmonary disease

	Overall (n=59)	Non-converted group (n=20)	Converted group (n=39)	*p* Value*
Micronodules	3.8 ± 1.6	4.3 ± 1.4	3.6 ± 1.8	NS
Nodules	1.4 ± 1.0	1.1 ± 0.8	1.6 ± 1.2	NS
Mass	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.1	NS
Consolidation	0.5 ± 1.2	0.8 ± 1.5	0.4 ± 1.0	NS
Bronchiectasis	2.1 ± 1.5	2.9 ± 1.8	1.7 ± 1.4	0.006
Atelectasis	1.3 ± 1.3	1.9 ± 1.4	1.0 ± 1.3	0.02
Cavity formation	0.5 ± 0.8	1.0 ± 1.1	0.3 ± 0.7	0.02
Pleural thickening	0.6 ± 1.1	1.2 ± 1.1	0.3 ± 1.0	0.0002

*: Non-converted group versus converted group

Table 4. – Improvements of HRCT findings on follow-up examinations

	Overall	Not-converted group	Converted group	*p* Value*
Micronodules	65% (15/23)	43% (3/7)	75% (12/16)	NS
Nodules	60% (12/20)	20% (1/5)	73% (11/15)	NS
Mass	67% (2/3)	0% (0/0)	67% (2/3)	-
Air space consolidation	71% (5/7)	33% (1/3)	80% (4/5)	NS
Bronchiectasis	5% (1/19)	14% (1/7)	0% (0/12)	NS
Atelectasis	33% (4/12)	20% (1/5)	50% (3/6)	NS
Cavities	30% (3/10)	0% (0/5)	60% (3/5)	NS
Pleural thickening	0% (0/8)	0% (0/6)	0% (0/2)	-

Data are percentages. In parentheses, the numerators are numbers of improvement cases, the denominator are the numbers of available cases. *: Non-converted group versus converted group