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ORIGINAL ARTICLE

Effect of coexisting advanced extrapulmonary solid cancer on progression of *Mycobacterium avium* complex lung disease

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ABSTRACT

Objective: Although *Mycobacterium avium* complex (MAC) lung disease has been shown to be associated with lung cancer and hematologic malignancies, there have been few studies of its relationships with other types of cancer. The aim of this study was to assess the effect that coexisting advanced extrapulmonary solid tumors have on the progression of MAC lung disease. **Methods:** This was a retrospective study of patients diagnosed with MAC lung disease, on the basis of the American Thoracic Society (ATS) criteria, between October of 2005 and March of 2019. The patients were divided into three groups: those with advanced-stage cancer (A-SC group); those with early-stage cancer (E-SC group); and those without cancer (control group). Progression of MAC lung disease was defined as exacerbation seen on imaging. Patient characteristics and the time to progression were compared among the three groups. **Results:** A total of 286 patients met the ATS diagnostic criteria for MAC lung disease, and 128 of those were excluded. Of the remaining 158 patients, 20 (7.0%) were in the A-SC group, 36 (12.6%) were in the E-SC group, and 102 (35.7%) were in the control group. The median time to progression in the A-SC, E-SC, and control groups was 432, 3,595, and 2,829 days, respectively ($p < 0.01$). A proportional hazards model showed that the significant predictors of MAC lung disease progression were advanced-stage cancer (hazard ratio [HR] = 6.096; 95% CI: 2.688-13.826; $p < 0.01$), cavitary lesions (HR = 2.750; 95% CI: 1.306-5.791; $p < 0.01$), and a high Nodule-Infiltration-Cavity-Ectasis score (HR = 1.046; 95% CI: 1.004-1.091; $p = 0.033$). **Conclusions:** A coexisting advanced extrapulmonary solid tumor could hasten the progression of MAC lung disease.

Keywords: Nontuberculous mycobacteria; Mycobacterium avium complex; Neoplasms; Radiography.

INTRODUCTION

The prevalence of lung disease caused by nontuberculous mycobacteria (NTM) is increasing worldwide,[1-4] and *Mycobacterium avium* complex (MAC) lung disease is the most common type.[5-8] However, advances in treatment have improved the prognosis of patients with malignant tumors.[9,10] Although NTM lung disease has been associated with lung cancer and hematologic malignancies,[11-15] there have been few studies of its relationships with other cancers. Therefore, we decided to investigate the relationships that MAC lung disease has with malignancies other than lung cancer and hematologic malignancies. The specific objective of this study was to assess the effect that a coexisting advanced extrapulmonary solid tumor has on the progression of MAC lung disease.

METHODS

This was a retrospective study of patients who underwent AFB testing between October of 2005 and March of 2019 at Yokohama City University Hospital and Yokohama City University Medical Center. We selected patients meeting the American Thoracic Society (ATS) diagnostic criteria for NTM lung disease.[16] We further selected only those with MAC lung disease (caused by infection with *M. avium* or *M. intracellulare*), with or without cancer. The patients who had been diagnosed with cancer after being diagnosed with MAC lung disease were excluded, as were those with lung cancer or hematologic malignancies. The patients with a pre-existing diagnosis of an extrapulmonary solid malignant tumor were divided into two groups: those with advanced-stage cancer and those with early-stage cancer. The advanced-stage cancer group included those having no indication for curative treatment, including surgery and radiation therapy. The early-stage cancer group consisted of those who could be treated curatively. Separate from the advanced-stage cancer group and the early-stage cancer group, we evaluated a control group of patients with MAC lung disease who had no history of cancer or complications. Specifically, patients with chronic respiratory diseases, autoimmune diseases, or diseases that can affect the immune system were excluded.

The groups were compared in terms of baseline patient characteristics such as age; gender; smoking status;

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number of lung segments involved; the *Mycobacterium* species involved; symptoms; AFB smear status; cavitary disease; the Nodule-Infiltration-Cavity-Ectasis (NICE) score[17]; and the history of chemotherapy (defined as having receiving cytotoxic chemotherapy before the diagnosis of MAC lung disease). To assess disease progression, each lung was divided into three segments (upper lobe, middle lobe, and lower lobe for the right lung; and superior segment, lingular segment, and lower lobe for the left lung), and the lesion sites were counted. The lesions counted were recorded as the number of lung segments involved. Lesions were defined as nodules, cavities, or bronchiectasis with multiple small nodules and were assessed by chest CT.

The NICE scoring system was used as another method of image evaluation.[17] The system is used in order to score the extent and contents of NTM lung disease on chest X-rays. In brief, the left and right lungs were each divided into three zones, for a total of six zones. The left and right lungs were divided into the part above the carina, the part between the carina and the lower pulmonary vein, and the part below the lower pulmonary vein. In each zone, each of the four items (N, nodule; I, infiltration; C, cavity; E, ectasis) was assigned a score of 0 if there were no abnormal findings, 1 if there was involvement of < 25% of the zone, 2 if there was involvement of 25-50% of the zone, 3 if there was involvement of 50-75% of the zone, or 4 if there was involvement of > 75% of the zone. Therefore, the maximum score was 96 points (4 points for each of four items in each of six zones).

The main outcome measure was the progression of MAC lung disease, defined as progressively increasing nodules, infiltration, cavities, or bronchiectasis on follow-up chest X-rays,[18,19] as judged by two pulmonologists. Factors that could be predictors of that outcome were identified and analyzed.

The study was approved by the institutional review boards of Yokohama City University Graduate School of Medicine (Reference no. B171200032) and Yokohama City University Medical Center (Reference no. B190300054). The requirement for written informed consent was waived because of the retrospective nature of this study.

Statistical analysis

The times to progression in the advanced-stage cancer, early-stage cancer, and control groups were compared by using Kaplan-Meier curves. A time-to-event model was chosen on the basis of previous studies.[20,21] Multivariate analysis was performed to assess the effect that a coexisting advanced extrapulmonary solid tumor had on the progression of MAC lung disease. Variables were extracted through stepwise regression analysis, and a proportional hazards model was used for the extracted variables. The stepwise regression analysis included the following variables: advanced-stage cancer, early-stage cancer, age, gender, smoking status; number of lung segments involved; the *Mycobacterium* species involved; symptoms; AFB smear status; cavitary disease; NICE score; and history of chemotherapy. By using the proportional hazards model for those variables, with progression of MAC lung disease as the outcome, we were able to identify and analyze the factors that could be predictors of that progression.

Data are presented as mean ± standard deviation or as median (range) values. All statistical analyses were performed with the JMP statistical software package, version 15 (SAS Institute Inc., Cary, NC, USA). Continuous variables were compared with the t-test or the Mann-Whitney U test. Comparisons were made with Pearson's chi-square test or Fisher's exact test for nominal variables. Values of $p < 0.05$ were considered statistically significant, and all tests were two-tailed. Predictors of the progression of MAC lung disease were determined by stepwise regression analysis based on the Akaike information criterion and a proportional hazards model. Kaplan-Meier curves were used in order to compare the time to progression of MAC lung disease by group. A log-rank test was used in order to compare the time to progression of MAC lung disease among the groups.

RESULTS

Figure 1 shows the patient selection process. A total of 286 patients met the ATS criteria, of whom 83 were diagnosed with cancer prior to being diagnosed with MAC lung disease. Of the 83 eligible patients with cancer, 27 had lung cancer or a hematologic malignancy and were therefore excluded. Thus, we included 56 patients with a pre-existing diagnosis of an extrapulmonary solid malignant tumor. Of those 56 patients, 20 were assigned to the advanced-stage cancer group, and 36 were assigned to the early-stage cancer group. A total of 197 patients had no cancer, although 95 of those had a chronic respiratory disease or a disease that could lead to impaired immune function and were excluded. Therefore, the group of patients without complications (the control group) comprised 102 patients.

Table 1 shows the characteristics of the patients. Of the 20 patients in the advanced-stage cancer group, 10 (50.0%) were female, compared with 24 (66.7%) of the 36 patients in the early-stage cancer group and 79 (77.5%) of the 102 patients in the control group, and the difference between the advanced-stage cancer group and the control group was significant ($p = 0.042$). The mean age was significantly higher in the advanced-stage cancer group than in the control group (74.8 ± 7.9 vs. 66.3 ± 11.8 years; $p < 0.01$). In addition, the proportion of never smokers was lower in the advanced-stage cancer group than in the control group (65.0% vs. 81.3%; $p = 0.045$). Furthermore, the mean NICE score at the time of MAC lung disease diagnosis was higher in the advanced-stage cancer group than in the control group (14.8 ± 8.1 vs. 10.2 ± 7.2; $p = 0.013$).

Figure 2 shows the Kaplan-Meier curves for the comparison among the three groups in terms of the

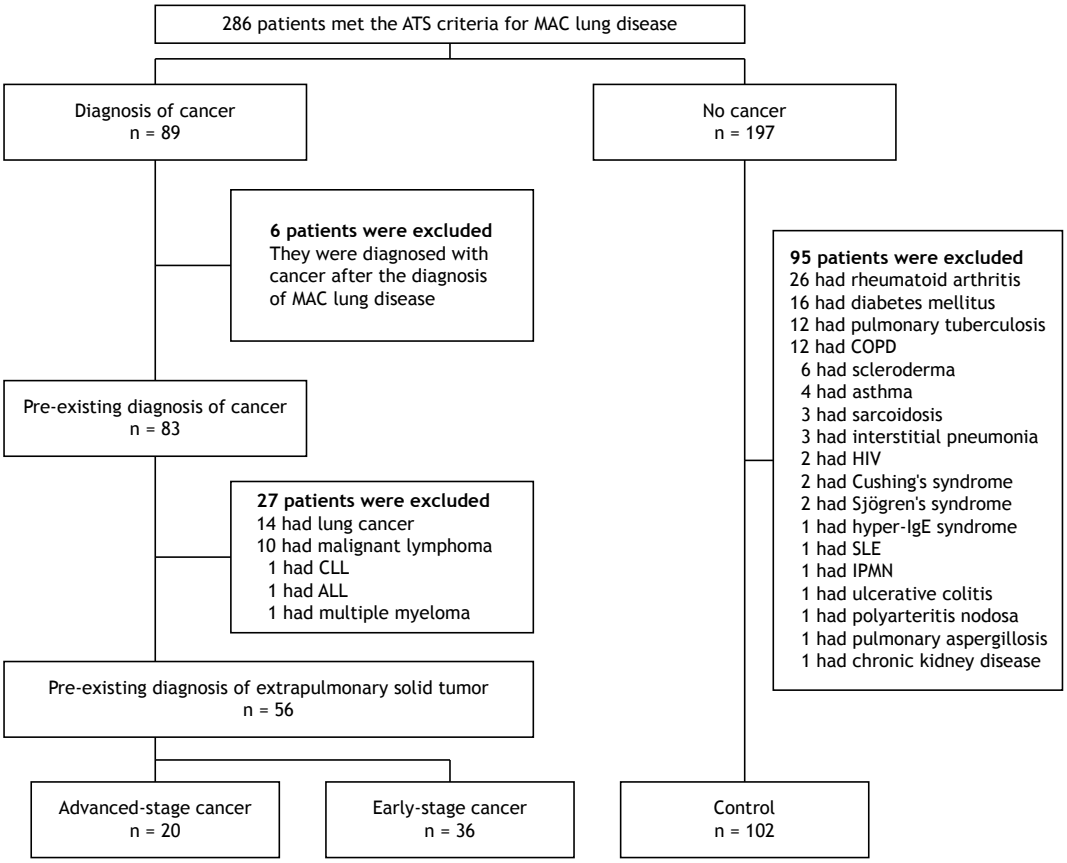

Figure 1. Flow chart of the process of selecting patients with *Mycobacterium avium* complex (MAC) lung disease. ATS: American Thoracic Society; CLL: chronic lymphocytic leukemia; ALL: acute lymphocytic leukemia; SLE: systemic lupus erythematosus; and IPMN: intraductal papillary mucinous neoplasm.

time to progression of MAC lung disease. The median time to progression in the advanced-stage cancer group, early-stage cancer group, and control group was 432, 3,595, and 2,829 days, respectively ($p < 0.01$). In the final analysis, progression of MAC lung disease was seen in 9 (45.0%), 11 (30.6%), and 30 (29.4%) of the patients in the advanced-stage cancer, early-stage cancer, and control groups, respectively. The proportional hazards model with stepwise regression showed that the following were significant predictors of MAC lung disease progression (Table 2): advanced-stage cancer (hazard ratio [HR] = 6.096; 95% CI: 2.688-13.826; $p < 0.01$); cavitary disease (HR = 2.750; 95% CI: 1.306-5.791; $p < 0.01$); and the NICE score (HR = 1.046; 95% CI: 1.004-1.091; $p = 0.033$).

DISCUSSION

The results of the present study suggest that a coexisting advanced extrapulmonary solid tumor can hasten the progression of MAC lung disease. In addition, severely abnormal radiological imaging patterns at the diagnosis of MAC lung disease also seemed to be related to progression.

The incidence of cancer has been shown to be higher at advanced ages and in men.[22] In addition, smoking is thought to be associated with an increased risk of developing not only lung cancer. but also other types of cancer.[23,24] That might explain the fact that the proportions of men and former or current smokers, as well as the mean age, were higher in the advanced-stage cancer group than in the control group. In a search of the literature, we found no clear evidence of an association between chest X-ray severity at the time of MAC lung disease diagnosis and advanced-stage cancer. However, in the present study, the NICE scores were higher in the advanced-stage cancer group patients. That suggests that MAC lung disease can be more severe in patients with an advanced extrapulmonary solid tumor, although further studies are needed in order to test that hypothesis.

In the present study, a coexisting advanced extrapulmonary solid tumor seemed to hasten the progression of MAC lung disease. Previous studies have suggested that a low BMI and the presence of autoimmune diseases can also accelerate the progression of MAC lung disease.[18,25] Coexisting solid tumors, including lung cancer, have also been shown to increase the probability of tuberculosis reactivation.[26] Exposure to chemotherapy has also been shown to accelerate the progression of tuberculosis.[26,27] In

Table 1. Characteristics of patients with *Mycobacterium avium* complex lung disease, by group.[a]

Characteristic	Group			p*
	A-SC (n = 20)	E-SC (n = 36)	Control (n = 102)	
Gender (male/female)	10/10	12/24	23/79	0.042
Age (years)	74.8 ± 7.9	72.1 ± 8.8	66.3 ± 11.8	< 0.01
Smoking status (current/former/never)	0/7/13	1/14/21	0/18/78[†]	0.045
Species[b]	14/6	29/7	92/10	0.055
Symptomatic	9 (45.0)	13 (36.1)	44 (43.1)[‡]	0.642
AFB smear-positive status	13 (65.0)	20 (55.6)	54 (52.9)	0.605
Number of lung segments involved	3 [2-6]	4 [1-6]	4 [1-6]	0.099
NICE score	14.8 ± 8.1	9.9 ± 7.9	10.2 ± 7.2	0.013
Cavitary lesions	6 (30.0)	14 (38.9)	19 (18.6)	0.051
Chemotherapy[c]	7 (35.0)	1 (2.8)	0 (0.0)	< 0.01
Type of cancer[d]				
Gastrointestinal	7 (35.0)	16 (44.4)		
Breast	2 (10.0)	10 (27.8)		
Urinary tract	5 (25.0)	6 (16.7)		
Liver, bile duct, and pancreatic	6 (30.0)			
Gynecologic	3 (15.0)	3 (8.3)		
Head and neck	4 (20.0)	3 (8.3)		
Thyroid		1 (2.8)		
Skin		1 (2.8)		

A-SC: advanced-stage cancer; E-SC: early-stage cancer; and NICE: Nodule-Infiltration-Cavity-Ectasis. [a]Data are presented as n, mean ± SD, median [range], or n (%). [b]*Mycobacterium avium* or *M. intracellulare*. [c]Cytotoxic chemotherapy. [d]In the advanced-stage cancer group, there were six patients who had a history of two or more types of cancer: one had prostate, gastric, and esophageal cancer; one had bladder and laryngeal cancer; one had breast and esophageal cancer; one had hepatocellular and uterine cancer; one had hepatocellular and laryngeal cancer; and one had pancreatic and prostate cancer. In the early-stage cancer group, there were four patients who had a history of two types of cancer: one had renal cell and bladder cancer; one had tongue and esophageal cancer; one had gastric and colorectal cancer; and one had gastric and esophageal cancer. *For the variables age, number of lung segments involved, and NICE score, the p-value represents a comparison between the advanced-stage cancer group and the control group. [†]n = 96. [‡]n = 98.

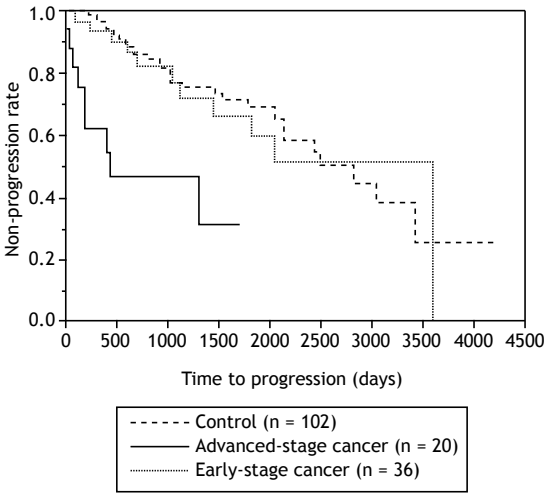

Figure 2. Comparison of the time to progression of *Mycobacterium avium* complex lung disease in each group.

addition, our findings suggest that cavitary lesions and high NICE scores at diagnosis of MAC lung disease favor progression. Previous studies have also shown that the presence of cavitary lesions leads to a worse prognosis in MAC lung disease,[28] as well as that high NICE scores are related to MAC lung disease progression.[18]

Our study has some limitations. First, not all medical records contained complete data regarding smoking status and symptoms. Therefore, the number of patients evaluated was not the same for every variable. In addition, the fact that some of the patients in the advanced-stage cancer group had complications other than the advanced extrapulmonary solid tumor might represent a selection bias. However, the decision was made to include them in order to maintain the statistical power. Furthermore, it was unclear why a coexisting advanced extrapulmonary solid tumor would accelerate the progression of MAC lung disease. Moreover, the small size of our sample of patients with advanced-stage cancer might explain our finding that cytotoxic chemotherapy had no significant influence on MAC lung disease progression. Nevertheless, future studies, including larger patient samples, might reveal such an association.

The reported five-year mortality rate for MAC lung disease exceeds 25%, and the presence of MAC lung disease may be related to an increase in the overall (all-cause) mortality rate and shorter life expectancy.[29,30] In addition, as seen in the present study, MAC lung

Table 2. Multivariate analysis using a proportional hazards model to identify predictors of *Mycobacterium avium* complex lung disease progression.

Variable	HR	95% CI	p
Advanced-stage cancer	6.096	2.688-13.826	< 0.01
Cavitary lesions	2.750	1.306-5.791	< 0.01
NICE score	1.046	1.004-1.091	0.033

HR: hazard ratio; and NICE: Nodule-Infiltration-Cavity-Ectasis.

disease progression may be accelerated by a coexisting advanced extrapulmonary solid tumor, and some patients with MAC lung disease deteriorate rapidly.[31,32] Because advances in treatment have improved the prognosis of patients with cancer year by year,[9,10] it may be necessary to address MAC lung disease that worsens during the treatment of an advanced extrapulmonary solid tumor. Clinicians should consider the possibility of MAC lung disease progression in patients with an advanced extrapulmonary solid tumor.

In conclusion, a coexisting advanced extrapulmonary solid tumor could hasten the progression of MAC lung disease. Therefore, clinicians should exercise caution in the treatment of patients with an advanced extrapulmonary solid tumor who also have MAC lung disease.

AUTHOR CONTRIBUTIONS

RI and KW: conception, administrative support, data collection, data analysis, writing/revision of the manuscript; YS: data collection and analysis; NH: conception and data collection; YH: conception and data analysis; NK and MK: administrative support; and TK: conception and data analysis.

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