Original article

Pulmonary mycobacterium avium complex disease complicated by cancer: an 11-year survey at a single-center

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Abstract

Objective: Pulmonary mycobacterium avium complex (MAC) disease is increasing significantly worldwide. Several studies have investigated the clinical features of pulmonary MAC disease in the setting of cancer. Here, we aimed to clarify the clinical characteristics of patients with cancer with recent onset of pulmonary MAC disease and the effect of cancer on the onset of this disease.

Patients and Methods: Of the 323 consecutive Japanese patients newly diagnosed with pulmonary MAC disease at Jichi Medical University Hospital between 2006–2017, we retrospectively reviewed 79 consecutive patients with cancer.

Results: Seventeen patients had lung cancer (21.0%), while 62 had non-lung cancer. Of the 17 patients with lung cancer, 16 had adenocarcinoma of which 10 had stage I to III disease; 8 of the 10 patients had not received chemotherapy. Sixteen patients with lung cancer had a MAC infection in the ipsilateral lung. Notably, 9 of the 11 lung cancer patients who did not undergo surgery had a MAC infection in the affected lobe. Of the 39 patients with the most common types of non-lung cancer (14 had gastric cancer, 13 had colorectal cancer, and 12 had breast cancer), 22 had stage I to III disease, and 18 of these 22 had not received chemotherapy.

Conclusion: Lung cancer may act as a local factor contributing to the onset of pulmonary MAC disease in the ipsilateral lung. However, the underlying mechanism by which a history of cancer might affect the onset of pulmonary MAC disease remains unclear. Further investigation into this mechanism is needed.

Keywords: mycobacterium avium complex, epidemiology, risk factors, lung cancer

Introduction

The incidence of non-tuberculous mycobacteria (NTM) disease is increasing worldwide, including in the United States, Canada, Australia, and East Asia¹. This trend is also seen in Japan, with the estimated prevalence increasing from 5.7 per 100 thousand population in 2007 to 14.7 per 100 thousand population in 2014². Pulmonary mycobacterium avium complex (MAC) disease accounts for 88% of the total incidence of NTM disease, pulmonary M. kansasii infection, 4.3%; pulmonary M. abscessus infection, 3.3%; and others, 3.6%. Therefore, there is a pressing need to elucidate the features of pulmonary NTM disease, especially pulmonary MAC disease³.

The reported risk factors for pulmonary MAC disease in Western countries include female sex, old age, low BMI, as well as history of diabetes, rheumatoid arthritis treated with tumor necrosis factor inhibitors, tuberculosis, cancer, bronchiectasis, chronic obstructive pulmonary disease, and thoracic skeletal abnormalities⁴. Several studies have investigated the clinical features of pulmonary MAC disease in the setting of cancer¹,⁴.

Against this background, we aimed to clarify the clinical characteristics of patients with cancer with recent onset of pulmonary MAC disease and the effect of cancer on the on-
set of this disease. To evaluate the relationship between the history of cancer and the development of pulmonary MAC disease, we excluded those with new cancer.

### Patients and Methods

#### Study population

We retrospectively reviewed medical records of 323 consecutive patients newly diagnosed with pulmonary MAC disease at Jichi Medical University Hospital (Tochigi Prefecture, East Japan) between January 2006 and August 2017 (excluding pre-existing diseases and cases diagnosed at other hospitals). Those who met the 2008 diagnostic criteria of the Japanese Society for Tuberculosis and the Japanese Respiratory Society, which is based on radiological, pathological, laboratory, and bacteriological findings, were diagnosed with pulmonary MAC disease. Of the 323 patients, we retrospectively reviewed 79 consecutive patients with a history of cancer and investigated their cancer types and treatments. We excluded patients with cancer diagnosed less than 3 months before pulmonary MAC disease.

It was difficult to obtain consent from patients and family members because this was a retrospective study. Therefore, an opt-out consent process was used (via a form posted on our hospital website). The study and consent procedure were approved by the Jichi Medical University Ethics Committee (Approval no.: Rin-A18-015, June 11, 2018).

#### Results

##### Cancers in patients who developed pulmonary MAC disease

The study population comprised 37 men and 42 women. Among these patients, we identified 17 patients with lung cancer (21.0%), 14 with gastric cancer (17.3%), 13 with colon cancer (16.0%), 12 with breast cancer (14.8%), 7 with cervical cancer (8.6%), 4 with lymphoma (4.9%), 4 with prostate cancer (4.9%), 3 with uterine cancer (3.7%), 2 with hepatoma, 2 with oropharynx carcinoma, 2 with esophageal cancer, 2 with bladder cancer, 1 with papillary thyroid cancer, 1 with ovarian cancer, 1 with skin squamous cell carcinoma, 1 with laryngeal cancer, 1 with malignant glioma, and 1 with cancer of unknown primary. Eleven patients had lung cancer alone, 62 had non-lung cancer alone, and 6 had both lung and non-lung cancer.

##### Patients with lung cancer who developed pulmonary MAC disease

The population of patients with lung cancer who recently developed pulmonary MAC disease (n=17) comprised 9 men and 8 women (Table 1). The age distribution pattern was monophasic in both men and women, with a peak in men aged 70–79 years and women aged 60–79 years. Smoking history was present in all male patients (100%), but in only two female patients (25%). Of the 17 patients with lung cancer, 16 had adenocarcinoma and 1 had small cell carcinoma (Table 1). All patients had a history of lung cancer before the diagnosis of pulmonary MAC disease. Clinical stages were stage I in 8 patients, stage II and III in 1 patient each, stage IV/postoperative recurrence in 6 patients, and unknown in 1 patient. At least 10 patients (58.8%) had stage I to III disease. In these 10 patients, treatment was surgery alone (7 patients), radiation therapy alone (1 patient), chemotherapy alone (1 patient), and unknown (1 patient). At least 8 of these patients (80%) did not receive chemotherapy (Table 2). Cancer and MAC lesions were present on the same side of the lung in all 11 patients who were not surgically treated, in the same lobe in 9 patients, and in different lobes in 2 patients. Five of the six patients who were surgically treated had an ipsilateral MAC lesion in a remnant lobe, and only one had a MAC lesion in the contralateral lung (Table 3).

##### Patients with non-lung cancer who developed pulmonary MAC disease

The population of patients with non-lung cancer who newly developed pulmonary MAC disease (n=68) comprised 32 men and 36 women (Table 4). The age distribution pattern was monophasic in both men and women, with a peak in men aged 70–79 years and women aged 60–69 years. Among patients with non-lung cancer, gastric cancer,
colorectal cancer, and breast cancer had the largest number of cases. We extracted these cases and examined the clinical stage and treatment of these three cancers. Of the 39 patients with the most common types of non-lung cancer (14 gastric cancer, 13 colon cancer, and 12 breast cancer), at least 22 cases had stage I to III disease, and 18 of these 22 did not receive chemotherapy. The details are shown in Table 5.

### Table 2 Clinical stages and treatments in patients with lung cancer complicated by pulmonary MAC disease (n=17)

| Stages                        | n  | Treatment, n                                      |
|-------------------------------|----|--------------------------------------------------|
| Stage I                       | 8  | Surgery 6, radiation 1, unknown 1                 |
| Stage II                      | 1  | Surgery 1                                         |
| Stage III                     | 1  | Chemotherapy 1                                   |
| Stage IV/postoperative recurrence | 6  | Chemotherapy 5, best supportive care 1           |
| Unknown                       | 1  | Surgery 1                                         |

### Table 3 Locations of lesions due to lung cancer and pulmonary MAC disease on CT (n=17)

| No.                  | Lung cancer Location of lesion on CT | Pulmonary MAC disease Location of lesion on CT | Shadow on CT | Specimens positive for MAC |
|----------------------|---------------------------------------|-----------------------------------------------|--------------|-----------------------------|
| No lung cancer surgery, with lung cancer and MAC lesions in the same lobe (n=9) | | | | |
| 1                    | Right upper lobe | Right upper lobe | Mass | BALF (right B1) |
| 2                    | Right upper lobe | Right upper lobe | Mass | Sputum, BALF (right B1/2) |
| 3                    | Bilateral, multiple | Bilateral, multiple | Nodular | Sputum, BALF (right B2/4) |
| 4                    | Right lower lobe | Right lower lobe | Nodular | Sputum |
| 5                    | Right lower lobe | Right lower lobe | Mass | Sputum |
| 6                    | Right middle lobe | Right middle lobe | Consolidation | Sputum, BALF (right B8) |
| 7                    | Right upper and lower lobe | Right upper lobe | Consolidation | BALF (right B1) |
| 8                    | Right upper lobe | Right upper, middle, and lower lobe | Consolidation, cavity | Sputum, BALF (right B2) |
| 9                    | Right upper lobe | Right upper lobe, Left upper lobe | Consolidation, cavity, mass | Sputum |

| No lung cancer surgery, with lung cancer and MAC lesions in different lobes on the same side (n=2) | | | | |
| 10                   | Left upper lobe | Left multiple, Right multiple | Nodular | Sputum, BALF (left B1+2) |
| 11                   | Right lower lobe | Right middle lobe, Left lingula | Consolidation | Sputum |

| Lung cancer surgery, with an ipsilateral MAC lesion in a remnant lobe (n=5) | | | | |
| 12                   | Left upper lobectomy | Left lower lobe | Reticular | Sputum |
| 13                   | Right upper lobectomy | Right lower lobe, Left lingula | Nodular | BALF (right B6) |
| 14                   | Right lower lobectomy | Right upper lobe | Nodular | Sputum |
| 15                   | Left upper lobectomy | Left lower lobe | Mass | Sputum |
| 16                   | Left lower lobectomy | Left upper lobe | Cavity | Sputum |

| Lung cancer surgery, with a MAC lesion in a lobe on the contralateral side (n=1) | | | | |
| 17                   | Left upper lobectomy | Right lower lobe | Nodular | Sputum |

MAC: mycobacterium avium complex; BALF: bronchoalveolar lavage fluid.

### Discussion

This study highlighted three key observations. First, pulmonary MAC disease was found to develop most frequently in patients with lung cancer, which suggested a link between lung cancer and the onset of pulmonary MAC disease. This study was limited to patients with a history of lung cancer prior to the diagnosis of pulmonary MAC disease. In Japanese men, the most prevalent cancer is gastric cancer, followed by lung, colon, prostate, liver, and pancreatic cancer. Breast cancer is the most prevalent cancer in Japanese women, followed by colon, gastric, lung, and uterine cancer. Our epidemiological findings were not consistent with these recorded statistics. Lung cancer has been suggested as a local factor contributing to the onset of pulmonary MAC disease, and we observed a similar trend in our results.

The second key observation was that lung cancer and MAC lesions were often present in the same lobe on the same side. This suggested that pulmonary MAC disease can develop out of a disorder of the local environment due to lung cancer. This observation is consistent with another
Japanese report\(^6\). Tamura \textit{et al.} used pathological specimens to investigate cases in which pulmonary NTM disease occurred in lobes affected by lung cancer\(^9\). They noted that NTM invaded and proliferated due to an impairment of the cleaning function of the bronchial mucosa in the vicinity of existing lung lesions or cancer lesions, possibly causing pulmonary NTM disease in the same lobe. Since the present study was a retrospective review of medical records, the

### Table 4 Characteristics of patients with pulmonary MAC disease complicated by non-lung cancer (n=68)

|                      | All (n=68) | Male (n=32) | Female (n=36) |
|----------------------|------------|-------------|---------------|
| Age, median (IQR)    | 69 (62–76) | 71 (66.5–77) | 67 (60.8–71.3) |
| Smoking status, n (%)|            |             |               |
| Former/current smoker| 24 (35.3)  | 22 (68.8)   | 2 (5.3)       |
| Non-smoker           | 44 (64.7)  | 10 (31.2)   | 34 (94.7)     |
| Brinkman index (mean ± SD) | 406.7 ± 713.0 | 852.1 ± 855.3 | 14.5 ± 78.5 |
| Malignant tumor, n (%)|            |             |               |
| Gastric cancer       | 14 (20.6)  | 9 (28.1)    | 5 (13.9)      |
| Colon cancer         | 13 (19.1)  | 7 (21.9)    | 6 (16.7)      |
| Breast cancer        | 12 (17.6)  | 0 (0)       | 12 (33.3)     |
| Cervical cancer      | 7 (10.3)   | 0 (0)       | 7 (19.4)      |
| Lymphoma             | 4 (5.9)    | 4 (12.5)    | 0 (0)         |
| Prostate cancer      | 4 (5.9)    | 4 (12.5)    | 0 (0)         |
| Uterine cancer       | 3 (4.4)    | 0 (0)       | 3 (8.3)       |
| Hepatoma             | 2 (2.9)    | 2 (6.3)     | 0 (0)         |
| Oropharynx carcinoma | 2 (2.9)    | 2 (6.3)     | 0 (0)         |
| Esophageal cancer    | 2 (2.9)    | 1 (3.1)     | 1 (2.8)       |
| Bladder cancer       | 2 (2.9)    | 2 (6.3)     | 0 (0)         |
| Papillary thyroid cancer | 1 (1.5)   | 0 (0)       | 1 (2.8)       |
| Ovarian cancer       | 1 (1.5)    | 0 (0)       | 1 (2.8)       |
| Skin squamous cell carcinoma | 1 (1.5) | 1 (3.1) | 0 (0) |
| Laryngeal cancer     | 1 (1.5)    | 1 (3.1)     | 0 (0)         |
| Malignant glioma     | 1 (1.5)    | 0 (0)       | 1 (2.8)       |
| Cancer of unknown primary | 1 (1.5) | 1 (3.1) | 0 (0) |

### Table 5 Stages and treatment in patients with pulmonary MAC disease complicated by gastric cancer (n=14), colon cancer (n=13), and breast cancer (n=12)

| Stages                            | n   | Treatment, n                                      |
|-----------------------------------|-----|--------------------------------------------------|
| Gastric cancer                    | 14  |                                                  |
| Stage I                           | 7   | Surgery 6, endoscopic therapy 1                  |
| Stage II                          | 1   | Surgery + postoperative adjuvant chemotherapy 1  |
| Stage III                         | 0   |                                                  |
| Stage IV/postoperative recurrence | 2   |                                                  |
| Unknown                           | 4   |                                                  |
| Colon cancer                      | 13  |                                                  |
| Stage I                           | 4   | Surgery 2, endoscopic therapy 2                  |
| Stage II                          | 3   | Surgery 3                                        |
| Stage III                         | 2   | Surgery 2                                        |
| Stage IV/postoperative recurrence | 1   |                                                  |
| Unknown                           | 3   |                                                  |
| Breast cancer                     | 12  |                                                  |
| Stage I                           | 3   | Surgery + postoperative radiation therapy 2, surgery + postoperative adjuvant chemoradiation therapy 1 |
| Stage II                          | 1   | Surgery + postoperative adjuvant chemoradiation therapy 1 |
| Stage III                         | 1   | Surgery + preoperative chemotherapy + postoperative adjuvant chemoradiation therapy 1 |
| Stage IV/postoperative recurrence | 0   |                                                  |
| Unknown                           | 7   |                                                  |
detailed relationship between lesions needs to be further investigated by investigating histopathological tissue specimens.

Our third key observation was that at least 22 of the 39 non-lung cancer patients (14 gastric cancer, 13 colon cancer, and 12 breast cancer) had stage I to III disease, 18 of whom had not received chemotherapy. Impairment of systemic immunity due to the presence of a malignant tumor itself may be associated with the development of pulmonary MAC disease, rather than any immunosuppression by treatment. Evidence for this is limited to case reports and thus the link not clear. Further studies with a control group for comparison are needed.

A strength of this study was that it involved a consecutive series of patients spanning approximately 12 years. Through continuous evaluation, we could assess the influence of the presence and history of cancer or cancer treatment on the onset of pulmonary MAC disease. The limitations of this study were its small number of patients and single-center setting, which may have introduced bias. A future study should involve a larger number of patients and include data from general hospitals. Frequent imaging examinations in cancer patients and the frequent sampling of lung tissue in lung cancer patients can increase the likelihood of detecting pulmonary MAC disease. In addition, many male patients with pulmonary MAC disease were smokers. We could not rule out smoking as a confounding factor in the onset of pulmonary MAC disease and cancer. Additional surveys are necessary to confirm our observations.

**Conclusion**

Our results suggest that lung cancer may be a local factor contributing to the onset of pulmonary MAC disease in the ipsilateral lung. However, this study could not elucidate the mechanism by which a history of cancer might affect the onset of pulmonary MAC disease. The number of patients with a history of cancer who develop pulmonary MAC disease is likely to continue to increase, and this mechanism requires further investigation.

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