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Pulmonary *Mycobacterium avium* Complex Disease Requiring Differentiation from Recurrence of Lung Cancer during the Follow-Up Period for Lung Cancer

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Abstract

Case 1 was a 49-year-old woman who visited with a dry cough. She had an underlying disease of lung adenocarcinoma and received cancer immunotherapy because of an ALK-positive response and several cancer chemotherapies. The clinical effect was a complete response. Chest CT was performed because of continuous dry cough, and a new tumor shadow was recognized in the lingula portion of the left upper lobe. We performed CT-guided lung biopsy and could aspirate pus-fluid. The culture test for acid-fast bacilli was positive and the causative microorganism was identified as *Mycobacterium avium* by the DDH method. The final diagnosis was pulmonary abscess due to *M. avium*. Treatment using combined chemotherapy including CAM was performed and a good clinical response was obtained. Case 2 was a 67-year-old man who had a past history of surgical resection of lung adenocarcinoma eight and two years ago and received several cancer chemotherapies and radiation therapy. Because a new nodular shadow appeared in the right middle lobe one year ago and showed strong positivity on PET/CT, surgical resection was performed with the suspected recurrence of lung cancer. Subsequently, the histological diagnosis was epithelioid granuloma and a culture test of acid-fast bacilli was positive, with the identification of *Mycobacterium intracellulare* by the DDH method. Combined chemotherapy was not performed because the lesion was completely resected. Afterwards, a new nodular shadow appeared in the left lower lobe again and bronchoscopy was performed. Because *M. intracellulare* was isolated from the local specimen, we diagnosed the patient with recurrence of pulmonary MAC disease and combined chemotherapy including CAM was performed for one year. Finally, the nodular lesion disappeared. It is difficult to differentiate pulmonary MAC disease

from lung cancer. Therefore, careful follow-up of patients with lung cancer while keeping in mind the possible complication of pulmonary MAC disease is necessary.

Keywords

Pulmonary *Mycobacterium avium* Complex (MAC) Disease, Lung Cancer, Complication

1. Introduction

Mycobacterium avium complex (MAC) is the most common nontuberculous mycobacterial infectious disease in Japan [1] [2] [3]. The incidence of this disease has been increasing worldwide and accounting for 80% of the identified NTM cases [4] [5] [6]. The nodular bronchiectatic type of pulmonary MAC disease has been reported to show a high rate in elderly women without underlying diseases (54% - 92%) [7] [8]. On the other hand, there are several reports concerning the solitary nodular type of pulmonary MAC disease that required differentiation from lung cancer [9] [10]. Because the radiological findings are similar, it is difficult to distinguish the recurrence of lung cancer from the complication of pulmonary MAC disease. Recently, we encountered two interesting cases of pulmonary MAC disease requiring differentiation from recurrence of lung cancer during the follow-up period for lung cancer. Therefore, we introduce these cases and consideration based on the literature.

2. Case

Case 1: A 49-year old woman with a past history of lung adenocarcinoma (T3N3M1b) and the operation of right renal cell cancer was visited to our hospital complaining of dry cough three year later. She had received cancer immunotherapy such as crizotinib, alectinib, and ceritinib because of an ALK-positive response and standard chemotherapies such as carboplatin plus pemetrexed or carboplatin plus paclitaxel for lung adenocarcinoma during the three years. The clinical effect of cancer immunotherapy and standard chemotherapies were good responses. She had no other underlying diseases and no smoking history. Because dry cough continued for one month, chest CT was performed, which revealed a new tumorous shadow in the lingula of the left upper lobe. There were no abnormal physical findings on admission. Slight anemia (Hb 10.8 g/dL) and mild inflammatory findings (CRP 4.10 mg/dL) were recognized in the peripheral blood or on chemical screening. Although T-SPOT showed a negative response, MAC antibody was positive (2.61 ng/mL). Tumor markers such as CEA and SLX were not elevated. A chest radiograph showed a tumorous shadow in the left lower lung field. Chest CT showed a tumor shadow in the lingula portion of the left upper lobe (**Figure 1**). Because we could not make a definite diagnosis using bronchoscopy, we performed CT guided lung biopsy and could aspirate

pus-fluid. The culture of a pus-fluid specimen generated acid-fast bacilli and DNA-DNA hybridization (DDH) identified *M. avium*. Finally, she was diagnosed with pulmonary abscess due to *M. avium*. Afterwards, treatment using combined chemotherapy consisting of rifampicin (RFP), ethambutol (EB), clarithromycin (CAM), and streptomycin (SM) was performed. A good clinical response was obtained and the tumor shadow was improved on chest CT seven months later (**Figure 2**).

Case 2: A 67-year-old man was visited to our hospital complaining of a newly appeared abnormal chest shadow. He had a smoking history (20 cigarettes/day, 30 years) and a past history of diabetes mellitus, hyperlipidemia and surgical resection of lung adenocarcinoma (T1bN2M0) twice eight and two years ago. He had received standard chemotherapies such as Cisplatin plus paclitaxel or carboplatin plus gemcitabine and radiation therapy. There were no clinical symptoms. There were no abnormal physical findings. There were no abnormal laboratory findings in the peripheral blood or on chemical screening. Because the new nodular shadow appeared in the right middle lobe on chest CT one year ago (**Figure 3**) and showed strong positivity on PET/CT, surgical resection of the right middle lobe was performed with a suspicion of recurrence of lung cancer. Subsequently, the histological diagnosis was epitheloid granuloma with caseating necrosis, the culture of a surgical specimen generated acid-fast bacilli, and the result of DDH was *M. intracellulare*. After the diagnosis of pulmonary MAC disease, the chemotherapy was not performed because the lesion was completely resected. Although he had been followed without treatment, a new nodular shadow appeared in the left lower lobe again on chest CT (**Figure 4**). Mild cough and weight loss (5 kg/one year) were recognized as clinical symptoms. There were no abnormal physical findings. There were no abnormal laboratory findings in the peripheral blood or on chemical screening. Tumor markers such as CEA or SLX were normal. QuantiFERON (QFT) and MAC antibody were also negative. Therefore, bronchoscopy was performed to determine the recurrence of lung cancer or pulmonary MAC disease. Finally, because *M. intracellulare* was isolated from the bronchoscopic specimen, we diagnosed the patient with pulmonary MAC disease. Combined chemotherapy consisting of RFP, EB, and CAM was performed for one year, and the new nodular shadow disappeared (**Figure 5**).

3. Discussion

We recently encountered two patients with pulmonary MAC disease requiring differentiation from recurrence of lung cancer during the follow-up period for lung cancer. Because these two patients had a past history of lung adenocarcinoma including cancer treatment and there was a solitary tumor in the peripheral lung field with strong positivity on PET/CT in case 2, it was difficult to distinguish the recurrence of lung cancer from the solitary nodular type of pulmonary MAC disease. Other common diseases with a solitary pulmonary tumor on chest CT are as follows: primary or metastatic lung cancer, a benign tumor,

and inflammatory granuloma such as tuberculoma. In fact, there were no characteristic radiological findings such as a cavity, calcification, or satellite lesion in our two patients, necessitating CT-guided lung biopsy or surgical resection (bronchscopic lung biopsy) to obtain a correct diagnosis. High FDG uptake on PET/CT imaging was recognized in the solitary tumor in case 2. FDG-PET is capable of demonstrating glucose metabolism and the active lesion regardless of being a benign or malignant lesion. Granulomatous tumors such as tuberculoma or pulmonary NTM disease frequently show positive results [11] [12] [13]. FDG-PET is not a test of malignant disease but of metabolism.

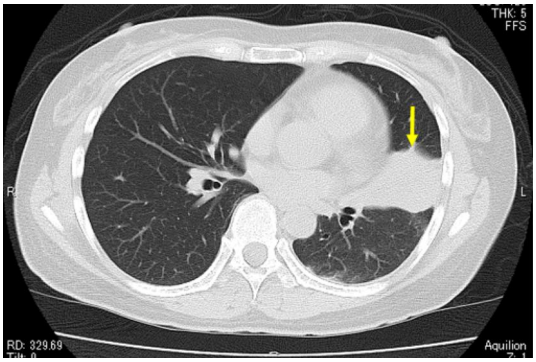

Figure 1. Chest CT showed a tumor shadow in the lingual portion of the left upper lobe (arrow) (Case 1).

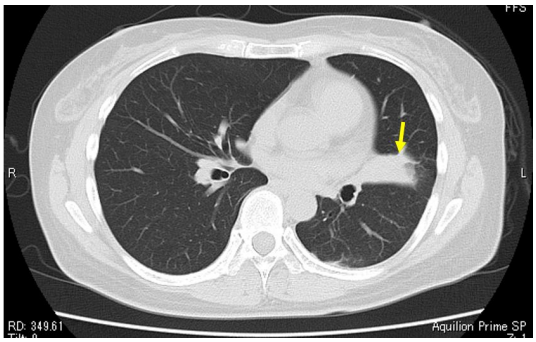

Figure 2. Chest CT showed an improved tumor shadow due to combined chemotherapy seven months later (arrow) (Case 1).

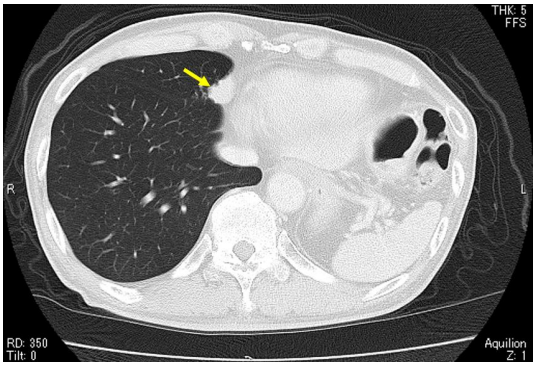

Figure 3. Chest CT showed a nodular shadow in the right middle lobe one year ago (arrow) (Case 2).

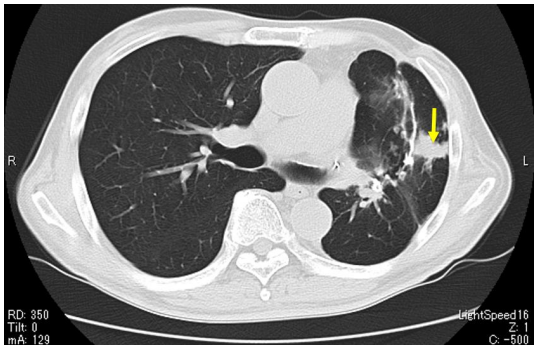

Figure 4. Chest CT on this visit showed a nodular shadow that had newly appeared in the left lower lobe (arrow) (Case 2).

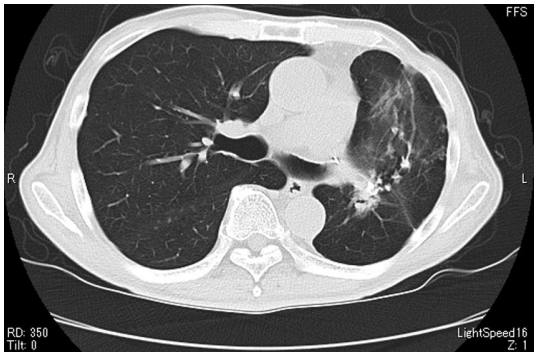

Figure 5. The newly appeared nodular shadow in the left lower lobe had disappeared due to combined chemotherapy one year later (Case 2).

The clinical disease types of pulmonary MAC disease are classified into the following five groups: 1) small nodular and bronchiectatic type, 2) fibrocavitary type, 3) solitary nodular type, 4) hypersensitivity type, and 5) disseminated type. The solitary nodular type occurs the third position in this classification. Gribetz *et al.* first reported 20 patients with a solitary pulmonary nodule due to pulmonary NTM disease in 1982 [14]. Twelve of the 20 were due to MAC infection. Hahm *et al.* and Yonemori *et al.* reported 16 and 24 patients with solitary pulmonary nodules due to MAC infection, respectively [15] [16]. They reported that the solitary nodular type was not so rare among patients with pulmonary MAC disease.

Most of the previous reports regarding the complication of lung cancer and pulmonary MAC disease described clinical characteristics of patients diagnosed with pulmonary MAC disease before lung cancer or diagnosed simultaneously with pulmonary MAC disease and lung cancer [10] [17] [18] [19]. To our knowledge, there are a few reports about the clinical characteristics of patients diagnosed with pulmonary MAC disease after lung cancer [17] [20] [21]. The rate of pulmonary MAC disease diagnosed after lung cancer was low (0.55% - 1.37%) in previous reports [17] [20] compared with that of pulmonary MAC disease diagnosed before lung cancer (2.5% - 7%) [10] [17]. The reason may be that the follow-up period following a diagnosis of pulmonary MAC disease after lung can-

cer was shorter than that of lung cancer after pulmonary MAC disease because of the poor prognosis associated with lung cancer compared with that of pulmonary MAC disease.

Meier *et al.* and Lei *et al.* reported that there were no other apparent underlying risk factors for a high prevalence of pulmonary NTM disease during the follow-up period for lung cancer [21] [22]. However, the risk factor of our two patients was immunosuppression due to chemotherapy. The presence of immunosuppression suggests that the decrease of patient immunity or the damage of lung parenchyma may affect the development of pulmonary MAC disease. Otherwise, our two patients showed lung adenocarcinoma from the peripheral lung field. Pulmonary MAC disease also tends to appear in small bronchi and bronchioles in the peripheral lung field [17]. Therefore, it is possible that destruction of the distal airways due to previous lung cancer may induce MAC airway colonization and the subsequent development of pulmonary MAC disease.

Based on these two patients complicated by pulmonary MAC disease during the follow-up period for lung cancer, because it is difficult to distinguish the recurrence of lung cancer from infectious disease such as pulmonary NTM disease, a positive approach such as transbronchial lung biopsy (TBLB), CT-guided lung biopsy, and video-assisted thoracoscopic surgery (VATS) and careful observation using chest CT are necessary.

4. Conclusion

When we found new nodular shadow in the peripheral shadow during the follow-up period of lung cancer, it is difficult to distinguish the recurrence of lung cancer from the infectious disease such as pulmonary MAC disease. Therefore, we should select a positive approach such as bronchoscopy, CT-guided lung biopsy, and VATS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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