Development of *Mycobacterium avium* complex lung disease in patients with lung cancer on immune checkpoint inhibitors

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Abstract

Immunotherapy with immune checkpoint inhibitors (ICIs), though ameliorates lung cancer, can cause infectious diseases, including tuberculosis, in addition to immune-related non-infectious complications. In clinical setting, efficacy of ICIs to treat mycobacterial infection remains controversial. We report three cases of acute *Mycobacterium avium* complex lung disease during immunotherapy with ICIs.

Keywords: *Mycobacterium avium* complex, lung cancer, immune checkpoint inhibitors, nontuberculous mycobacteria
Introduction

Recent advances in immunotherapy with immune checkpoint inhibitors has improved the outcomes of patients with lung cancer [1, 2]. Although immune checkpoint inhibitors manifest drastic effects, unique adverse events, including skin rash, hepatotoxicity, and endocrine disturbances, are known to occur during treatment. These events are termed immune-related adverse events (irAEs). Among the several types of irAEs, cases of infectious diseases have been increasing steadily [3]. Cases of mycobacterial infection have been particularly alarming because of multiple reported cases [4-7].

We experienced three cases of acute development of Mycobacterium avium complex lung disease (MAC-LD) in patients with lung cancer on immune checkpoint inhibitors. These may emerge as thought-provoking cases.
Case presentation and summary

Case 1.

A 66-year-old woman underwent surgical resection of the right lower lobe lung adenocarcinoma. Her adenocarcinoma recurred after 12 years. Computed tomography (CT) images acquired at that time showed no bronchiectasis or nodules in the bilateral lobes. She received 60-Gy stereotactic radiotherapy. On disease progression, she received one cycle of combined carboplatin and pemetrexed as initial therapy. Because of adverse events, her chemotherapy regimen was revised to gemcitabine.

However, her disease progressed. She received nivolumab as the 3rd line therapy. After 15 cycles of nivolumab, she developed wet cough with excessive sputum. CT images showed infiltration in the upper left lung lobe and lingula. Two consecutive sputum cultures were positive for *Mycobacterium intracellulare* at 17th cycle of nivolumab therapy. A diagnosis of MAC-LD was established and specific treatment for MAC was initiated along with continued nivolumab therapy.
Case 2.

An 80-year-old man was diagnosed with stage 3a right upper lobe non-small cell lung cancer by bronchoscopy. Although lung cancer was diagnosed, CT images only showed bilateral emphysema but no bronchiectasis or nodules. Sequential chemoradiotherapy was initiated. He received one cycle of combined carboplatin and nanoparticle albumin-bound paclitaxel (nabPTX) therapy, followed by radiotherapy (66 Gy). He attained 3 years of progression-free survival. However, the cancer recurred because of a single brain metastasis and multiple lower left nodules. He underwent gamma knife therapy for brain metastasis and was initiated on 2nd line systemic immunotherapy with atezolizumab.

At 23rd cycle of atezolizumab therapy, he developed wet cough and excessive sputum production. CT images revealed multiple reticulonodular infiltrates in the lower left lung lobe. Two consecutive sputum cultures at 24th cycle of atezolizumab were positive for *M. avium* and *M. intracellulare*. He was diagnosed with MAC-LD; specific treatment was initiated for MAC alongside the atezolizumab therapy.
Case 3.

A 66-year-old man was diagnosed with stage 4a advanced squamous cell carcinoma of the right upper lung lobe. Although lung cancer was diagnosed, CT images showed bilateral emphysemas but no bronchiectasis or nodules. He received initial therapy with 6 cycles of combined carboplatin and nabPTX. However, tumor progression was confirmed after 3 months. Second line therapy with nivolumab was initiated. However, disease progression was confirmed after 6 cycles of nivolumab therapy. As the 3rd line therapy, he received 7 cycles of docetaxel, and subsequently, 4th line therapy with atezolizumab after docetaxel failure. Concomitantly, he experienced right main bronchus stenosis because of tumor progression, and palliative radiotherapy (37.5 Gy) was administered. CT images acquired during atezolizumab therapy revealed rapidly worsening right lower lobe infiltration.

Two consecutive sputum cultures at the 4th cycle of atezolizumab therapy were positive for *M. intracellulare*, and a diagnosis of MAC-LD was established. However, because of severe debilitation, treatment for MAC-LD was not initiated and atezolizumab immunotherapy was discontinued.
Summary of cases

Table 1 shows the summary of all 3 cases. In this study, CT images were retrospectively reviewed to assess possible changes of MAC-LD predating ICI immunotherapy. All patients had advanced lung cancer and received cytotoxic chemotherapy before treatment with ICIs. Moreover, they received thoracic radiotherapy before the pathogenesis of MAC-LD. ICI immunotherapy was continued in two patients after they were diagnosed with MAC-LD. The median time to MAC-LD diagnosis from induction of initial ICI were 17 months (range, 17–19 months).

Discussion

We experienced three acute cases of MAC-LD during ICI immunotherapy. Previous reports indicate that development of tuberculosis during ICI immunotherapy has become an emerging concern [4-7]. Multiple cases of tuberculosis were suspected reactivation of latent infection. Some authors have suggested the development of tuberculosis to be similar to immune reconstitution inflammatory syndrome [4, 7]. A similar presentation is expected of nontuberculous mycobacterial infection;
however, till date, no paper had reported the development of nontuberculous mycobacterial infection.

In our three cases, no fibro-cavitary or reticulonodular shadow was noted that could indicate nontuberculous mycobacteria (NTM) infection at the initial diagnosis of lung cancer. Therefore, it is unclear whether MAC-LD developed from reactivation of existing disease or whether it was a de novo infection.

Although the precise mechanisms underlying MAC-LD are unknown, anti-PD-1/PD-L1 antibodies are known to have possible anti-microbial effects that are mediated by upregulation of T cell-mediated immunity [8]. A previous report suggested favorable effect of nivolumab for the treatment of *Mycobacterium abscessus* lung disease [9]. Our present cases might partly reflect this paradoxical reaction, i.e., overresponse to mycobacteria. In contrast, Barber et al. reported that PD-1/PD-L1 knockout mice displayed increased susceptibility to tuberculosis through enhanced CD4 T cell-mediated tissue destruction [10]. In patients receiving ICIs, Barber et al. also discovered similar profiles for CD4 T cell, CD8 T cell, and T cell-mediated cytokine dynamics [11]. These data suggested that Th1 function with anti-PD-1/PD-L1 antibodies might cause the development of tuberculosis. In actual clinical settings, treatment with anti-PD-1/PD-L1 antibodies is expected to
show similar responses. Therefore, the effects of ICIs with regard to mycobacterial diseases in clinical setting remains controversial.

Alternatively, ICI immunotherapy might initiate a state of autoimmunity that mimics diseases like rheumatoid arthritis, which are known to be strongly associated with NTM-LD. Well-designed population-based studies are required to investigate such causal associations. Cumulative experience will reveal the complete picture. Presently, all patients had advanced stage lung cancer and received relatively long-term treatment, including cytotoxic chemotherapy; therefore, the influence of both the cancer and the treatment in the development of MAC-LD cannot be ignored. Furthermore, cytotoxic chemotherapy can exacerbate NTM disease [12]. Previous cytotoxic chemotherapy before induction of ICIs might favor the clinical outcome moderately.

The following alternate interpretation is also important. Japan has one of the highest burdens of NTM globally [13, 14]. Moreover, ICI immunotherapy is becoming popular in Japan. Therefore, physicians in high burden of NTM should pay more attention to the development of MAC-LD during immunotherapy regimens with ICIs.
Conclusion

Physicians should be cautious towards the development of MAC-LD in patients on immunotherapy with ICIs, especially in countries such as Japan, which has a high burden of NTM.
Conflicts of interest

All authors declare no conflicts of interest.

Patients consent

We have obtained written consent forms from all patients described in this study.

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Table 1. Characteristics of the patients who developed *Mycobacterium avium* complex lung disease

|                              | Case 1   | Case 2                | Case 3                |
|------------------------------|----------|-----------------------|-----------------------|
| Age at diagnosis of MAC, years| 78       | 80                    | 66                    |
| Sex                          | Female   | Male                  | Male                  |
| Smoking status (pack-year)   | Never    | 45                    | 20                    |
| Cavities/Bronchiectasis before ICI | None     | None                  | None                  |
| Histopathology               | Adenocarcinoma | Not otherwise specified | Squamous cell carcinoma |
| Staging at diagnosis         | Post-operative recurrence | cT1bN2M0; stage 3a | cT4N2M1a; stage 4a |
| Driver oncogene alteration   | wild type | wild type             | NE                    |
| PD-L1 expression             | NE       | NE                    | <1%                   |
| Type of ICI                  | Nivolumab | Atezolizumab          | Nivolumab + Atezolizumab |
| Infected MAC strain          | *M. intracellulare* | *M. avium + M. intracellulare* | *M. intracellulare* |
| Time to MAC-LD diagnosis*, month | 17       | 17                    | 19**                  |
| Cycles of ICI, number        | 38       | 24                    | 6 (nivolumab) + 4 (atezolizumab) |
| Prior radiotherapy           | 60 Gy    | 60 Gy                 | 37.5 Gy               |
Prior chemotherapy

| Line  | Treatment 1          | Treatment 2          | Treatment 3          |
|-------|----------------------|----------------------|----------------------|
| 1st   | Carboplatin + Pemetrexed | Carboplatin + nabPTX | Carboplatin + nabPTX |
| 2nd   | Gemcitabine            | -                    | Nivolumab            |
| 3rd   | -                     | -                    | Docetaxel            |
|       | Response to MAC treatment | Good              | Fair                 | No medication       |

MAC, Mycobacterium avium complex; NE, not evaluated; PD-L1, programmed cell death-ligand 1; ICI, immune checkpoint inhibitor; nabPTX, nanoparticle albumin-bound paclitaxel

*Time from initiation of immune checkpoint inhibitor therapy to diagnosis of Mycobacterium avium complex lung disease

**Duration included that of docetaxel treatment