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【 CASE REPORT 】

Safe Concurrent Use of Anti-tuberculosis Drugs and Pembrolizumab in a Patient with Non-small-cell Lung Cancer Who Was Infected with *Mycobacterium tuberculosis*

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Abstract:
A 68-year-old Japanese man was diagnosed with lung adenocarcinoma stage IVB. We introduced a first-line chemotherapy of four cycles of carboplatin and pemetrexed and pembrolizumab, followed by pemetrexed and pembrolizumab maintenance therapy. Approximately four months after anticancer therapy, a small nodule appeared in the right peripheral S3 lesion. After five months, the nodule was confirmed as a *Mycobacterium tuberculosis* (TB) nodule. We initiated anti-TB therapy without stopping pembrolizumab, and the right S3 nodule shrank immediately. This report supports the concurrent use of anti-TB treatment with an immune checkpoint inhibitor when the TB infection area is limited.

Key words: pembrolizumab, lung cancer, tuberculosis, adverse event, immune checkpoint inhibitor

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Introduction

Lung cancer is the most common cause of cancer-related death worldwide. Recently, the emergence of immune checkpoint inhibitors (ICIs) for the treatment of advanced lung cancer has resulted in considerable improvements in the prognosis of lung cancer (1). Pembrolizumab is an ICI that binds to programmed cell death-1 (PD-1) on immune cells to disrupt the interaction of PD-1 with the programmed cell death ligand-1 (PD-L1) and PD-L2 ligands. ICIs are less toxic than conventional cytotoxic chemotherapy but are associated with unique adverse events known as immune-related adverse events (irAEs).

Mycobacterium tuberculosis infection (TB) is a global infectious disease; the number of TB incident cases worldwide in 2015 was 10.2 million, and that of TB-related deaths was 1.3 million (2). Furthermore, approximately 16,000 individuals develop TB annually in Japan, with over 2,000 TB-related deaths (3). Patients with lung cancer often develop TB simultaneously (4). Although several cases of TB development during ICI treatment in patients with lung cancer have been reported (5-7), the influence of ICIs on TB remains unclear. Furthermore, the best treatment strategy for TB that develops during ICI treatment remains unknown.

We herein report a patient with advanced lung cancer who developed TB during pembrolizumab treatment and received safe TB treatment while continuing pembrolizumab.

Case Report

We encountered a 68-year-old Japanese man who was a current smoker (50 pack-years) and a heavy drinker. His Eastern Cooperative Oncology Group performance status was 0. He was diagnosed with lung adenocarcinoma stage IVB (T3N2M1c) in our hospital. The patient had a history of bleeding from a cavernous hemangioma in the brain 10 months before the diagnosis of lung cancer. The primary

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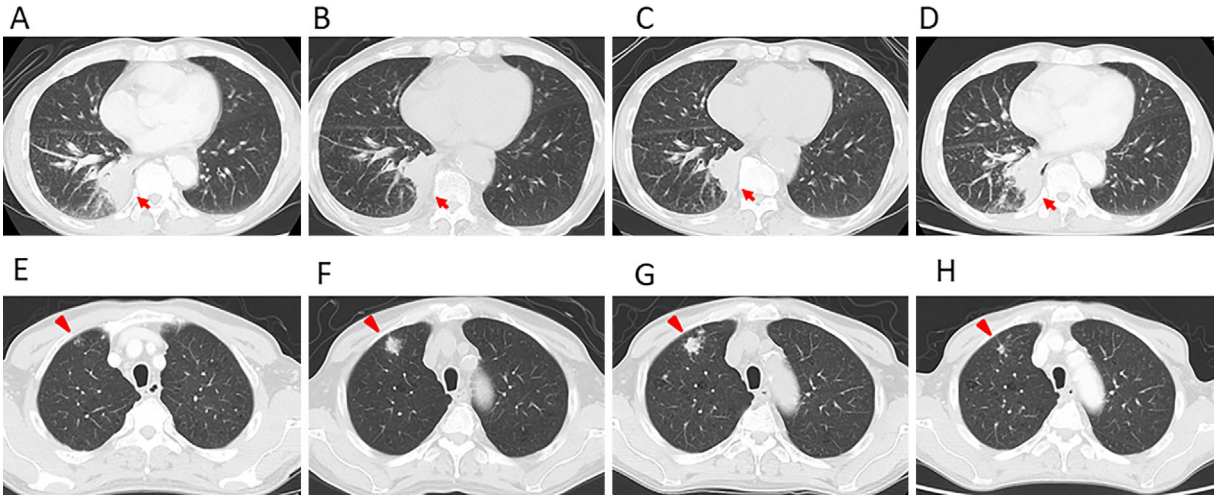

Figure 1. Computed tomography images of the primary lesion of lung cancer (arrows) in the right lower lobe on (A) at the start of anticancer therapy, (B) 4 months later, (C) 7 months later, and (D) 57 days after from the start of anti-TB treatment as well as computed tomography images of TB in the right S3 lesion (arrowheads) (E) at the start of anticancer therapy, (F) 4 months later, (G) 7 months later, and (H) 57 days after from the start of anti-TB treatment.

lung cancer lesion with a maximum diameter of 59 mm was located in the right lower lobe (Fig. 1A). Mediastinal lymphadenopathy and two brain metastases, 7.0 and 4.0 mm in size, were observed. Adenocarcinoma was diagnosed based on the pathological examination of a biopsy specimen from the primary lesion obtained by bronchoscopy.

A mutation analysis of the biopsied tissue revealed that the tumor had neither an epidermal growth factor receptor gene mutation nor an echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase fusion. Owing to the shortage of biopsy tissue, the presence of a variant with c-ros oncogene 1 translocation and valine-glutamine substitution in codon 600 of the serine/threonine kinase *BRAF* could not be determined. The PD-L1 expression with a tumor proportion score of 1-24% was confirmed. As serum hepatitis B virus (HBV)-DNA was detected (<0.1 IU/mL), entecavir was administered until negative conversion.

After stereotactic ablative surgery of the 2 small brain metastases, we introduced first-line chemotherapy of 4 cycles of carboplatin (area under the curve =5) and pemetrexed (500 mg/m^2) and pembrolizumab (200 mg/body), followed by pemetrexed (500 mg/m^2) and pembrolizumab (200 mg/body) maintenance therapy. Owing to gradually worsening anemia, pemetrexed was stopped after two cycles of maintenance therapy, and only pembrolizumab was continued.

Approximately 4 months after treatment initiation, a 1.9-mm nodule appeared in the right S3 lesion (Fig. 1B), whereas the lung cancer showed some response to the treatment (Fig. 1F). When retrospectively reviewed, very small nodules were confirmed in the right S3 lesion at the time of the diagnosis of lung cancer (Fig. 1E). Because there were no respiratory symptoms or elevation in the C-reactive protein (CRP) level (0.09 mg/dL), pembrolizumab administration was continued. After three months (seven months after anticancer therapy initiation), there was no significant change in the right S3 nodule in terms of the size or lung cancer (Fig. 1C and G). We conducted three consecutive sputum tests for acid-fast bacilli. Although all smears of the sputum samples were negative, the culture was positive for acid-fast bacilli 17 days after incubation, and the causative agent was confirmed to be *M. tuberculosis* by polymerase chain reaction. We also conducted the QuantiFERON-TB Gold Plus (QFT) test, and the results were negative.

We started anti-TB medication using a combination of isoniazid 0.3 g/day, rifampicin 0.6 g/day, ethambutol 0.75 g/day, and pyrazinamide 1.2 g/day without stopping pembrolizumab therapy. After anti-TB treatment, the nodule in the upper right S3 shrank immediately (Fig. 1H and Fig. 2). Around one month after anti-TB therapy, liver dysfunction was observed in the patient. By discontinuing anti-TB drugs, the liver disorder was immediately alleviated. No other major adverse events occurred, and there was no significant change in the size of the lung cancer at one month after TB treatment. After the liver disorder was alleviated, anti-TB treatment was resumed by changing the anti-TB drugs. Anti-TB treatment is ongoing at 10 months after resumption and will be completed after a total of 12 months.

Discussion

We encountered a patient with non-small-cell lung cancer (NSCLC) who developed TB during pembrolizumab treatment. Notably, we were able to safely introduce anti-TB therapy without stopping pembrolizumab treatment. To our knowledge, this is the first report of initiating anti-TB therapy without discontinuing ICI treatment in a patient with advanced NSCLC.

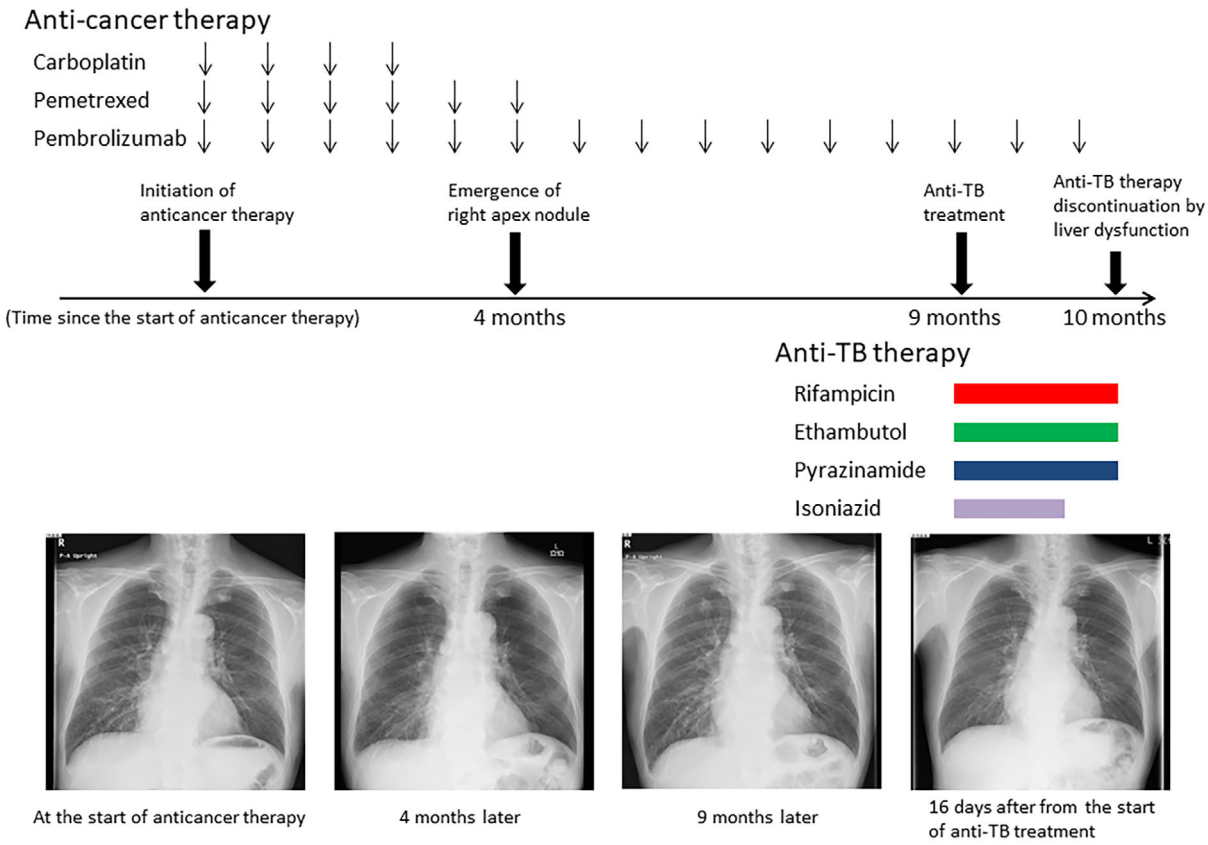

Figure 2. **Clinical course of the present case from the initiation of anticancer therapy. Chest X-ray (bottom) was performed at the start of anticancer therapy, 4 months later, 9 months later, and 16 days after from the start of anti-TB treatment (sequentially from the left). Anti-TB treatment was started nine months from the start of anticancer therapy. In the upper right lesion, the TB nodule gradually appeared and disappeared after anti-TB treatment.**

Lung cancer and TB rarely occur simultaneously. Our patient had important risk factors for TB, such as smoking and polydipsia. Reportedly, 1.38% of patients with lung cancer developed TB in Japan in 2016 (4). However, information on the association between ICI treatment and TB incidence is limited. Several cases of TB development during ICI treatment have been reported (6-8). The inhibition of PD-1 might induce TB via excessive tumor necrosis factor-α secretion (9). In South Korea, of 1,144 patients with lung cancer who received ICIs, only 3 (0.3%) developed TB; of these 3 patients, 2 received systemic steroid therapy before TB development (5). In Japan, among 297 patients with lung cancer receiving ICIs, 5 (1.7%) developed TB (10). Although these findings suggest that ICI treatment does not necessarily affect the incidence of TB in patients with advanced NSCLC, subsequent caution and routine screening for TB in patients with lung cancer during treatment with ICI and cytotoxic agents have been proposed (11). In the present case, the QFT test result was negative, suggesting new-onset TB, rather than the recurrence of latent TB. However, given that there were very small nodules in the same lesion of TB at the diagnosis of lung cancer, the possibility of false-negative of QFT and recurrence should be considered.

The PD-1/PD-L1 axis plays an important role in cancer immunity and infectious diseases (12). Anti PD-1/PD-L1 blockade activates not only cytotoxic T cells but also regulatory T cells, one of the causes of hyper-progressive disease in cancer treatment. *Mycobacterium abscessus* pulmonary disease, well known as a refractory chronic pulmonary infectious disease, improved after the initiation of nivolumab in a patient with NSCLC (13). This suggests that ICIs might have some favorable influence on chronic diseases via the activation of T lymphocytes. However, ICIs might trigger infectious diseases via the activation of regulatory T cells (14). In the present case, the TB nodule showed only a slight change during five months of pembrolizumab maintenance monotherapy.

Another major concern for physicians is whether or not ICI therapy affects the TB treatment. A paradoxical response, defined as clinical or radiological worsening, is often observed in patients receiving anti-TB treatment. The frequency of a paradoxical response during TB treatment has been reported to be 3.3-14%, and such a response is more likely to occur when the spread of TB is broad and/or associated with a significantly elevated CRP level (15). The paradoxical response is considered to occur because of the allergic response to the tuberculosis component in the anti-

TB treatment (15). Because ICI activates T lymphocytes, there is concern regarding whether or not ICIs might induce a paradoxical response. In fact, Takata et al. reported a paradoxical response after the initiation of anti-TB therapy in a patient who developed TB during nivolumab treatment (8). In the present case, at the time of the TB diagnosis, pembrolizumab had been administered for five months since the appearance of a small TB nodule, and there was no significant change in the size of the TB nodule during this period. Furthermore, the serum CRP level was normal. As the risk of a paradoxical response was considered to be low, we carefully started anti-TB treatment without stopping pembrolizumab, and the TB nodule shrank immediately. Although liver dysfunction appeared one month after anti-TB medication, it was promptly alleviated by stopping the anti-TB drugs. While liver dysfunction has been suggested to be caused by anti-TB drugs rather than an irAE, it is difficult to completely distinguish them.

Despite the increasing risk of TB development with ICI treatment, information on the treatment of TB that develops during ICI treatment is limited. Murakami et al. reported a case of TB that developed during pembrolizumab treatment in a patient with NSCLC. Although they discontinued pembrolizumab and started anti-TB treatment, due to the recurrence of lung cancer, they resumed pembrolizumab (16). Similar to our case, a patient with Merkel cell carcinoma who developed mild TB during pembrolizumab treatment was safely treated with anti-TB drugs without pembrolizumab discontinuation (6). We recommend concurrent treatment with ICIs and anti-TB drugs if a patient with lung cancer develops mild TB during ICI treatment.

It is essential to clarify the association between ICIs and TB development and establish effective treatment strategies. Although our case report provides some insights into this association, a larger cohort study is warranted.

The patient provided his written informed consent for the publication of this case and any identifying images or data.

Author's disclosure of potential Conflicts of Interest (COI).
Hiroyasu Kaneda: Others, MSD. Shigeki Mitsuoka: Others, MSD. Tomoya Kawaguchi: Others, MSD.

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