Case report

Pembrolizumab-associated bronchiolitis in an elderly lung cancer patient required the treatment with an inhaled corticosteroid, erythromycin and bronchodilators

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have been used to treat lung cancer. Several types of ICI-related interstitial lung diseases have been reported, including organizing pneumonia, non-specific interstitial pneumonia, and diffuse alveolar damage. However, pembrolizumab-associated bronchiolitis requiring treatment for persistent cough has not yet been reported. Here, we describe a patient who developed dry cough while being treated with pembrolizumab for lung adenocarcinoma. Radiography and lung biopsy findings indicated bronchiolitis. His cough improved after the discontinuation of pembrolizumab and treatment with erythromycin, an inhaled corticosteroid, a long-acting muscarinic antagonist, and a long-acting β2 agonist.

1. Introduction

Immune checkpoint inhibitors (ICIs) have been used to treat non-small cell lung cancer and other malignancies, such as melanoma. ICIs activate the immune system to produce anti-tumor effects via mechanisms different from those of cytotoxic chemotherapy. Specific side effects of ICIs, also known as immune-related adverse events (irAEs), have been reported [1]. Among several irAEs, interstitial lung disease (ILD) may be life-threatening. Patients with ILD related to ICI (ICI-ILDs) present several types of radiographic patterns on computed tomography (CT), including organizing pneumonia (OP), non-specific interstitial pneumonia (NSIP), and diffuse alveolar damage (DAD) [2,3]. ICI-associated bronchiolitis is very rare [2,3]; Delaunay et al. reported five cases of this pattern [3]. Blanchard et al. and Ueno et al. reported a case with pembrolizumab-induced bronchiolitis [4] and pneumonitis [5], respectively. However, to the best of our knowledge, there are no cases of pembrolizumab-induced bronchiolitis with persistent cough even after treatment with respiratory drugs.

When serious irAEs occur, ICIs should be discontinued and the irAEs should be treated with systemic glucocorticoids [2]. However, glucocorticoids have many adverse effects, such as hyperglycemia, infection and osteoporosis. In addition, because they suppress the immune system, the immune-mediated anti-tumor effects initially induced by the ICI may be diminished [5]. Therefore, avoiding oral glucocorticoids may maintain the results of the ICI therapy and prevent the side effects of glucocorticoids. Here, we describe the case of an elderly patient with lung cancer with pembrolizumab-associated bronchiolitis who required treatment to improve persistent cough.

2. Case presentation

A 76-year-old man with a 37.5 pack-year history of smoking was admitted to our hospital for the assessment of a right upper lung mass observed on chest CT (Fig. 1A). The chest CT also revealed right axillary lymphadenopathy and diffuse small pulmonary nodules (Fig. 1B), indicating extra- and intrapulmonary metastases. Biopsy of the axillary lymph nodes revealed lung adenocarcinoma. He was treated with carboplatin and nab-paclitaxel as the first line chemotherapy.

After four weeks of treatment, his chest radiography revealed rapid enlargement of a right axillary lymph node (Fig. 2A), suggesting progression of the lung cancer. Immunohistochemistry performed with 22C3 pharmDX (Agilent, Tokyo, Japan) on the tumor biopsy specimen revealed a programmed death-ligand 1 (PD-L1) tumor proportion score of ≥95%. Based on these results, second-line treatment with pembrolizumab (2 mg/kg, every 3 weeks) was initiated. Although the lesions appeared to increase in size as revealed by chest radiographs obtained during the first course, this radiological finding was thought to represent pseudo-progression, and treatment with pembrolizumab was
During the second course, chest radiography revealed reduction in the lesion size, and the treatment with pembrolizumab was continued for a total of five courses.

After the fifth course, the patient started experiencing dry cough. His body temperature was 36.7 °C, blood pressure was 140/63 mmHg, heart rate was 88 bpm, and percutaneous oxygen saturation was 97%. Physical examination, including chest auscultation, was unremarkable. Peripheral blood and serum tests results indicated slight inflammation based on the elevated serum C-reactive protein levels; however, the patient's white blood cell count and serum Krebs von den Lungen-6 levels were normal (Table 1). Pulmonary function tests results indicated the worsening of obstruction [FVC, 2.57 L (83.0%); FEV1, 1.51 L/s; FEV1/FVC, 58.8%; %FEV1, 60.5%] compared with the results before treatment with pembrolizumab [FVC, 2.99 L (96.6%); FEV1, 1.99 L/s; FEV1/FVC, 66.6%; %FEV1, 79.5%]. Chest CT revealed diffuse micronodules (Fig. 2B), suggesting diffuse bronchiolitis. The patient was treated with azithromycin for 3 days; however, neither his cough nor the micronodules on chest radiography improved. Bronchoscopy was performed, and cytology of the bronchoalveolar lavage fluid (BALF) revealed an increased number of neutrophils in the BALF. Histologically, transbronchial lung biopsy specimens contained inflammatory cell infiltrates in the bronchioles, including lymphocytes; however, there were no specific histological characteristics of OP, NSIP, DAD, or diffuse panbronchiolitis (DPB) (Fig. 2C). No bacteria, including acid-fast bacilli and Mycobacterium tuberculosis, were isolated from the BALF or sputum. Based on all these findings, the patient was diagnosed with bronchiolitis type of ICI-ILD [2,3]. Treatment with pembrolizumab was discontinued, and he was treated with low-dose erythromycin (400 mg/day). As the patient complained of persistent cough, he was treated with a long-acting muscarinic antagonist and a long-acting β2 agonist. An inhaled corticosteroid was subsequently administered when the cough only slightly improved. With this regimen, the cough finally resolved. The lung mass decreased in size, and the micronodules suggesting bronchiolitis also improved (Fig. 3).

3. Discussion

The present case is remarkable for two reasons. First, it demonstrates that pembrolizumab-associated bronchiolitis can occur. Second, discontinuation of pembrolizumab and treatment directed at bronchiolitis improved the patient's condition without the need for systemic steroids; furthermore, the tumor continued to regress.

Among the various reported irAEs, ICI-ILD has been estimated to occur in 3%–5% of all patients treated with ICIs [7,8]. The precise mechanisms underlying ICI-ILD are uncertain; however, irAEs are considered to develop because of a unique set of toxicities due to their mechanisms of action [3]. Moreover, the cytotoxic effects induced by ICIs affect cells other than the tumor, e.g., in the bronchioles and...
M. tuberculosis chest radiographs improved. PD-1 therapy is reportedly associated with not prescribed azithromycin; however, treatment with this drug alone was possible causes of bronchiolitis. Because infections with the BALF or sputum. In addition, the histological findings of the biopsy specimens were not consistent with that of the other types of ILD, although oral corticosteroids are generally recommended to treat ICI-ILDs, our patient improved without using them. The disadvantage of systemic corticosteroids is that they regulate T cells. Therefore, oral corticosteroids may decrease any ongoing antitumor effects via T cells. A recent study showed that corticosteroid uses were associated with decreases in the overall response rate, progression-free survival time, and overall survival in patients treated with PD-L1 inhibitors [6]. Thus, if patients with irAEs can be treated without using systemic corticosteroids, the therapeutic effects of the ICI may persist even if the ICI itself must be discontinued. In fact, our patient continued to demonstrate partial tumor response for 6 months after pembrolizumab was discontinued and also without any other chemotherapy.

To the best of our knowledge, this is the first case of pembrolizumab-associated bronchiolitis that was treated with an inhaled corticosteroid, erythromycin, and bronchodilators; however, the patient's cough improved by treatment without oral corticosteroids. This case illustrates that this type of ICI-ILD can be improved by treatment without oral corticosteroids, which may maintain the anti-tumor benefits of pembrolizumab.

4. Conclusion

It is important to consider drug-related bronchiolitis in patients with non-small cell lung cancer who are being treated with pembrolizumab. Treatment with a combination of macrolides, inhaled corticosteroids, a long-acting muscarinic antagonist, and a long-acting β2 agonist along with the discontinuation of pembrolizumab can successfully improve refractory cough in such cases without the need of systemic steroids.

Author's contribution

All authors made substantial contributions to the investigations presented in this manuscript. Takafumi Yamaya wrote the article. Takafumi Yamaya, Hwang Moon Hee, Takayuki Aoyagi, Tatsuya Ogimoto, Naoki Yamada, Ryoichi Ishikawa, Erika Nakai, Kenta Nishi, Takafumi Yamaya, Hwang Moon Hee, Takayuki Aoyagi, Tatsuya Ogimoto, Naoki Yamada, Ryoichi Ishikawa, Erika Nakai, Kenta Nishi, Chie Yoshimura, and Yasuo Nishizaka collected clinical data. Takafumi Yamaya drafted the manuscript with the help of Yasuo Nishizaka. All authors read and approved the final manuscript.

Competing of interest

None.

Conflicts of interest

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Conflicts of interest and source of funding

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