Pulmonary Lymphangitis Carcinomatosa Mimicking Immunotherapy-Related Interstitial Pneumonitis: A Case Report

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Keywords
Non-small cell lung cancer · Immunotherapy-related adverse event · Interstitial pneumonia · Pulmonary lymphangitis carcinomatosa

Abstract
While immunotherapy with immune checkpoint inhibitors has achieved promising effects in advanced lung cancer treatment, it can induce some unique adverse events, known as immunotherapy-related adverse events (irAEs). Immunotherapy-related interstitial pneumonitis is one of the irAEs, and its incidence is reported as 3.5–8.3% in phase III trials of nivolumab with or without ipilimumab for advanced non-small cell lung cancer patients. However, in the real-world setting, pathology is not routinely used in the diagnostic process of interstitial pneumonitis because diagnosis is usually made using chest computed tomography (CT). Here, we report an educational case of pathologically diagnosed pulmonary lymphangitis carcinomatosa mimicking immunotherapy-related interstitial pneumonitis. The patient was diagnosed with advanced adenocarcinoma of the right lung (stage IVA) and received immunotherapy for 6 months. He manifested acute respiratory failure, and a chest CT scan revealed the emergence of diffuse grand-grass opacity predominantly in the left lung. Immunotherapy-induced interstitial pneumonitis was clinically suspected because the primary lesion was stable, and the level of the serum carcinoembryonic antigen decreased. However, the detection of adenocarcinoma cells in the bronchoalveolar lavage sample from the left lung confirmed the diagnosis of pulmonary lymphangitis carcinomatosa. Clinicians’ assumptions can sometimes mislead treatment methods; hence, this case draws attention to the perils of misdiagnoses.
Introduction

Immunotherapy with immune checkpoint inhibitors (ICIs) has shown promising effects in advanced lung cancer treatment [1–5]. In recent years, ICIs have been administered not only as monotherapies but also as combination therapy with cytotoxic agents [1–3] or different types of ICIs [4, 5]. Despite the promising efficacy of combination immunotherapy, the predictive biomarkers of response or toxicity have not yet been clarified, and identifying them is an urgent unmet need regardless of the cancer type [6–8].

Immunotherapy can induce some unique adverse events, known as immunotherapy-related adverse events (irAEs), which are sometimes life-threatening or difficult to manage [9, 10]. Immunotherapy-related interstitial pneumonitis is one of the irAEs [11], and its incidence is reported as 3.5–8.3% in phase III trials of nivolumab with or without ipilimumab for advanced non-small cell lung cancer patients [4, 5, 12, 13]. However, pathology is not routinely used in the diagnostic process of interstitial pneumonitis because diagnosis is usually made using chest computed tomography (CT) [14]. Here, we report a case of pathologically diagnosed pulmonary lymphangitis carcinomatosa mimicking immunotherapy-related interstitial pneumonitis.

Case Report/Case Presentation

A 67-year-old man diagnosed with advanced adenocarcinoma of the right lung (cT3N0M1a, stage IVA) was referred to our hospital in March 2021 (Fig. 1a). His medical history was notable for squamous cell carcinoma of the right lung, for which he had received chemoradiotherapy and lung lobectomy of the right upper lobe 19 years ago. He had a smoking history of 30 pack-years. Regarding the adenocarcinoma, no driver oncogenes were detected, and the tumor proportion score of programmed cell death ligand-1 was 20–30%. In April, immunochemotherapy with nivolumab, ipilimumab, carboplatin, and pemetrexed was started as the induction therapy. He received 11 cycles of nivolumab (360 mg intravenously every 3 weeks) and six cycles of ipilimumab (1 mg/kg intravenously every 6 weeks) combined with carboplatin and pemetrexed for the first two cycles (every 3 weeks). Carcinoembryonic antigen levels gradually decreased from 23.8 ng/mL at referral to 5.2 ng/mL at the 10th cycle of nivolumab. A CT scan at the 11th cycle of nivolumab revealed a stable disease (Fig. 1b).

On October 20 (the scheduled day of the 12th cycle of nivolumab), he complained of dyspnea and manifested acute respiratory failure (arterial blood oxygen saturation measured by pulse oximetry was 85% under room air conditions). A chest CT scan revealed the emergence of diffuse grand-grass opacity predominantly in the left lower lobe of the lung (Fig. 1c). The primary lesions in the right lung did not progress (Fig. 1d). The serum carcinoembryonic antigen was 6.2 ng/mL. We initially suspected interstitial pneumonitis induced by immunotherapy. Other differential diagnoses, such as infection or pulmonary lymphangitis carcinomatosa, were thought to be less likely but should be ruled out. The next day, he underwent bronchoscopy and bronchoalveolar lavage (BAL) fluid sampling. Transbronchial lung biopsy (TBLB) was withheld concerning complications (particularly pneumothorax). The detection of adenocarcinoma cells in the BAL sample confirmed the diagnosis of pulmonary lymphangitis carcinomatosa (Fig. 2). Before this result was revealed, although oral administration of prednisolone (1 mg/kg/day) was started at provisional diagnosis of immunotherapy-related interstitial pneumonia, his respiratory condition did not improve. He was diagnosed with progressive disease and was scheduled to receive second-line treatment. After the administration of two cycles of docetaxel and ramucirumab, a CT scan revealed a regression of diffuse grand-grass opacity in the lungs (Fig. 1e).
Discussion/Conclusion

Here, we report a case of pulmonary lymphangitis carcinomatosa mimicking immunotherapy-related interstitial pneumonitis, in which bronchoscopy (BAL) allowed diagnosis by distinguishing these diseases. Immunotherapy with ICIs can induce irAEs. Immunotherapy-related interstitial pneumonitis is one of the irAEs, and its incidence was 5.3% and 8.3% of advanced NSCLC patients who were administered nivolumab and ipilimumab, respectively, in phase III clinical trials (CheckMate 9LA [4] and 227 [5] trials). A systematic review and
meta-analysis including 20 trials of PD-1 inhibitors for melanoma, NSCLC, and renal cell carcinoma reported that the incidence of pneumonitis during PD-1 inhibitor monotherapy was 2.7% for any grade and 0.8% for grade 3 or higher. It tends to be higher among NSCLC patients [15] and in patients who received combination therapy [16].

When patients experience dyspnea, cough, or fatigue during immunotherapy, interstitial pneumonitis should be suspected. Differential diagnoses are divergent (e.g., infectious pneumonia, pleural effusion, pulmonary embolism, pulmonary metastases, or lymphangitis). Physical examinations or chest CT imaging are usually helpful in the diagnostic process. Bronchoscopy (BAL) is also helpful, especially in ruling out infections and cancer progression. In the clinical practice guidelines of the American Society of Clinical Oncology or European Society for Medical Oncology, bronchoscopy with BAL is recommended for pneumonitis of grade 2 or higher (routine TBLB is not recommended) [17, 18]. However, bronchoscopy cannot always be performed because of its invasiveness, especially in patients with moderate or severe respiratory failure. In clinical settings, pathology is not routinely used in the diagnostic process of interstitial pneumonitis because diagnosis is made mainly by chest CT imaging. Baba et al. [14] reported that only 15 out of 144 patients (10%) underwent bronchoscopy for the diagnosis of pneumonitis according to nationwide nivolumab postmarketing surveillance in Japan. There should be some cases of pulmonary lymphangitis carcinomatosa in cases diagnosed and reported as immune-related interstitial pneumonitis without pathological assessments.

In this case, because the response to immunotherapy (combination of two cycles of cytotoxic chemotherapy) was stable and serum tumor marker levels decreased, we clinically suspected treatment-induced interstitial pneumonitis and less suspected cancer progression. Fortunately, his respiratory condition was considered feasible for bronchoscopy, and cytological examination revealed adenocarcinoma cells from the BAL sample. Without performing bronchoscopy, he would be managed as treatment-induced pneumonitis and would experience an unnecessary delay in recognizing progressive disease and starting the next line of treatment.

A limitation of this case report is that we did not perform a TBLB and histological assessment concerning the complication of pneumothorax. The possibility of cancer cells contaminating the BAL sample was not ruled out rigorously. However, his clinical course was not compatible with immunotherapy-induced pneumonitis because steroid administration did not improve his respiratory condition, and the second-line treatment regressed the opacity in the lungs.

In conclusion, this case implies the difficulty in clinically distinguishing between immunotherapy-related interstitial pneumonitis and pulmonary lymphangitis carcinomatosa without pathological assessment. Bronchoscopy should be considered if the patient’s respiratory condition is feasible. This leads to a confirmation of the diagnosis and a prompt shift to the next line of treatment in cases of cancer progression.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.
Conflict of Interest Statement

The authors have no conflicts of interests to declare.

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Author Contributions

Takuma Imakita drafted the manuscript. Takuma Imakita, Kohei Fujita, Osamu Kanai, and Tadashi Mio were involved in the treatment of the patient. Kohei Fujita, Osamu Kanai, and Tadashi Mio contributed to the manuscript review before submission and approved the final version of the manuscript.

Data Availability Statement

All available data for this research are included in this article. Further enquiries can be directed to the corresponding author.

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