Clinical Case Report

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Platinum-doublet chemotherapy followed by pembrolizumab therapy for lung cancer with lymphangitis carcinomatosa mimicking interstitial pneumonitis

A case report

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Abstract

Rationale: Pembrolizumab, an immune-checkpoint inhibitor (ICI), has been shown to be effective for treatment-naive patients with non–small cell lung cancer (NSCLC) and high expression of programmed death-ligand 1 (PD-L1). Therefore, treatment regimens containing pembrolizumab have become a standard therapy for these patients. However, the use of pembrolizumab is limited owing to the side effects of ICIs.

Patient concerns and diagnoses: The patient was a 65-year-old man with a left lung mass surrounded by interstitial shadow. The tumor was diagnosed as adenocarcinoma, cT4N3M0, stage IIIC, and the tumor cells showed high PD-L1 expression. It was unclear whether the interstitial shadow was interstitial lung disease (ILD) or lymphangitis carcinomatosa.

Interventions and outcomes: The patient received carboplatin and *nab*-paclitaxel, a less risky regimen for ILD, as the first-line therapy. Administration of 2 cycles of this regimen markedly improved both the tumor diameter and interstitial shadow. The interstitial shadow was clinically diagnosed as lymphangitis carcinomatosa and not ILD. Subsequently, the patient was treated with pembrolizumab, and the tumor showed much further shrinkage with no deterioration of the interstitial shadow. To date, the patient is alive with no complaints and no disease progression, and has continued pembrolizumab treatment for a total of 12 months.

Lessons: In patients at a high risk of ICI-related side effects, platinum-doublet chemotherapy may be permitted as the first-line therapy for NSCLC with high PD-L1 expression. However, if the risk associated with ICIs is resolved, early switching from chemotherapy to pembrolizumab might be desirable, even if the chemotherapy is effective.

Abbreviations: CT = computed tomography, ICI = immune-checkpoint inhibitor, ILD = interstitial lung disease, NSCLC = non–small cell lung cancer, PD-L1 = programmed death-ligand 1.

Keywords: induction chemotherapy, interstitial lung disease, lymphangitis carcinomatosa, non–small cell lung cancer, pembrolizumab

1. Introduction

Pembrolizumab is an immune-checkpoint inhibitor (ICI) that has been shown to be efficacious for treatment-naive non–small cell lung cancer (NSCLC) with a high expression of programmed death-ligand 1 (PD-L1).[1,2] Regardless of PD-L1 expression, pembrolizumab with platinum-doublet chemotherapy has been shown to be effective for treatment-naive NSCLC.[3,4] Therefore, treatment regimens containing pembrolizumab have become one of the standard therapies for these patients. However, there is a reluctance to administer pembrolizumab to patients with high risk for ICI-related side effects.[5,6]

Herein, we report a case of NSCLC with high PD-L1 expression surrounded by interstitial shadow treated with pembrolizumab therapy following induction platinum-doublet chemotherapy. At the initiation of treatment, it was unclear whether the interstitial shadow was interstitial lung disease (ILD) or lymphangitis carcinomatosa; therefore, platinum-doublet chemotherapy was initiated as the first-line therapy.

2. Case report

A 65-year-old man with a 57 pack-year smoking history presented to a hospital with a left lung mass identified based on chest x-ray results (Fig. 1A). No personal medical history was reported, except for his pulmonary nontuberculous mycobacte-

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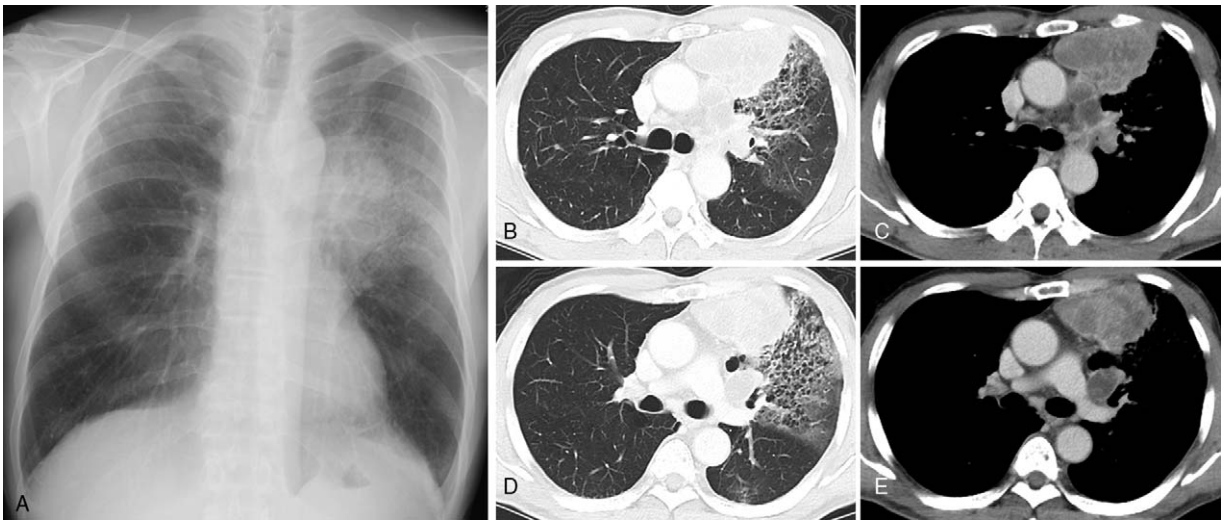

Figure 1. A, Chest x-ray and (B, C, D, and E) computed tomography (CT) before anticancer treatments. The chest x-ray shows the left lung mass, and the CT scans show the mass surrounded by the interstitial shadow.

rium infection 13 years ago. A physical examination revealed no remarkable abnormalities. Chest and abdominal computed tomography (CT) scans were performed, and the mass surrounded by interstitial shadow was detected (Fig. 1B, C, D, and E). Laboratory examinations revealed elevated levels of cytokeratin-19 fragments (CYFRA 21-1; 21.4 ng/mL). The patient underwent CT-guided needle biopsy of the pulmonary tumor, and it was diagnosed as an adenocarcinoma via pathological examination. The tumor showed high PD-L1 expression (tumor proportion score: 100%). Epidermal growth factor receptor mutation, anaplastic lymphoma kinase gene rearrangement, and c-ros oncogene 1 rearrangement were not detected. After further examination, he was diagnosed with adenocarcinoma, cT4N3M0, stage IIIC.

He was referred to our hospital for treatment of lung cancer; however, the interstitial shadow existed broadly around the tumor. Therefore, carboplatin and *nab*-paclitaxel were initiated as first-line therapy. Carboplatin was administered on day 1 at a dose of targeted area under the concentration-time curve of 6, and *nab*-paclitaxel was administered at a dose of 80 mg/m^2 on days 1, 8, and 15, every 4 weeks. Two cycles of this regimen were administered, and the chest x-ray and CT scan revealed a marked reduction of tumor diameter and improvement of interstitial shadow (Fig. 2A, B, and C); therefore, the interstitial shadow was clinically diagnosed as lymphangitis carcinomatosa and not ILD. The serum concentration of CYFRA 21-1 was also markedly improved (1.7 ng/mL). Only grade 1 adverse events, such as anemia, thrombocytopenia, anorexia, constipation, and alopecia, were observed.

Subsequently, he was administered pembrolizumab (200 mg/body, every 3 weeks). After 6 cycles of pembrolizumab administration, chest x-ray and CT scan showed much further shrinkage of the tumor, with no deterioration of the interstitial shadow (Fig. 2D, E, and F); no elevation of CYFRA 21-1 was observed (1.5 ng/mL). In addition, no adverse events were observed. To date, the patient is alive with no complaints and no disease progression, and has continued pembrolizumab treatment for a total of 12 months.

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

3. Discussion

In this case report, we have presented 2 important clinical observations. First, platinum-doublet chemotherapy might be considered a first-line therapy for patients with NSCLC at high risk of ICI-related side effects. Pre-existing autoimmune diseases[5] and ILD[6] are well known risk factors for ICI therapy. In particular, acute exacerbation of ILD is a life-threatening adverse event of ICIs.[6] In the present case, an interstitial shadow was detected on the chest CT; therefore, carboplatin and *nab*-paclitaxel, a less risky regimen for ILD,[7,8] were administered. Fortunately, chemotherapy was effective for the tumor and did not induce any severe adverse events, and the interstitial shadow improved.

Second, if the risks associated with ICI are resolved, early switching from chemotherapy to pembrolizumab may be desirable, even if the chemotherapy is effective. It has been described that early use of pembrolizumab showed beneficial effects on the overall survival of patients with NSCLC with high PD-L1 expression. In a randomized phase III study, survival after first-line pembrolizumab therapy for NSCLC with high PD-L1 expression was superior to that after first-line platinum-doublet chemotherapy despite the use of pembrolizumab after chemotherapy.[1,2] The reason for this is unclear; however, it may be attributed to undernutrition, bone marrow suppression, and the deterioration of performance status caused by continuation of chemotherapy. In cases with high PD-L1 expression NSCLC, as in the present case, the early use of pembrolizumab might be better than continuation of first-line chemotherapy.

The choice of therapy for NSCLC with high PD-L1 expression is controversial; it is unclear whether pembrolizumab monotherapy or pembrolizumab with platinum-doublet chemotherapy as second-line therapy is better in cases such as the present case. It has been demonstrated that first-line pembrolizumab with platinum-doublet chemotherapy was superior to platinum-doublet chemotherapy in terms of survival of advanced non-squamous NSCLC regardless of PD-L1 expression status.[3,4] However, the efficacy of addition of pembrolizumab to carboplatin and *nab*-paclitaxel has been demonstrated only on

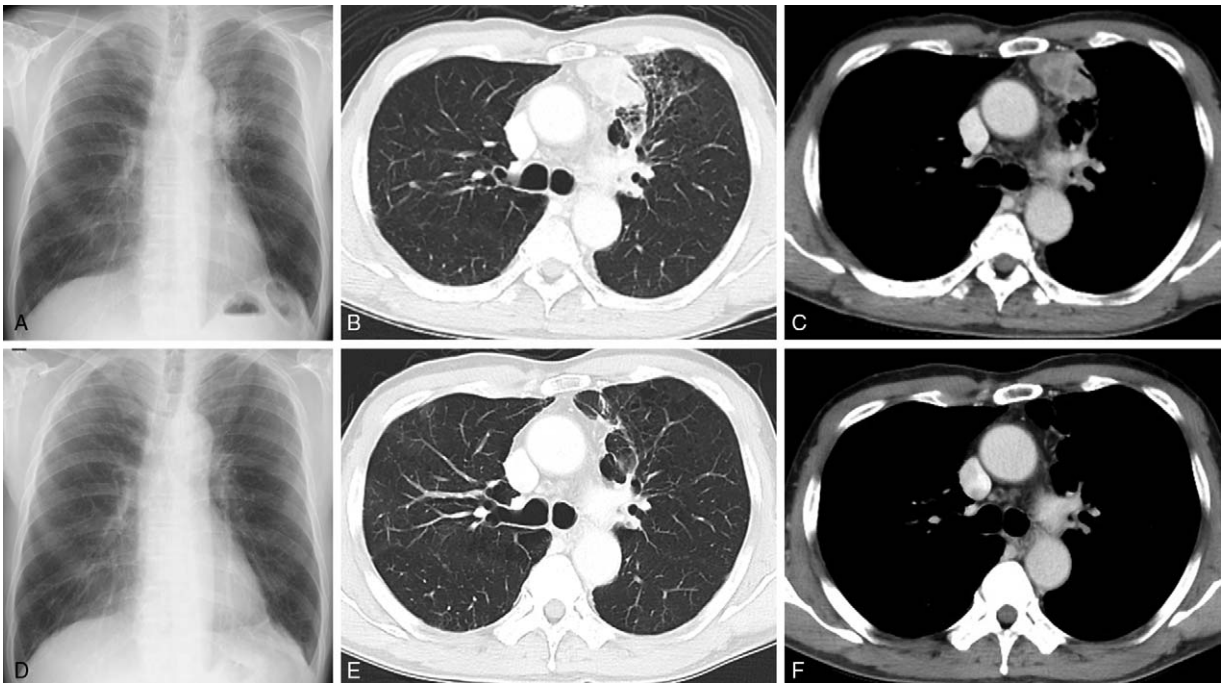

Figure 2. A, Chest x-ray and (B, C) computed tomography (CT) after 2 cycles of chemotherapy. The chest x-ray and CT scans show the marked reduction in tumor diameter and improvement of the interstitial shadow. D, Chest x-ray and (E, F) CT scans after 6 cycles of pembrolizumab administration. The chest x-ray and CT scans show much greater shrinkage of the tumor, with no deterioration of interstitial shadow.

the survival of patients with squamous cell carcinoma[4] and not on the survival of patients with nonsquamous NSCLC. Moreover, for NSCLC with 50% or greater PD-L1 expression, both pembrolizumab monotherapy and pembrolizumab with platinum plus pemetrexed chemotherapy resulted in a 12-month overall survival rate of approximately 70%.[1,3] Pembrolizumab monotherapy may be used as second-line therapy in cases such as the present case with high PD-L1 expression.

The reduction in tumor burden might be an explanation for the efficacy of pembrolizumab in the present case. It has been reported that the magnitude of reinvigoration of exhausted-phenotype CD8 T cells after pembrolizumab administration was related to pretreated tumor burden, and this was correlated with the clinical response.[9] In the present case, the reduction in total amount of tumor by the preceding chemotherapy might lead to reinvigoration of exhausted-phenotype CD8 T cells and antitumor response after pembrolizumab administration.

In conclusion, we reported a case of NSCLC with high PD-L1 expression surrounded by interstitial shadow treated with pembrolizumab therapy following induction platinum-doublet chemotherapy. Patients with NSCLC who are at a high risk of ICI-related side effects could receive platinum-doublet chemotherapy as first-line therapy. However, if the risk associated with ICIs is resolved, early switching from chemotherapy to pembrolizumab may be desirable, even if chemotherapy is effective.

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Author contributions

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