

Case Report

Response to pembrolizumab in lung squamous cell carcinoma with PD-L1 overexpression and EGFR rare mutation: a case report

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Abstract: The goal of this study was to investigate whether the low response rate to PD-1/PD-L1 inhibitors is different between EGFR common mutation and rare mutation in NSCLC patients. Methods: The patient was treated with Pembrolizumab monotherapy for three cycles in third line therapy. Results: a metastatic lung squamous cell cancer with EGFR V843I mutation and PD-L1 overexpression was evaluated as PR. Conclusion: this is the first case report of response to PD-L1 inhibitors for a lung squamous cell carcinoma patient with PD-L1 overexpression and EGFR rare mutation, which helps future immunity therapy for patients with EGFR rare variants in NSCLC.

Keywords: Lung squamous cell carcinoma, PD-1 inhibitor, PD-L1 overexpression, EGFR rare mutation

Introduction

The field of immune-oncology has dramatically changed the landscape of malignant diseases, becoming a mainstay of cancer therapy in solid tumors while advanced non-small cell lung cancer with EGFR or ALK variants was widely considered that these diseases couldn't benefit from immune checkpoint inhibitors. However, it is unclear that whether the low response rate to PD-1/PD-L1 inhibitors is different between EGFR common mutation and rare mutation in NSCLC patients. Here, a metastatic lung squamous cell cancer with EGFR V843I mutation and PD-L1 overexpression was examined and evaluated as PR after treatment with Pembrolizumab monotherapy for three cycles as third line therapy. Written informed consent was obtained before preparation and submission of this manuscript.

Case report

A man of 41 years old with smoking history, who sought medical advice in November of 2016 because of "coughing and expiratory dys-

pnea" and the pathological diagnosis showed "lung squamous cell carcinoma" (**Figure 1A**). Based on iconography, right-sided hydrothorax and metastases (including right-sided pleura were present in the pericardium, right-sided pulmonary, and liver S2). Gemcitabine combined with cisplatin (GP) scheme was offered with two cycles and the evaluation is SD. It is reported that the cough did not improve significantly, so the patient refused to continue the chemotherapy. From January 21st in 2017 to April 30th in 2018, S-1 (40 mg po bid d1-14, q21d) combined with apatinib (0.5 g po qd) was offered for ten cycles. The evaluation after two cycles of this treatment is PR. Afterwards, the evaluation after every two cycles of treatment is SD. On March 30th in 2018, the result of enhanced CT showed multiple nodules in the right lung, which grew forward. Also, pleural effusion in the right lung increased more than previously while mediastinal lymph node enlargement and pericardium multiple nodules grew slightly larger than those of intrahepatic S2 nodules (**Figure 2**). The comprehensive evaluation of curative effect was PD.

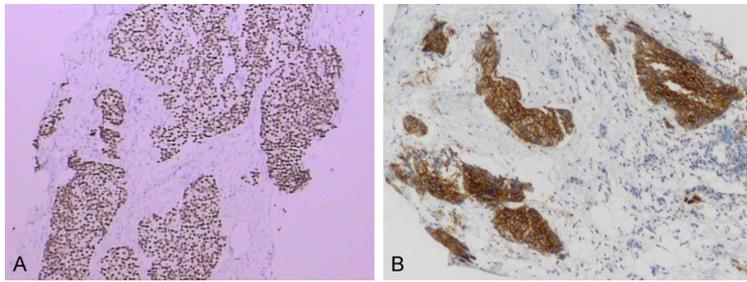


Figure 1. A: HE; B: PD-L1 Immunohistochemistry (100 \times).

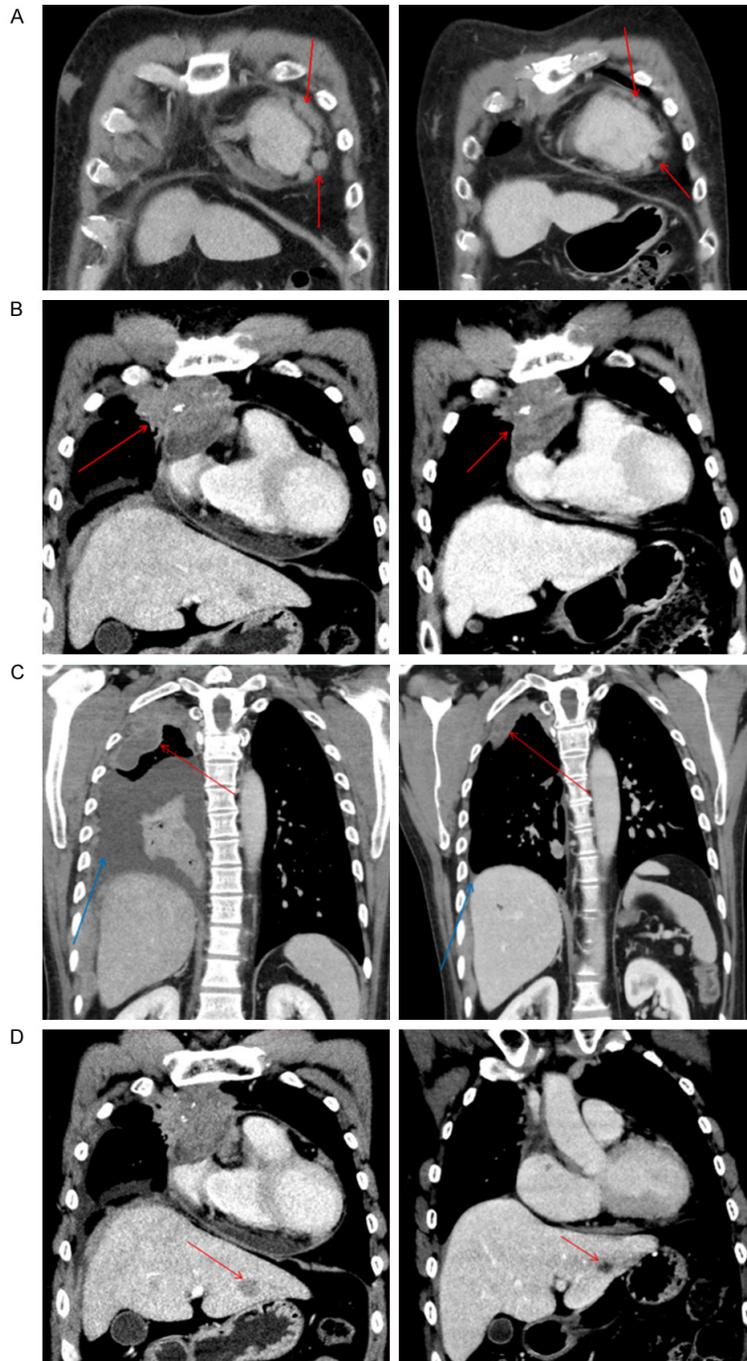


Figure 2. Representative lesions showing response after three cycles Pembrolizumab therapy. Left of each pictures show lesions before Pembrolizumab therapy (2018. 3. 30), and right ones show after three cycles therapy (2018. 7. 11). A. Pericardium multiple nodules; B. The right-sided pleural effusion and anterior mediastinum and intra-pericardial cystic lesions; C. Right pleural multiple nodular masses and pericardial effusion; D. Liver S2 lesion.

On April 3rd of 2018, CT-guided percutaneous needle biopsy was operated in the right anterior upper mediastinal mass, with IHC and gene sequencing performance. The result shows that expression of PD-L1 is 50% (SP263, Roche Group Ventana) (**Figure 1B**), at the same time EGFR V843I is detected by circulating tumor DNA (ctDNA) through NGS as previous described [1]. After comprehensive consideration, the patient decided receive immune checkpoint inhibitor therapy. From May 1st of 2018 to July 13 of 2018, Pembrolizumab (200 mg d1 q21d) in monotherapy was performed. After the first cycle of treatment, symptoms of cough almost disappeared and the patient had no signs of chest distress or expiratory dyspnea. After three cycles of treatment, based on the enhanced CT on July 11 in 2018, multiple nodules in the right lung were reduced compared to the previous result. Right pleural multiple nodular masses of varying size were smaller and pericardial effusion was less than before, so did the pericardium multiple nodules. The right-sided pleural effusion and anterior mediastinum and intra-pericardial cystic lesions have decreased. Comprehensive evaluation of

curative effect was PR (**Figure 2**) and the effect of Pembrolizumab was judged to be stable disease (progression-free survival) for 7.5 months.

Adverse events were immune peripheral neuritis and autoimmune myocarditis. Immunity peripheral neuritis including oculomotor nerve, abducens nerve and pneumogastric nerve were damaged. The symptoms were ptosis of eyelid, diplopia, hoarseness etc. Treatment included a combination of steroids hormone and pyridostigmine tablets. After treatment, these symptoms disappeared. As for autoimmune myocarditis, which came with the increase of cardiac enzymology index, treatment of cardiotrophin (trimetazidine) was offered. Cardiac enzymology index had been significantly improved after the treatment of hormone and cardiotrophin.

Discussion

Based on clinical trials of advanced NSCLC treated with nivolumab, pembrolizumab, and atezolizumab, patients with EGFR variants have an extremely low response rate towards immune checkpoint inhibitors [2-6]. Therefore, in the clinical trial of the first line treatment of Pembrolizumab on advanced NSCLC, the patients with EGFR and ALK variants were eliminated and its expression of PD-L1 was $\geq 50\%$ [7]. The clinical trial had tremendous success, which contributes to the standard treatment for first-line advanced NSCLC patients with Pembrolizumab.

In previous research, the EGFR mutation is generally defined as "EGFR positive". However, the most common variants of EGFR are 19del and L858R, which account for more than 85% and the rest of other EGFR are defined as rare variants [8]. The impact of common and rare variants of EGFR on the response of first generation EGFR TKI is different [9]. Previous research has not explained or analyzed the difference between the impact of EGFR common variants and EGFR rare variants on the response of PD-1/PD-L1 inhibitors. It is taken into consideration that there is a low percentage of EGFR rare variants coming up, so it is not clear about the impact of EGFR rare variants and high expression PD-L1 of NSCLC on the response of immune checkpoint inhibitors. From the description of Wu Yilong, a patient with lung cancer with EGFR19del and 50% PD-L1 ex-

pression, after three cycles of treatment with Pembrolizumab, there was no significant clinical benefit and the tumor progressed [10]. This case had the opposite therapeutic effect, which suggests that there was a completely different predictive effect for the impact of EGFR rare variants and common variants on immune checkpoint inhibitors.

Therefore, this is the first case report of response to PD-L1 inhibitors for a lung squamous cell carcinoma patient with PD-L1 overexpression and EGFR rare mutation, and may help future immunologic therapy for patients with EGFR rare variants NSCLC.

Disclosure of conflict of interest

None.

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