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Case Report

Extremely Rapid Response to Pembrolizumab in a SMARCA4 Mutant PD-L1 Highly Expressive Advanced Lung Adenocarcinoma: A Case Report

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ABSTRACT

SMARCA4 mutant non-small cell lung cancer (*SMARCA4m*-NSCLC) has a poor prognosis owing to rapid growth. Effective treatments for *SMARCA4m*-NSCLC have not yet been established. Recently, many preclinical studies support the hypothesis that *SMARCA4m*-NSCLC may be vulnerable to immune checkpoint inhibitors. Here, we report a patient with programmed death-ligand1 (PD-L1) highly expressive *SMARCA4m*-NSCLC who showed an extremely rapid and long-term response to pembrolizumab. He was referred to our hospital for a mass of the right lung. Positron emission tomography-computed tomography showed right lung tumor, hilar, mediastinal and bone metastases. Pathological and immunohistochemical results showed it was a lung adenocarcinoma and revealed the tumor proportion score of PD-L1 was 80%. *SMARCA4* and *K-RAS* genes were co-mutations. BRG1 protein expression was negative. Subsequently, pembrolizumab treatment as the first line of therapy was commenced for the patient. With only one dose, pembrolizumab significantly inhibited tumor growth and a partial response was obtained. To date, pembrolizumab treatment has been continued for about 29 months. Severe immune-related adverse events were not observed. Our case showed that an extremely rapid and long-term response can be achieved with pembrolizumab for PD-L1 highly expressive *SMARCA4m*-NSCLC. Immune checkpoint inhibitors treatment may be a promising strategy for PD-L1 positive *SMARCA4m*-NSCLC.

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Introduction

Over the past 20 years, NSCLC treatment has changed dramatically with the development of molecular profiling detection and targeted therapeutic agents [1]. *EGFR* somatic mutation and *ALK*, *ROS1* rearrangements have been validated as “driver” genes in NSCLC and corresponding target drugs have been established [2-4]. *SMARCA4* is the most frequent mutated member of the SWI/SNF complex, with mutations happening in 10% of NSCLC patients [5]. The prognosis for *SMARCA4m*-NSCLC is relatively poor, with median overall survival

(OS) around seven months because no effective anti-*SMARCA4* inhibitors are currently used in clinical practice. Recently, a study reported that immune checkpoint inhibitors (ICIs) as a treatment method in *SMARCA4m*-NSCLC might improve OS [6]. These results indicated that ICIs might be effective and could obtain clinical benefits for patients with *SMARCA4m*-NSCLC. However, the mechanisms of ICIs anti-tumor activities have not been fully elucidated. In our case, we reported an extremely rapid and long-term response to pembrolizumab in a *SMARCA4* mutant PD-L1 highly expressive advanced lung adenocarcinoma.

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Case Report

A 67-year-old man was referred to our hospital for a mass of the right upper lung. Positron emission tomography-computed tomography (PET-CT) showed right upper lung tumor, hilar, mediastinal, and bilateral supraclavicular lymph node metastasis and bone metastases (Figure 1A). Transbronchial biopsy and right supraclavicular lymph node biopsy were performed, and he was diagnosed with lung adenocarcinoma in April 2019. Five days after the biopsy, his voice became hoarse. We found that the mediastinal lymph node had invaded the right recurrent

laryngeal nerve resulting in the abnormality (Figure 1A). Pathological and immunohistochemical results revealed that the tumor proportion score of PD-L1 was 80% (Figure 1B). Next-generation sequencing was also performed. The results showed that no somatic mutation or rearrangements were found for *EGFR*, *ALK*, *ROS1* and *C-MET* genes. *SMARCA4* and *K-RAS* co-mutations were found. BRG1 protein expression was negative (Figure 1B). Taken together, the patient was diagnosed with clinical stage IV, PD-L1 highly expressive *SMARCA4*-NSCLC.

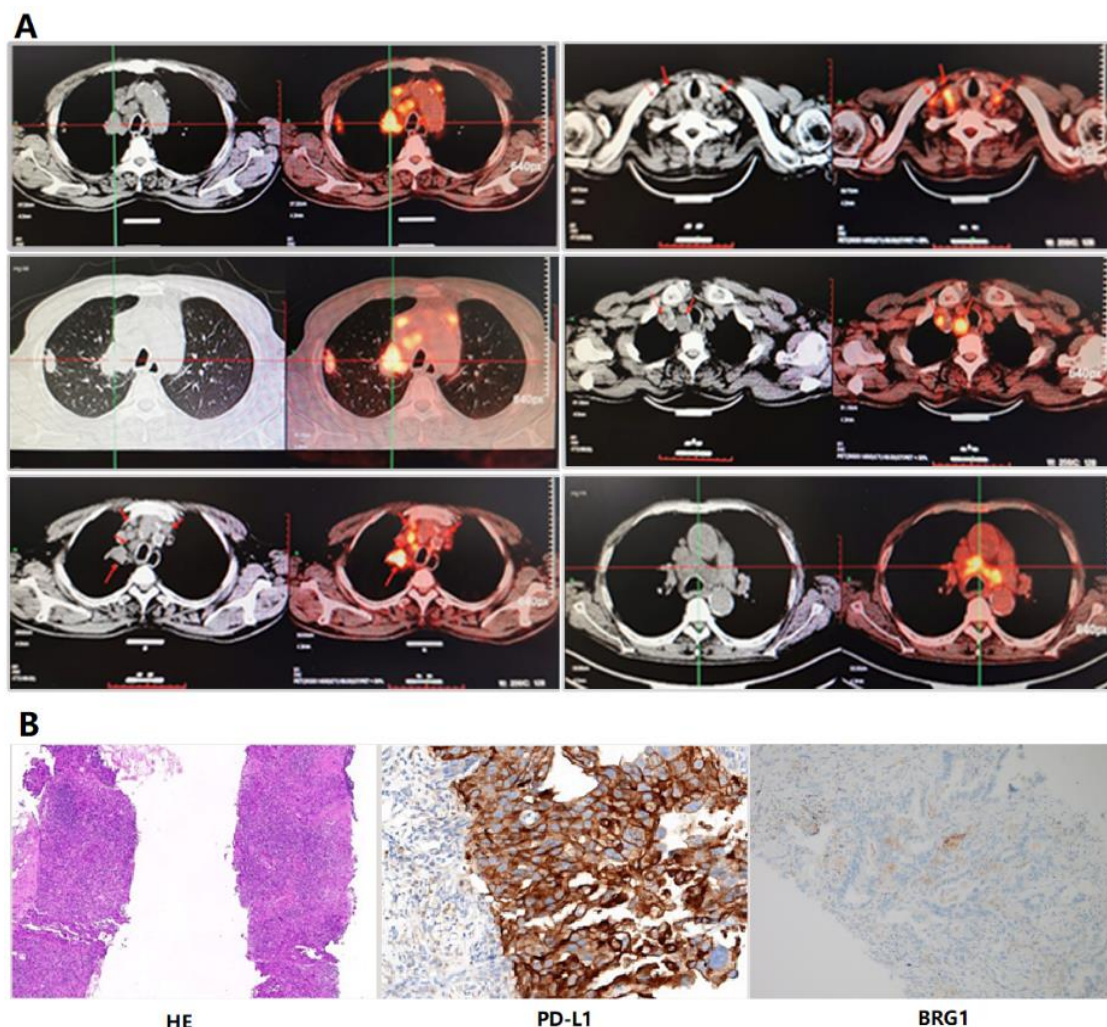


Figure 1: The image of positron emission tomography-computed tomography, pathology and immunohistochemistry. **A)** The image of positron emission tomography-computed tomography. Arrows indicate tumors. **B)** Hematoxylin and eosin (H&E) staining (100×magnification); Immunohistochemistry stained with PD-L1 antibody (SP263) in a fresh tissue of right supraclavicular lymph node before treatment, exhibiting strong membrane staining in 80% of tumor cells (400×magnification). Immunohistochemistry stained with BRG1 primary antibody.

Subsequently, we treated the patient with pembrolizumab as the first line of therapy because of PD-L1 high expression on April 26, 2019. Before treatment, a CT scan was performed (Figure 2A). After one pembrolizumab infusion (200mg/3 weeks), the patient's voice sound improved, suggesting pembrolizumab may be effective and inhibited tumor growth. After infusion twice, a CT scan was performed. As shown in (Figure 2B), the size of the tumor significantly decreased compared to pre-treatment, resulting in a partial response. After 4 cycles of pembrolizumab treatment, the tumor was getting smaller (Figure 2C).

To date, pembrolizumab treatment for the patient has been continued for about 29 months. He had no obvious clinical symptoms and no severe adverse events. After 41 cycles of pembrolizumab treatment, a CT scan demonstrated that the size of the tumor was tiny compared to pre-treatment, indicating that pembrolizumab was sustained effective (Figure 2D).

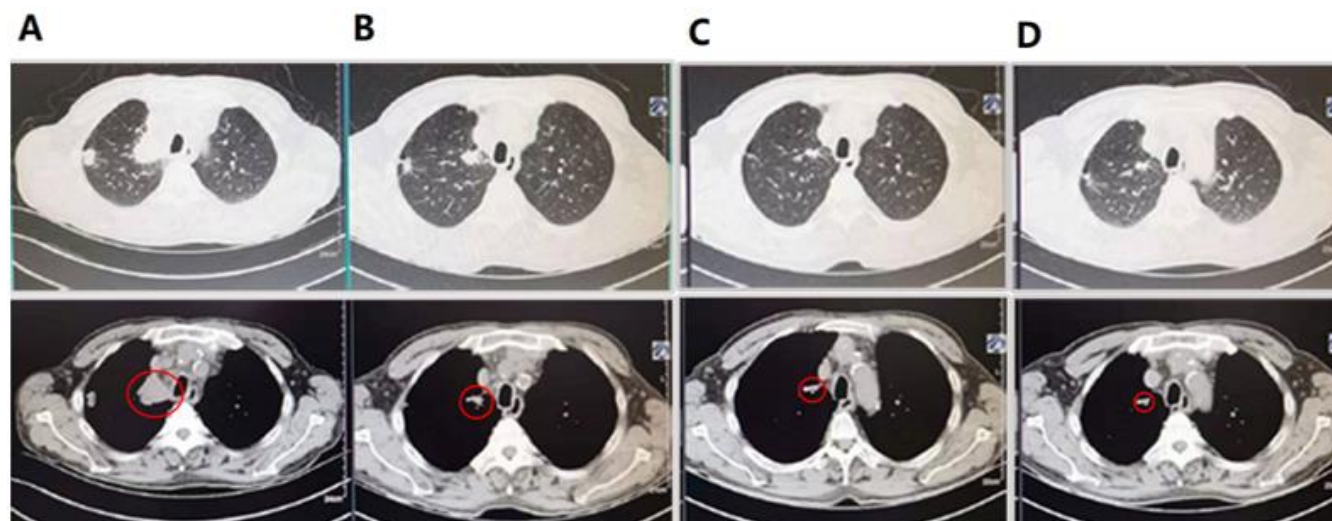


Figure 2: The image pre-treatment and after-treatment CT scan. **A)** Pre-treatment CT scan; **B)** CT scan after one cycle of pembrolizumab; **C)** CT scan after two cycles of pembrolizumab; **D)** CT scan after forty-one cycles of pembrolizumab. Red circles indicate tumors.

Discussion

In our case, we described a PD-L1 highly expressive *SMARCA4*m-NSCLC patient who obtained an extremely rapid and long-term response for pembrolizumab. To our knowledge, this is the first case of a *SMARCA4*m-NSCLC patient showing high expression of PD-L1 in the tumor. The survival outcome of *SMARCA4*m-NSCLC patients was significantly worse. Therefore, this report is important, indicating that PD-1 inhibitors may be effective for *SMARCA4*m-NSCLC. Recently, several reports showed that ICIs were effective and safe for patients with *SMARCA4*m-tumors. For example, Henon C *et al.* reported that ICIs treatment of *SMARCA4* deficient thoracic malignant rhabdoid-like tumor obtained long-lasting major response. In this report, TMB is remarkably low, PD-L1 expression was negative in tumor cells and immune cell infiltrates were rare [7]. Jelinic *et al.* also showed that PD-1 inhibitor was effective in *SMARCA4*-deficient small-cell carcinoma of the ovary [8]. Therefore, we have a hypothesis that whether *SMARCA4*m could be a predictor for ICIs response in NSCLC. Notably, there was one previous report that showed that PD-1 inhibitor was effective for a *SMARCA4* deficient NSCLC patient with a high TMB and PD-L1 not highly expressed [9]. However, there was another study that reported hyperprogressive disease was obtained after immune checkpoint inhibitor treatment in *SMARCA4* deficient SCLC [10].

In all, it remains unproven that whether the identification of *SMARCA4*m is enough to predict ICIs response. Nowadays, ICIs have been used as standard therapy in a majority of NSCLC patients. However, according to different molecular subtypes, how to select appropriate patients for ICIs treatment will be critical. To date, PD-L1, microsatellite instability and tumor mutation burden (TMB) have been recognized as a predictor of ICIs response [11, 12]. *SMARCA4*m is reportedly positively associated with PD-L1 expression [13]. In our case, we believe that *SMARCA4* and *K-RAS* co-mutations might have caused PD-L1 increase. Therefore, such a good response is mainly due to the combined effect of PD-L1 high expression and *SMARCA4* mutation.

Taken together, this is the first report showing that the patient with PD-L1 highly expressive *SMARCA4*m-NSCLC has an extremely rapid and

long-term response to pembrolizumab. In terms of PD-L1 positive *SMARCA4*m-NSCLC, ICIs may be an effective therapeutic option. Given the limitations of individual case reports, however, the efficacy of PD-1 inhibitor needs to be further verified in a larger patient cohort with *SMARCA4*m-NSCLC.

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Conflicts of Interest

None.

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