


## CASE REPORT

## Efficacy of pembrolizumab for patients with both high PD-L1 expression and an *MET* exon 14 skipping mutation: A case report

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### Keywords

*MET* exon 14 skipping mutation; non-small cell lung cancer; pembrolizumab; pemetrexed; programmed death-ligand 1.

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Received: 6 November 2018;

Accepted: 21 November 2018.

doi: 10.1111/1759-7714.12939

Thoracic Cancer **10** (2019) 369–372

## Introduction

Lung cancer is the leading cause of cancer-related death worldwide, although new agents targeting oncogenic gene alterations have significantly improved survival.<sup>1</sup> More recently, immune checkpoint inhibitors (ICIs) have led to significant changes in treatment strategies, and long-term survival may be possible in previously treated non-small cell lung cancer (NSCLC) patients.<sup>2–4</sup> Pembrolizumab monotherapy has become a standard option as the first-line treatment for advanced NSCLC patients with high PD-L1 expression and a tumor proportion score (TPS) of  $\geq 50\%$ .<sup>5</sup>

Somatic mutations in the *MET* gene can cause exon 14 skipping, and the resulting mutant receptor demonstrates increased *c-MET* signaling and oncogenic potential. This mutation is only detected in 1% of NSCLC patients, but is often found in sarcomatoid carcinoma, which is characterized by poor prognosis.<sup>6,7</sup> In clinical trials, crizotinib and other *MET* inhibitors have been shown to be effective for NSCLC with *MET* amplification or exon 14 skipping

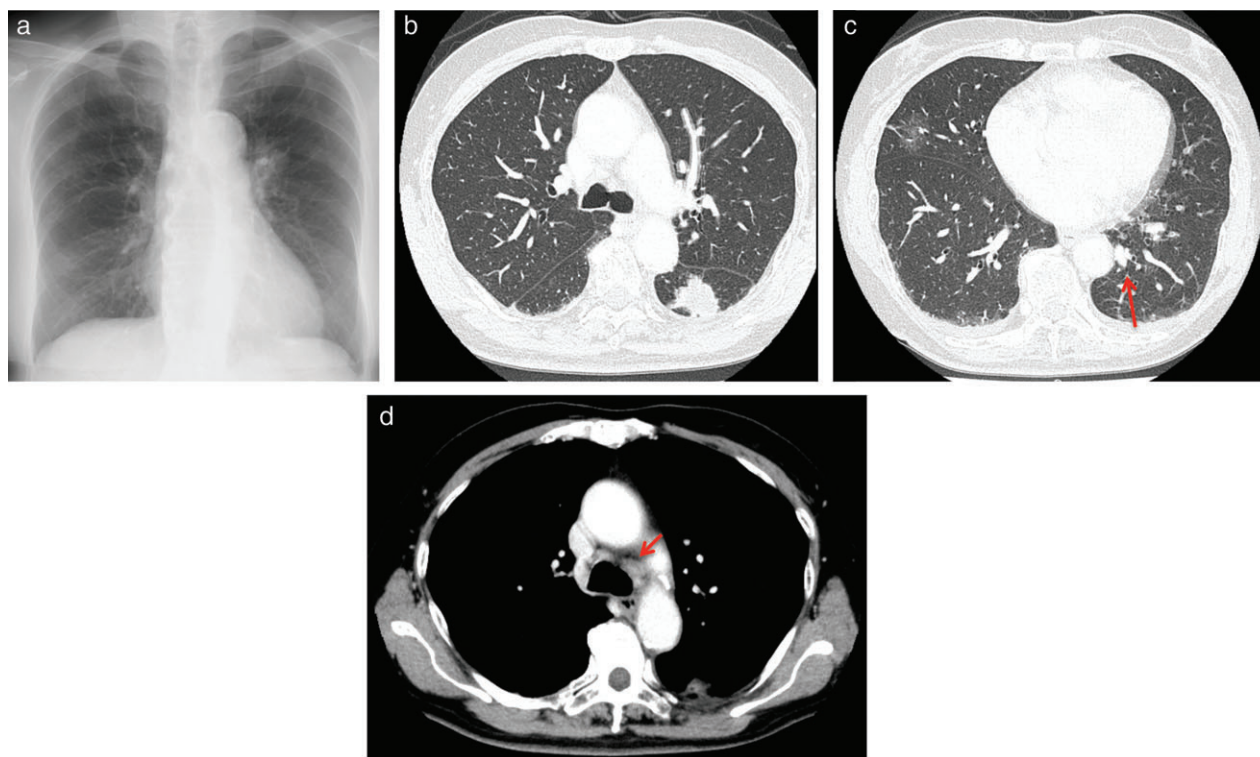
## Abstract

Pembrolizumab has become the standard first-line treatment for non-small cell lung cancer (NSCLC) patients with high PD-L1 expression. *MET* exon 14 skipping is a rare mutation typically found in older, female, and non-smoking patients with NSCLC. Herein, we report the case of a 71-year-old non-smoking woman who was diagnosed with NSCLC in the left lung. *EGFR* mutation and *ALK* fusion were not detected. Because the biopsy specimen showed high PD-L1 expression with a tumor proportion score of 95%, pembrolizumab was introduced as first-line therapy, but resulted in no clinical benefit. The patient was subsequently administered chemotherapy with carboplatin and pemetrexed, leading to remarkable tumor shrinkage. A next-generation sequencing panel analysis revealed a *MET* exon 14 skipping mutation. Thus, pembrolizumab might not be effective for NSCLC patients with *MET* exon 14 skipping mutations, even if PD-L1 expression is high.

mutation, although they have not yet been approved.<sup>8–11</sup> Herein, we present a case of NSCLC with both high PD-L1 expression and a *MET* exon 14 skipping mutation.

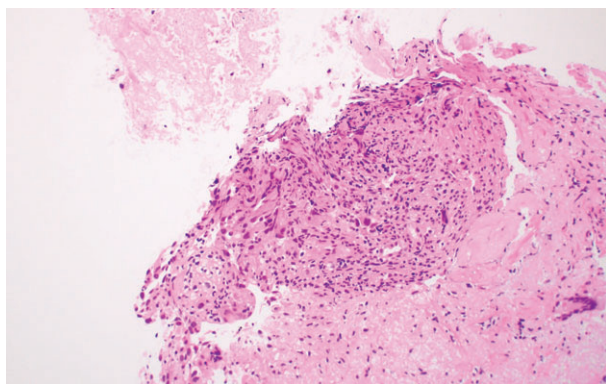
## Case report

A 71-year-old woman with no smoking history was referred to our hospital in November 2017 after an abnormal shadow was detected in the left lower lung on chest X-ray (Fig 1a). A physical examination revealed no significant abnormalities. Computed tomography (CT) of the chest revealed a tumor with a diameter of 30 mm in the left S6 with enlargement of the hilar and peritracheal lymph nodes and small pulmonary metastasis on the bilateral lungs (Fig 1b–d), indicating c-T3N2M1a (Union for International Cancer Control, 8th edition). Laboratory findings were within the normal ranges, except for a high cytokeratin 19 fragment serum level of 5.1 ng/mL. We conducted a transbronchial biopsy and the pathological diagnosis was



**Figure 1** (a) Chest X-ray on the first visit to our hospital showing a tumor in the left lower lung. (b–d) Computed tomography (CT) of the chest revealed a tumor (30 mm in diameter) in the left S6 with enlargement of the lymph nodes in the hilar and peritracheal regions, as well as a small pulmonary metastasis.

non-small cell lung cancer (NSCLC), which had neither *EGFR* mutation nor *ALK* fusion. Hematoxylin and eosin staining of the biopsy specimen revealed medium sized tumor cells of a polygonal shape, with medium cytoplasm and hyperchromatic nuclei (Fig 2). Immunohistochemistry revealed that tumor cells were negative for TTF-1 and p40. These findings indicated a pathological diagnosis of poorly differentiated lung adenocarcinoma and the pathology indicated histological features of sarcomatoid carcinoma.

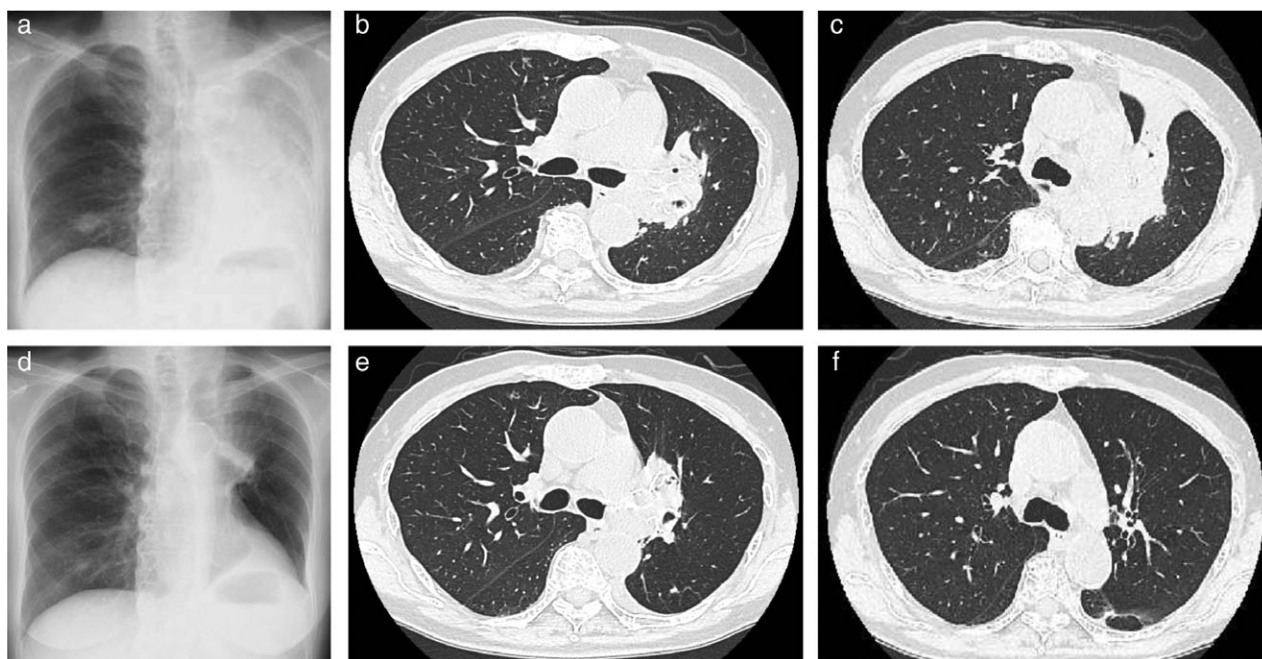


**Figure 2** Histopathology of the tumor, showing tumor cells were medium sized and had a polygonal shape with medium cytoplasm and hyperchromatic nuclei (hematoxylin and eosin stain, x20).

Because high PD-L1 expression with a TPS of 95% was confirmed by immunohistochemistry with a 22C3 antibody (Dako North America, Carpinteria, CA, USA), we commenced first-line treatment of pembrolizumab (200 mg abs. on day 1). After the first cycle of pembrolizumab, the tumor in the left lung increased in size and atelectasis appeared in the upper lobe as a result of hilar lymph node enlargement (Fig 3a–c). The patient complained of dyspnea and developed hypoxia. We considered obvious disease progression and introduced second-line chemotherapy of carboplatin (CBDCA, area under the curve = 5) and pemetrexed (PEM, 500 mg/m<sup>2</sup> on day 1). These cytotoxic agents were remarkably effective with apparent tumor shrinkage after two cycles of treatment (Fig 3d–f), representing a partial response. Because the patient was a non-smoker we conducted next-generation sequencing panel analysis, which revealed a *MET* exon 14 skipping mutation.

## Discussion

In our case, the patient had both high PD-L1 expression and a *MET* exon 14 skipping mutation. Cytotoxic chemotherapy with CBDCA plus PEM was effective, whereas pembrolizumab therapy was not, despite high expression



**Figure 3** (a) Chest X-ray performed after 38 days of pembrolizumab treatment showing tumor growth and the development of obstructive atelectasis. (b,c) Computed tomography (CT) scan taken on day 25 after the introduction of pembrolizumab, showing that the tumor had increased in size. The patient was re-hospitalized that day because of dyspnea and acute respiratory failure. (d) Chest X-ray taken after 19 days of carboplatin and pemetrexed treatment, showing significant reduction of the tumor in the left lung and recovery of the atelectasis. (e,f) A CT scan performed after 43 days of carboplatin and pemetrexed treatment showing further reduction of the tumor in the left lung.

of PD-L1. In general, ICIs are less effective in NSCLC with *EGFR* mutation, *EML4-ALK* fusion, or other rare mutations.<sup>12,13</sup> Sabari *et al.* reported that 40% of the NSCLC patients with a *MET* exon 14 skipping mutation express high PD-L1 (> 50%) and that the overall response rate of patients treated by ICIs was as low as 33%.<sup>14</sup> We considered that this low efficacy of ICIs in those with both high PD-L1 expression and a *MET* exon 14 skipping mutation might be explained by a low tumor mutation burden (TMB). Cancer with driver mutations is characterized by low TMB, even with high PD-L1 expression.<sup>15,16</sup> In fact, most patients with a *MET* exon 14 skipping mutation had low (56%) or low-intermediate (32%) TMB.<sup>17</sup> On the other hand, the responsiveness of pulmonary sarcomatoid carcinomas, which are likely to have a *MET* exon 14 skipping mutation, to ICIs can be explained by their high TMB.<sup>18,19</sup> Although we did not measure TMB in the present case, the lack of efficacy of pembrolizumab could be a result of low TMB. Mazieres and Gautschi reported that patients with a *MET* mutation showed intermediate progression-free survival (3.4 months) after immunotherapy compared to those with other driver mutations, although PD-L1 and TMB status were not shown.<sup>20</sup>

A therapeutic strategy for NSCLC with both high PD-L1 expression and driver mutation has not been established.

Chen *et al.* reported that PEM-based chemotherapy was effective in NSCLC patients with *EGFR* mutation, *ALK* fusion, and *ROS 1* rearrangement (overall response rates: 25.5%, 28.1%, and 57.9%, respectively).<sup>21</sup> Our case also indicated the effectiveness of pemetrexed-based chemotherapy for NSCLC with a *MET* exon 14 skipping mutation.

## Acknowledgments

The authors are grateful to the patients and their families, and the investigators, nurses, and staff members who participated in this study, especially Dr. Gotoh and Dr. Matsumoto at the National Cancer Center Central Hospital who performed next generation sequences.

## Disclosure

No authors report any conflict of interest.

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