CASE REPORT

First-line immune checkpoint therapy in metastatic squamous cell lung cancer harboring both EGFR mutation and high expression of PD-L1: A case report

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Keywords
Epidermal growth factor receptor (EGFR) mutation; pembrolizumab; programmed death-ligand 1 (PD-L1); squamous cell lung cancer.

Abstract
A 90-year-old female was admitted to our hospital with a history of a dry cough. Chest computed tomography (CT) scan showed a tumor shadow, and CT-guided lung biopsy revealed squamous cell carcinoma harboring an EGFR mutation. In addition, programmed death-ligand 1 (PD-L1) was highly expressed with a tumor proportion score (TPS) of >75%. Pembrolizumab therapy in the first-line setting was not effective, and the patient died at six months from the first visit. Squamous cell lung cancers (SCLCs) with both EGFR mutation and high expression of PD-L1 are very rare.

Introduction
Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) treatment is effective for lung cancer harboring EGFR mutations; a large number of these cases are nonsquamous cell carcinomas. The efficacy of EGFR-TKIs against squamous cell lung cancer (SCLC) harboring EGFR mutations is limited. Pembrolizumab therapy is recommended in the first-line setting for lung cancers with high expression of programmed death-ligand 1 (PD-L1).

In patients with nonsquamous cell lung cancer harboring EGFR mutations and high expression of PD-L1, EGFR-TKI therapy is used as the efficacy of pembrolizumab is limited. However, no previous reports have demonstrated the choice of therapy for SCLCs harboring EGFR mutations with high expression of PD-L1.

Case report
A 90-year-old female was admitted to our hospital with a history of a dry cough. Chest radiograph at hospitalization revealed a lung mass in the right upper field (Fig 1). Chest computed tomography (CT) scan showed a tumor shadow, and CT-guided lung biopsy revealed squamous cell carcinoma harboring an EGFR mutation. In addition, programmed death-ligand 1 (PD-L1) was highly expressed with a tumor proportion score (TPS) of >75%. Pembrolizumab therapy in the first-line setting was not effective, and the patient died at six months from the first visit. Squamous cell lung cancers (SCLCs) with both EGFR mutation and high expression of PD-L1 are very rare.
ipsilateral mediastinal lymph nodes, and 4.8 for the left adrenal gland (Fig 2b,c). Based on the PET-CT results, cT3N2M1b (ADR), stage IVA lung cancer was suspected. CT-guided needle biopsy from the tumor in the apical region of the right lung revealed squamous cell carcinoma (Fig 3a–c). The tumor tested positive for EGFR mutations (exon 21: L858R) and showed high expression of programmed death-ligand 1 (PD-L1), with a tumor proportion score (TPS) of >75% (Fig 3d). Three cycles of pembrolizumab therapy were administered in the first-line setting. However, the primary lesion, right subclavian and mediastinal lymph node size, and the right-sided pleural effusion significantly increased. It was difficult to continue treatment owing to poor PS, and the patient died at six months from the first visit.

Discussion

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are effective for nonsmall cell lung cancers harboring EGFR mutations, particularly in patients aged >75 years; gefitinib resulted in a progression-free survival (PFS) of 12.3 months and a 74% objective response rate (ORR) in the study by Goto et al. It has also previously been reported that primary treatment with pembrolizumab for lung cancer with high PD-L1 expression was better than conventional chemotherapy, with a PFS of 10.3 months, and a six-month survival rate of 80.2%. In particular, subset analysis of this trial showed pembrolizumab therapy to be more effective for squamous cell carcinoma (SCC) than for nonsquamous cell carcinoma.

The effectiveness of immune checkpoint inhibitors (ICIs) for EGFR mutation-positive lung cancer is limited. In a single-center retrospective study, the ORR of ICIs for driver mutation-positive lung cancer was 3.8%. In contrast, the ORR after using ICIs prior to EGFR-TKIs was 0%. Therefore, EGFR-TKIs are more effective than anti PD-1 antibodies for nonsquamous cell cancer with both EGFR mutations and high expression of PD-L1.

However, the efficacy of EGFR-TKI in SCC has been reported to be limited in EGFR mutation-positive cases. Furthermore, some reports have shown the proportion of EGFR mutation-positive lung cancer with high PD-L1 expression (≥50%) to be approximately 10%; the efficacy of EGFR-TKIs in such cases were inferior to that observed with lower expression of PD-L1. It was speculated that the efficacy of EGFR-TKI in our case may be inferior to that mentioned in a previous report on SCLC harboring EGFR mutations. Finally, the patient was presented with a
choice of injectable treatment or oral medication, and pembrolizumab therapy was selected.

There is no standard treatment for SCLC with EGFR mutations and high expression of PD-L1. In our case, the ICI was administered prior to EGFR-TKIs owing to its efficacy in SCC, and as per the patient’s choice; however, no effect was observed. In this case, the use of cytotoxic anti-cancer agents was not feasible owing to the age of the patient. The frequency of EGFR-TKI-induced interstitial lung disease after ICI use has been reported to increase,9 and it was also difficult to administer EGFR-TKIs when ICI was ineffective. In EGFR-mutated SCLC with high expression of PD-L1, EGFR-TKIs as the first-line treatment followed by ICI may be recommended. Thus, as SCLC with EGFR mutations and high expression of PD-L1 is very rare, further accumulation of treatment experience is required.

**Disclosure**

The authors report no conflict of interest.

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