The Long-term Survival of a Patient with Adenosquamous Lung Carcinoma Harboring EGFR-activating Mutations Who was Treated with Gefitinib

Kentaro Iwanaga, Naoko Sueoka-Aragane, Tomomi Nakamura, Daisuke Mori and Shinya Kimura

Abstract

A 56-year-old woman diagnosed with squamous cell lung carcinoma after a transbronchoscopic examination underwent left upper lobectomy, which revealed a pathological diagnosis of adenosquamous carcinoma containing moderately differentiated squamous cell carcinoma and bronchioloalveolar carcinoma. The epidermal growth factor receptor (EGFR) exon 19 delE746-A750 mutation was detected in deoxyribonucleic acid (DNA) isolated from specimens of both components using microdissection. Treatment with the EGFR tyrosine kinase inhibitor, gefitinib, resulted in a long-term tumor response lasting three years. Adenosquamous carcinoma is difficult to diagnose using transbronchoscopic procedures. Therefore, the examination of EGFR mutation status is important in order to determine the appropriate treatment, even in patients with non-adenocarcinoma.

Key words: lung adenosquamous carcinoma, EGFR-TKI, T790M, plasma DNA


Introduction

Adenosquamous lung carcinoma is an uncommon histological type of carcinoma with a prognosis reported to be worse than that of adenocarcinoma or squamous cell carcinoma (1-3). Although the pathogenesis of adenosquamous lung carcinoma has not been elucidated, molecular patterns, including epidermal growth factor receptor (EGFR) mutations, have been observed in this disease (4-8). Compared with adenocarcinoma and other pathological types of lung cancer harboring EGFR mutations, the prognoses of non-adenocarcinoma patients who undergo treatment with EGFR tyrosine kinase inhibitor (EGFR-TKI) have been reported to be poor (9-11). We herein report the case of an adenosquamous carcinoma patient with the EGFR exon 19 delE746-A750 mutation in both adenocarcinoma and squamous cell carcinoma components who achieved three years of tumor response following treatment with EGFR-TKI. In addition, substitution of threonine 790 with methionine (T790M) was observed in a liver metastatic lesion comprised of the squamous cell carcinomatous component after the patient acquired resistance to EGFR-TKI. This is the same molecular alteration as that observed in adenocarcinoma with EGFR mutations.

Case Report

A 56-year-old woman with a 30 pack-year history of smoking was diagnosed with lung squamous cell carcinoma after undergoing a transbronchoscopic examination. She was classified with clinical stage cT2N0M0, IB disease and underwent left upper lobectomy. Following the lobectomy, she was pathologically diagnosed with adenosquamous carcinoma containing moderately differentiated squamous cell carcinoma and bronchioloalveolar carcinoma (BAC) (Fig. 1).
The patient started gefitinib, multiple liver metastases occurred. A histological analysis revealed the presence of squamous cell carcinomatous and BAC components using microdissection, the EGFR-TKI gefitinib was administered as the second line of treatment. Nine months after treatment, chest computed tomography showed a remarkable shrinkage of the lymph nodes, and a complete response was eventually achieved. Three years after the patient started gefitinib, multiple liver metastases occurred. A histological analysis revealed the presence of squamous cell carcinoma (Fig. 1D) positive for p63 (Fig. 1E) and negative for TTF-1 (Fig. 1F). These pathologic findings were consistent with those of the squamous cell carcinomatous component in the primary lesion, and delE 746-A750 was detected in the liver metastatic lesion. A second EGFR mutation, T790M, was examined using a mutation-biased polymerase chain reaction (PCR) and quenched probe system (MBP-QP) method recently established in our laboratory (12). The mutation was found in the liver metastatic lesion (Fig. 2C); however, it was not found in either of the components of the primary lesion (squamous cell carcinoma (Fig. 2A) and BAC (Fig. 2B) (the black and white arrows in Fig. 2 indicate the wild-type and mutant, respectively)).

### Discussion

Adenosquamous lung carcinoma is an uncommon histological type of carcinoma, comprising only 2.1-3.4% of non-small cell lung carcinomas (1, 2). The cumulative five-year postoperative survival rate of patients with adenosquamous carcinoma is approximately 20%, worse than that of patients with adenocarcinoma or squamous cell carcinoma (40% for both groups) (1, 3). Although the pathogenesis of adenosquamous carcinoma has not yet been elucidated, similar molecular characteristics such as DNA aneuploidy, loss of heterozygosity and genomic alterations of p53 and K-ras have been detected in both adenomatous and squamous cell carcinomatous components (4-8). Recent reports have demonstrated that 27-40% of patients with adenosquamous carcinomas harbor EGFR-activating mutations, which are observed in both adenocarcinomatous and squamous cell carcinomatous components (6-8), as in our case. These findings suggest that squamous cell carcinomatous and BAC components might derive from a common origin and subsequently differentiate into separate histological types.

In general, EGFR mutations at exons 19 and 21 are known to be good predictive markers of a patient’s response to EGFR-TKI treatment. The response rate is approximately 70% and overall survival is 30.5 months among lung cancer patients with EGFR mutations (13). However, a recent pooled analysis of published reports indicated that, among
lung cancer patients with *EGFR*-sensitive mutations, there is a difference in prognosis following gefitinib treatment between patients with adenocarcinoma and those with non-adenocarcinoma, the latter group including patients with adenosquamous carcinoma (9). In that analysis, the response rate was 69% and median progression-free survival was 9.8 months among adenocarcinoma patients, whereas the response rate was 35% and median progression-free survival only 3.1 months among non-adenocarcinoma patients. Two adenosquamous carcinoma cases were included in that pooled analysis, and the tumor responses observed in both patients involved stable diseases (10, 11). Considering that our patient benefited from gefitinib for three years, tumor responses may differ among adenosquamous carcinoma patients. Detailed histological analyses of adenosquamous carcinoma have not so far been described in other reports, and a prospective investigation of the relationship between histological subtypes of adenosquamous carcinoma and tumor response to EGFR-TKI is therefore needed.

In the present case, both T790M and delE746-A750 were detected in the metastatic lesion consisting of a squamous cell carcinomatous component. The T790M mutation is known to appear in half of patients who acquire resistance to EGFR-TKI (14). In our case, T790M was observed in the squamous cell carcinomatous component of adenosquamous carcinoma after the patient acquired resistance to EGFR-TKI. Using our new detection system, MBP-QP, T790M was also observed in circulating plasma DNA (Fig. 2D).

Plasma DNA was isolated from 200 uL of the patient’s plasma using a QIAamp DNA mini kit (Qiagen). MBP-QP could therefore be an effective, alternative method for T790M detection, although a prospective study is needed to confirm its usefulness, as the detection was retrospectively observed in the present case.

In conclusion, an *EGFR* mutation analysis is helpful for selecting the appropriate treatment, even in patients with non-adenocarcinoma. In particular, when the component of adenocarcinoma is BAC, as in our case, it would be difficult to diagnose adenosquamous carcinoma with a transbronchoscopic biopsy. Although the prognosis of patients with adenosquamous carcinoma is poorer than that of patients with adenocarcinoma or squamous cell carcinoma, some adenosquamous carcinoma patients with *EGFR* mutations could benefit from EGFR-TKI. In addition, conducting examinations of circulating plasma DNA could be an effective method for monitoring acquired resistance to EGFR-TKI.

The authors state that they have no Conflict of Interest (COI).

**References**


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