Transformation from adenocarcinoma to squamous cell carcinoma associated with long-term administration of EGFR-TKIs

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Abstract. Although patients with non-small cell lung cancer exhibiting *EGFR* mutations generally respond to tyrosine kinase inhibitors (TKIs), the majority of patients acquire resistance ~1 year after treatment. *EGFR* T790M mutations, *MET* or *HER2* amplifications and phenotypic transformations contribute to the mechanism of EGFR-TKI resistance. The transformation of small cell lung cancer frequently occurs, although few convert to squamous cell carcinoma associated with the administration of EGFR-TKIs. The current study reports a case of *EGFR*-mutated adenocarcinoma of the lung that transitioned to squamous cell carcinoma in association with long-term EGFR-TKIs administration.

Introduction

Precision medicine enables patients with cancer with genetic alterations of driver oncogenes to receive effective treatment. Patients with non-small cell lung cancer (NSCLC) harboring mutations in the gene encoding epidermal growth factor receptor (EGFR) dramatically respond to the initial administration of EGFR tyrosine kinase inhibitors (TKIs). Unfortunately, tumors become drug-resistant after approximately 1 year. The most frequently encountered mechanism of resistance is associated with the presence of the secondary mutation *EGFR* T790M. Another major mechanism involves amplification of *MET* or *HER2* and activation of bypass signaling by MET (1). Furthermore, adenocarcinoma (ADC) cells may undergo transformation to a different phenotype. Most published cases involve transformation from ADC to small cell lung cancer (SCLC), and few cases convert from ADC to squamous cell carcinoma (SqCC) (2,3). Moreover, histological transformation during long-term treatment with EGFR-TKIs rarely occurs. Here we report a patient who underwent surgery for an ADC with a deletion of *EGFR* exon 19. The ADC underwent transformation to SqCC, which was associated with long-term administration of two EGFR-TKIs.

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Abbreviations: NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ADC, adenocarcinoma; SCLC, small cell lung cancer; SqCC, squamous cell carcinoma

Key words: epidermal growth factor receptor tyrosine kinase inhibitor, resistance, salvage surgery, squamous cell carcinoma transformation, MET amplification

Case report

A 56-year-old female who never smoked underwent left upper lobectomy and mediastinal lymph node dissection. She was diagnosed with pathological stage IIIA (p-T1N2M0), invasive ADC (acinar predominant) with an *EGFR* mutation (deletion of exon 19). She subsequently received four cycles of platinum doublet adjuvant chemotherapy, followed by gefitinib, for approximately 6 years because of chronic elevated concentrations of serum carcinoembryonic antigen (CEA). Seven years after initial surgery, a small nodule was detected in her right upper lobe that gradually enlarged. Histopathology of a transbronchial tumor biopsy revealed ADC and SqCC. The tumor harbored a secondary *EGFR* mutation (T790M) as well as inherent sensitive mutation. After some treatments, osimertinib was administered, and a partial response was achieved without adverse effects.

After 2 years, computed tomography (CT) detected growth of the tumor previously identified in the right upper lobe, which we suspected had acquired resistance to osimertinib. Positron emission tomography/CT showed active uptake of 2-deoxy-2-[18F] fluoroglucose into the tumor. However, lesions in the mediastinal and hilar lymph nodes indicating oligoprogression were not detected. The patient underwent salvage surgery involving a right upper lobectomy and mediastinal lymph node dissection (Fig. 1). Histological examination detected a keratinizing SqCC with mediastinal lymph node metastasis. There was no evidence of an ADC cells in the tumors or metastatic lymph nodes.

The serum levels of the tumor markers CEA and the cytokeratin 19 fragment (SqCC marker) were not elevated. Immunohistochemical analysis detected p63-positive tumor

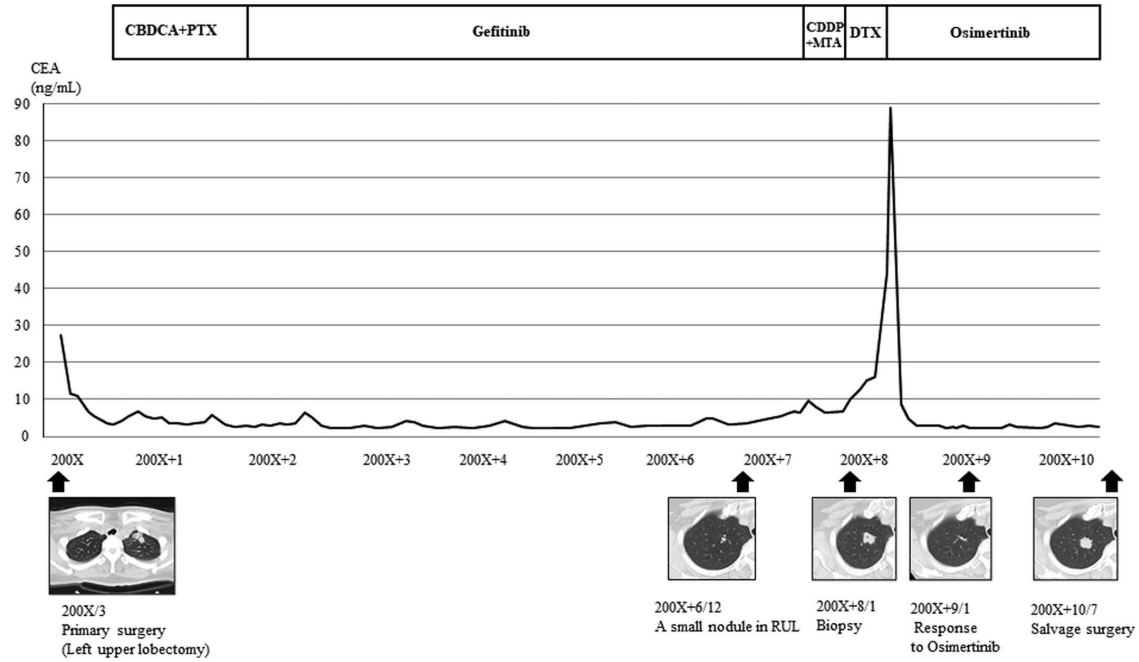

Figure 1. Clinical course. Left upper lobectomy and mediastinal lymph node dissection was initially performed. After surgery, gefitinib was administered for ~6 years. A recurrent small nodule was detected in right upper lobe and the patient exhibited a partial response to osimertinib. Salvage surgery was performed to remove the tumor as it acquired resistance to osimertinib during the 2-year course of its administration. CBDCA, carboplatin; PTX, paclitaxel; CDDP, cisplatin; MTA, pemetrexed; DTX, docetaxel; RUL, right upper lobe; CEA, carcinoembryonic antigen.

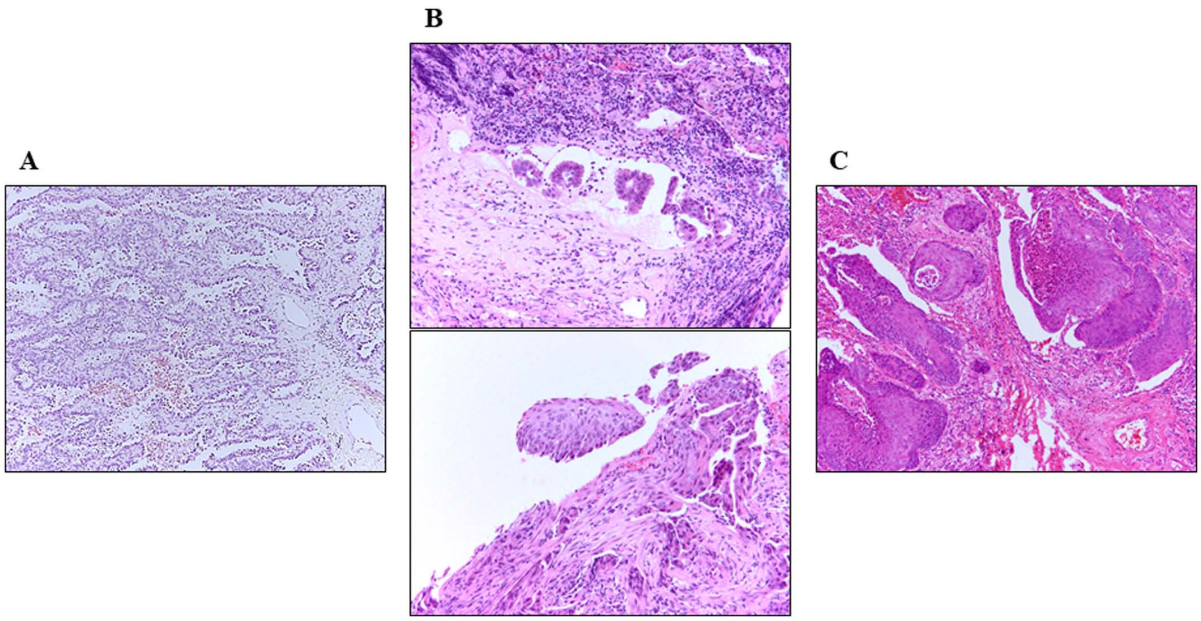

Figure 2. Pathology. (A) The primary tumor was diagnosed as an invasive ADC with a deletion of the *EGFR* exon 19 (E746-A750). SqCC cells were not detected in the tumor or metastatic lymph nodes (magnification, x100). (B) Histopathological analysis of a transbronchial biopsy of the recurrent tumor in the right upper lobe revealed adenocarcinoma and squamous cell carcinoma. The tumor exhibited a secondary *EGFR* mutation (T790M) and a deletion of *EGFR* exon 19 (magnification, x200). (C) After treatment with osimertinib, the recurrent tumor completely converted into a keratinizing SqCC that expressed p63 but not TTF-1. The tumor harbored *EGFR* T790M and the EGFR exon-19 deletion. *MET* amplification was newly detected. ADC, adenocarcinoma; EGFR, epidermal growth factor receptor; SqCC, squamous cell carcinoma; TTF-1, thyroid transcription factor 1.

cells but not TTF-1. The tumor was diagnosed as an SqCC harboring *EGFR* T790M, indicating that it arose from the recurred ADC (Fig. 2). Moreover, *MET* amplification was detected. The patient developed distant metastases in the kidneys and para-aortic lymph nodes 6 months after salvage surgery.

Discussion

Transformation from *EGFR*-mutated ADC to SCLC occurs in 3 to 14% of patients with acquired resistance to initial EGFR-TKI treatment (4). Transformation of ADCs to SqCC is less common. For example, a recent study (3) reported for

the first time, the transition from *EGFR*-mutated lung ADC to SqCC after osimertinib treatment. This same study (3) reviewed reports describing the development of an SqCC phenotype in 16 patients with *EGFR*-mutated NSCLC who were treated with TKIs (3). According to their report, most of the previous cases were diagnosed with affected lesions by limited biopsy because of the advanced staged diseases, so there were some possibilities of mixed tumor of ADC and SqCC in primary or recurrent sites. In our case, the possibility could be denied because the whole resected primary and recurrent tumors were completely evaluated by two surgeries, and our comprehensive analyses of these tumors clearly distinguish our studies from the others.

Although a recent study presents *in vitro* and *in vivo* evidence supporting the transdifferentiation of ADC to SqCC associated with *EGFR*-mutated lung cancers treated with TKIs (5), the underlying mechanism is unknown and therefore requires further study. In addition, the correlation between the duration of TKI treatment and the histological transformation also remains unclear. Roca reported that the TKI treatment times were from 4 to 69 months in the ADC patients with SqCC transformation, suggesting that there was a poor correlation between the treatment duration and the phenomenon (3). Further accumulation of similar cases is needed to clarify this point.

The few patients in which *EGFR*-mutated ADC converts to SqCC during the administration of EGFR-TKIs hinders development of a specific optimal treatment. For example, an *EGFR*-mutated ADC undergoing transformation to SqCC with undetectable *EGFR* T790M exhibited a durable response to afatinib (6), suggesting the possibility that the conversion to SqCC does not directly contribute to acquired resistance to EGFR-TKIs. Thus, further studies are required to determine if the conversion to SqCC is the 'cause' or 'outcome' of the development of resistance to EGFR-TKIs.

MET amplification, which was newly detected here in the recurrent tumor, may serve as a potential target of therapy. *MET* amplification enhances the proliferation of *EGFR*-mutated cultured NSCLC cells and increases the growth of tumors and their metastasis *in vivo* (7). Furthermore, a MET inhibitor achieves significant antitumor activity in patients with NSCLC with *MET* amplification (8,9). These findings suggest a strategy for developing effective therapeutics.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

TH treated the patient, acquired the data, performed the literature review, and wrote the manuscript. YoK analyzed the pathological findings. AN, SM, YaK, YTak, YTan and HN evaluated the patient and participated in the therapy. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Tottori University, Faculty of Medicine (Tottori, Japan) (grant no. 19A143).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of data and materials.

Competing interests

The authors declare that they have no competing interests.

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