# Squamous Cell Carcinoma Transformation from EGFR-mutated Lung Adenocarcinoma: A Case Report and Literature Review

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## Clinical Practice Points

- *Epidermal growth factor receptor* (*EGFR*)-mutated non–small-cell lung cancer responds dramatically to initial EGFR tyrosine kinase inhibitors (TKIs), although acquired resistance develops in ~1 year.
- Osimertinib, one of the T790M-specific EGFR TKIs, results in a favorable response in *EGFR*-mutated NSCLC that has developed acquired resistance with a secondary T790M mutation.
- We report a rare case of *EGFR*-mutated stage IB lung adenocarcinoma with a point mutation in exon 21 (L858R) in a 68-year-old man that showed histologic transformation to squamous cell carcinoma (SCC) concurrently with secondary T790M mutation and responded to osimertinib.
- T790M-specific third-generation EGFR TKIs, including osimertinib, could be a promising strategy for *EGFR* T790M mutation-positive NSCLC, regardless of the histologic findings.

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**Keywords:** Acquired resistance, Histologic transformation, Non–small-cell lung cancer, Osimertinib, T790M

## Introduction

Cases of non–small-cell lung cancer (NSCLC) harboring a somatic mutation in *EGFR* respond dramatically to initial EGFR tyrosine kinase inhibitors (TKIs), although acquired resistance will develop in ~1 year.[1-3] A variety of acquired resistance mechanisms have been reported, including secondary T790M mutation, bypass or alternative pathway activation, and histologic and phenotypic transformation.[4]

Osimertinib, one of the third-generation EGFR TKIs, is selective for sensitizing mutations and the T790M resistance mutation[5] and was approved for the treatment of advanced NSCLC in which T790M-mediated drug resistance has developed. Strategies for other resistance mechanisms are now under development.

We report a rare case of EGFR-mutated lung adenocarcinoma that showed histologic transformation to squamous cell carcinoma (SCC) concurrently with a secondary T790M mutation and responded to osimertinib.

## Case Report

Left upper lobe adenocarcinoma (T2aN0M0, stage IB) was diagnosed in a 68-year-old man, a 50 pack-year former smoker, during a medical examination. We performed radical surgery with lobectomy and lymph node dissection, followed by adjuvant chemotherapy with 250 mg of UFT (uracil, tegafur) bid for 2 years. During follow-up examinations, a solitary brain metastasis was found 4 years after the operation. The patient underwent stereotactic radiosurgery for the brain metastasis and was monitored without the use of systemic therapy. However, his disease subsequently relapsed, with detection of a right adrenal lesion 1 year after stereotactic radiosurgery. Molecular analysis of the resected lung demonstrated an *EGFR* point mutation (L858R) in exon 21. The

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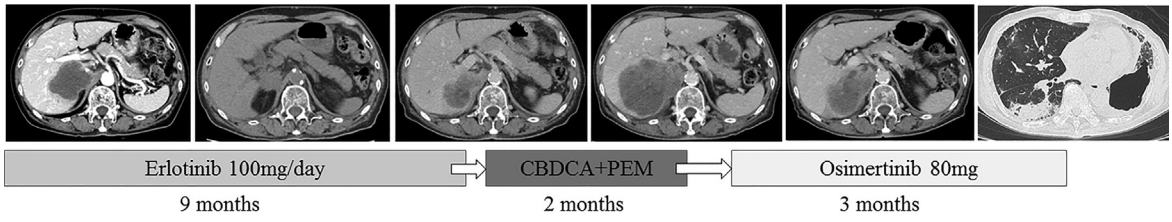
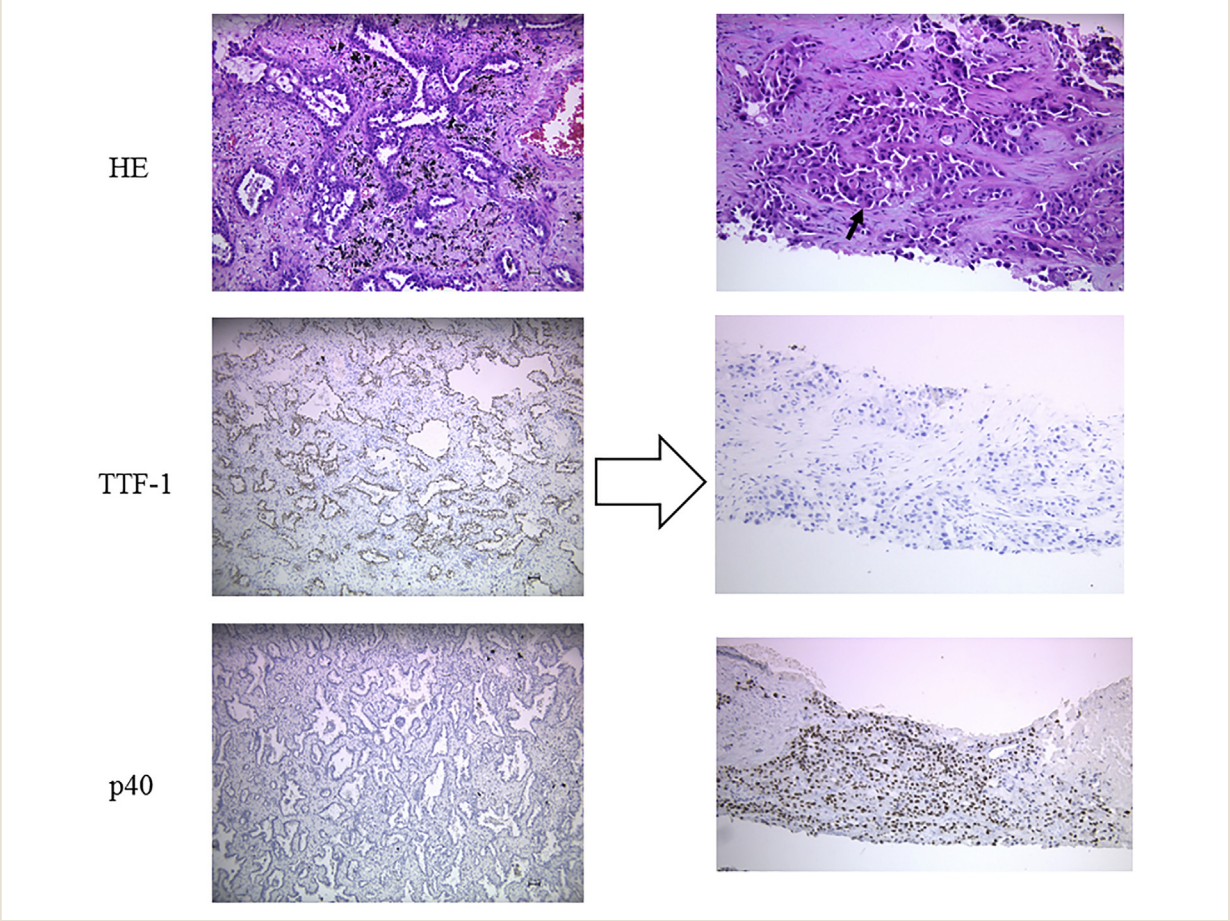
**Figure 1** Treatment Course With Corresponding Computed Tomography Scans




patient received erlotinib (100 mg once a day) as first-generation EGFR TKI therapy, and a partial response (PR) was achieved. However, disease progression of the known adrenal lesion occurred 9 months after the initiation of erlotinib. The adrenal lesion rapidly enlarged, with liver invasion, although 2 cycles of carboplatin (AUC = 5) plus pemetrexed (500 mg/m$^2$) were administered (Figure 1). We performed percutaneous re-biopsy of the liver, which revealed histologic transformation to SCC (Figure 2), with persistent L858R and a secondary T790M mutation of EGFR.

Thereafter, osimertinib (80 mg once a day), one of the third-generation EGFR TKIs, was administered. A PR was achieved, and the clinical symptoms, including anorexia and fatigue, quickly

**Figure 2** Histologic Change From Adenocarcinoma to Squamous Cell Carcinoma. (Left) Resected Lung Sample Showing Predominant Papillary Lung Adenocarcinoma, With Positive Nuclear Staining for Transcription Factor-1 (TTF-1) and Negative Staining for p40. (Right) Repeat Biopsy of Liver After Erlotinib Treatment Showing Transformation to Squamous Cell Carcinoma Characterized by a Keratin Pearl Formation (Arrow), With Negative Staining for TTF-1 and Positive Staining for p40




Abbreviation: HE = hematoxylin and eosin.

improved. Despite the radiologic and clinical response, we had to discontinue treatment with osimertinib owing to an adverse effect (grade 3 interstitial lung disease) 3 months after drug administration. Discontinuation of osimertinib and introduction of systemic steroid therapy (prednisolone 0.5 mg/kg/day) resulted in remission of interstitial lung disease. However, the known adrenal lesion enlarged and invaded into the stomach, resulting in severe bleeding. The patient could not receive additional chemotherapy and died of disease 3 months after discontinuation of osimertinib.

## Discussion

The most common acquired resistance mechanism after initial EGFR TKI treatment is the secondary T790M mutation of *EGFR* (> 50%-60% of patient cases), and histologic transformation to small-cell lung cancer (SCLC) has been reported in 3% to 14% of patients with acquired resistance to initial EGFR TKI treatment.[6,7] However, transformation to SCC in *EGFR*-mutated lung adenocarcinoma is a very rare mechanism of acquired resistance to EGFR TKI. In total, 10 cases of *EGFR*-mutated NSCLC that had transformed to SCC have been identified to date from PubMed (Table 1).[8-14]

As shown in Table 1, the age of all 11 patients, including our patient, ranged from 43 to 79 years (median age, 64 years). Of all 11 patients, 6 (54.5%) were never smokers and 3 (27.3%) were former smokers. All 11 patients had EGFR mutations: 7 patients had an exon 21 point mutation (L858R) and 4 patients had an exon 19 deletion. The patient characteristics were not different from those of patients with treatment-naive *EGFR*-mutated NSCLC.[1-3] All these patients received a first-generation EGFR TKI (gefitinib or erlotinib) as initial EGFR TKI treatment. Of the 8 patients available for evaluation of the response to initial EGFR TKI therapy, 7 (87.5%) achieved a PR and 1 had stable disease. The interval to treatment failure ranged from 5 months to 2 years (median, 9.5 months).

Unsampled combined components (adenosquamous carcinoma) might have been selected under the treatment pressure of EGFR TKIs in these cases. However, in 3 patients, including our patient, adenocarcinoma was diagnosed by evaluating surgically resected samples. In our patient, no squamous cell carcinoma lesion was present in the resected lung. In addition, the duration of response to EGFR TKI therapy in the remaining patients, diagnosed by small biopsy or cytology, was 5 to 15 months (median, 9 months), longer than that of the cases of non-adenocarcinoma NSCLC with an activating *EGFR* mutation (median, 3.1 months).[15] These results suggest that these cases, including our case (Table 1), actually developed histologic transformation from adenocarcinoma to SCC through the process of developing acquired resistance.

At present, among the acquired resistance mechanisms to EGFR TKIs, the cases with a secondary *EGFR* T790M mutation and those with SCLC transformation can receive treatment according to the resistance mechanisms. T790M-specific third-generation EGFR TKIs apparently prolong progression-free survival compared with standard platinum-based chemotherapy in patients with *EGFR* T790M mutations.[5] Sequist et al[7] reported that patients with *EGFR*-mutated NSCLC that had transformed to SCLC responded to chemotherapy regimens used for SCLC.

Because of the rarity of *EGFR*-mutated NSCLC developing SCC transformation, no specific treatment for these patients has been established. Pemetrexed-based chemotherapy is inferior to that of

**Table 1** Clinicopathologic Characteristics, Molecular Characteristics, and Treatment Course of *EGFR*-Mutated Adenocarcinoma With Squamous Cell Carcinoma Phenotype Transformation on Development of Acquired Resistance to EGFR TKIs

| Investigator | Age; Sex | Smoking (pack-y) | *EGFR* Mutation | Specimen (Before Treatment) | Stage | Initial EGFR TKI | Response (TTF) | Acquired Gene Alterations | Subsequent Therapy |
|---|---|---|---|---|---|---|---|---|---|
| Scher et al,[8] 2013 | 58; F | Former (5) | Exon 19 deletion | CTNB (lung) | IIIA | Erlotinib | PR (UK) | ND | Unknown |
| Kuiper et al,[9] 2015 | 63; F | Never | L858R | TBB | IV | Erlotinib | UK (5 mo) | PIK3CA exon 20 H1047R | Cisplatin + pemetrexed; gefitinib; carboplatin + gemcitabine |
| Levin et al,[10] 2015 | 66; F | Never | L858R | Pleural effusion | IV | Erlotinib | PR (8 mo) | ND | None |
| Hsieh et al,[11] 2015 | 51; F | UK | Exon 19 deletion | VATS (pleural) | IV | Gefitinib | PR (ND) | ND | Cisplatin + gemcitabine |
| | 61; F | Never | L858R | TBB | IV | Gefitinib | SD (1 y) | ND | Erlotinib |
| Jukna et al,[12] 2015 | 74; F | Former | Exon 19 deletion | TBB | IV | Gefitinib | PR (10 mo) | T790M | RT |
| | 79; F | Never | L858R | Pleural effusion TBB | IV | Gefitinib | PR (15 mo) | T790M | RT; gefitinib |
| Haratani et al,[13] 2016 | 48; F | Never | Exon 19 deletion | Surgery | IIIA | Gefitinib | UK (2 y) | ND | Platinum-based chemotherapy |
| | 64; F | Never | L858R + T790M | UK | IV | Gefitinib | UK (UK) | T790M[a] | Rociletinib |
| Longo et al,[14] 2017 | 43; F | Former (UK) | L858R | TBB | IV | Gefitinib | PR (8 mo) | S768I | None |
| Present case | 78; M | Former (50) | L858R | Surgery | IB | Erlotinib | PR (9 mo) | T790M | Carboplatin + pemetrexed; osimertinib |

Abbreviations: CTNB = computed tomography-navigated biopsy; EGFR = epidermal growth factor receptor; F = female; M = male; ND = not detected; PR = partial response; SD = stable disease; TBB = transbronchial biopsy; TKI = tyrosine kinase inhibitor; TTF = time to treatment failure; UK = unknown; VATS = video-assisted thoracic surgery.
[a]T790M mutation was detected at diagnosis.

other third-generation cytotoxic agents (eg, gemcitabine or docetaxel) for patients with SCC compared with those with non-squamous NSCLC.[16] Combined pemetrexed with carboplatin treatment did not result in a response in our patient. Thus, pemetrexed treatment might be less effective for SCC that has transformed from adenocarcinoma, similar to original SCC.

SCC transformation, concurrent with T790M mutation, has been reported in 3 cases to date[12,13]; however, the efficacy and safety of T790M-specific EGFR TKIs are unclear in this setting. Haratani et al[13] reported a case that was successfully treated with rociletinib, one of the third-generation EGFR-TKIs, in the same setting. To the best of our knowledge, our is the first case of *EGFR*-mutated adenocarcinoma transforming to SCC concurrent with a secondary T790M mutation that was treated with and responded to osimertinib, which is the only third-generation EGFR TKI available in clinical practice. T790M-specific third-generation EGFR TKIs, including osimertinib, could be a promising strategy for EGFR T790M mutation-positive NSCLC, regardless of the histologic findings. However, further studies are necessary to establish the optimal treatment for patients with EGFR-mutated NSCLC who have developed histologic transformation to SCC with a secondary T790M mutation.

## Conclusions

We report a rare case of EGFR-mutated lung adenocarcinoma that transformed to SCC concurrent with secondary T790M mutation. Osimertinib could be a promising strategy for patients with EGFR-mutated NSCLC with SCC transformation and a secondary T790M mutation and should be evaluated in further studies.

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## Disclosure

The authors declare that they have no competing interests.

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