

# Concomitant T790M mutation and small-cell lung cancer transformation after acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor

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## Keywords

Adenocarcinoma, epidermal growth factor receptor-tyrosine kinase inhibitor, small-cell lung cancer transformation, T790M mutation.

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## Abstract

A 70-year-old man was admitted to our hospital with an abnormal chest X-ray shadow. Bronchoscopy revealed an adenocarcinoma tumour with an epidermal growth factor receptor (EGFR) exon 19 deletion. Positron emission tomography-computed tomography scanning and magnetic resonance imaging showed advanced stage IV lung cancer. He was treated with erlotinib as a first-line drug, which maintained a clinical response for 16 months. After disease progression, a re-biopsy was done from the tumour in the right lower lobe. The obtained specimen harboured both small-cell lung cancer (SCLC) transformation with retention of the EGFR 19 deletion and the development of an EGFR T790M mutation. We came across a very rare condition of concomitant T790M mutation and SCLC transformation after acquired resistance to EGFR-tyrosine kinase inhibitor.

## Introduction

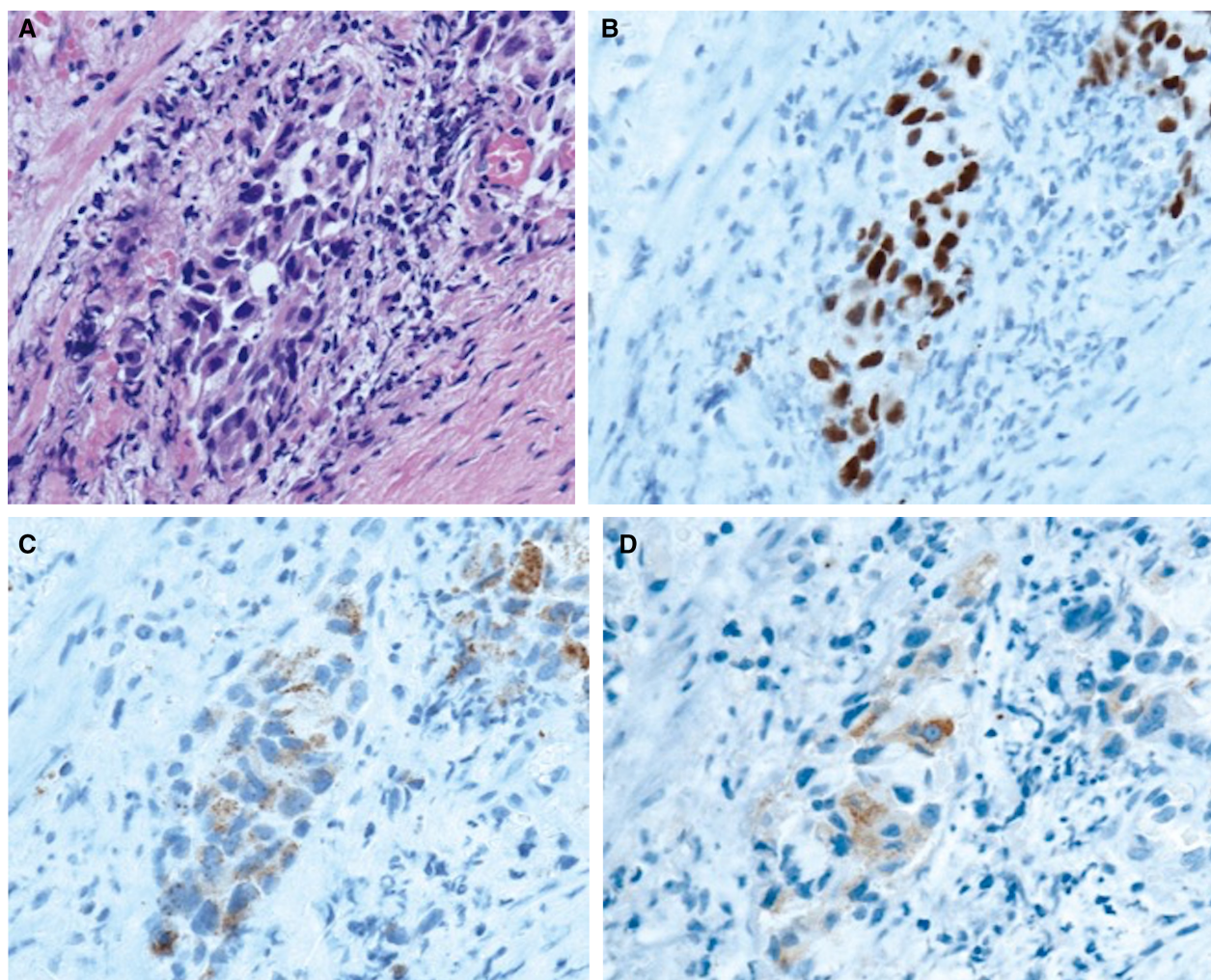
Although epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) drastically improves lung cancer with the EGFR mutation, drug resistance after long-term use is inevitable. The mechanisms underlying resistance have recently become clearer [1,2]. T790M mutation and small-cell lung cancer (SCLC) transformation are well known mechanisms of EGFR-TKI resistance [1–3]. Recently, a report showed a reciprocal relation between the SCLC transformation and the EGFR T790M mutation [4]. We came across a case of concomitant T790M mutation and SCLC transformation after acquired resistance to EGFR-TKI.

## Case Report

A 70-year-old man was admitted to our hospital with an abnormal chest X-ray shadow in November 2013. Positron

emission tomography-computed tomography and magnetic resonance imaging showed a right lower-lobe mass and multiple bone and brain metastases. Bronchoscopy revealed an adenocarcinoma (Fig. 1A–C) with an EGFR exon 19 deletion (E746-A750). His clinical stage was T2aN2M1b (stage IV).

He was treated with erlotinib as a first-line drug after whole-brain irradiation, which maintained a clinical response for 16 months. After disease progression was confirmed in April 2015, a re-biopsy was done from the tumour in the right lower lobe to check the mechanism of EGFR-TKI resistance. The obtained specimen harboured both SCLC transformation (Fig. 2A, B) with retention of the EGFR 19 deletion and the development of an EGFR T790M mutation. Cytotoxic chemotherapy targeting SCLC was selected for second-line therapy. He received six cycles of chemotherapy until October 2015 and achieved a modest



**Figure 1.** First biopsy specimens showing malignant cells with irregular papillary and tubular structures (A, haematoxylin and eosin staining,  $\times 100$ ). Immunohistopathological analysis demonstrated positive staining for thyroid transcription factor 1 (TTF-1) (B,  $\times 400$ ) and novel aspartic proteinase of the pepsin family (napsin A) (C,  $\times 400$ ), which are markers of adenocarcinoma. Immunohistopathological analysis also demonstrated positive staining for synaptophysin, which suggests neuroendocrine differentiation (D,  $\times 400$ ).

clinical response. After it was approved in May 2016, he began receiving osimertinib continuously as the third-line therapy, which has maintained a clinical response.

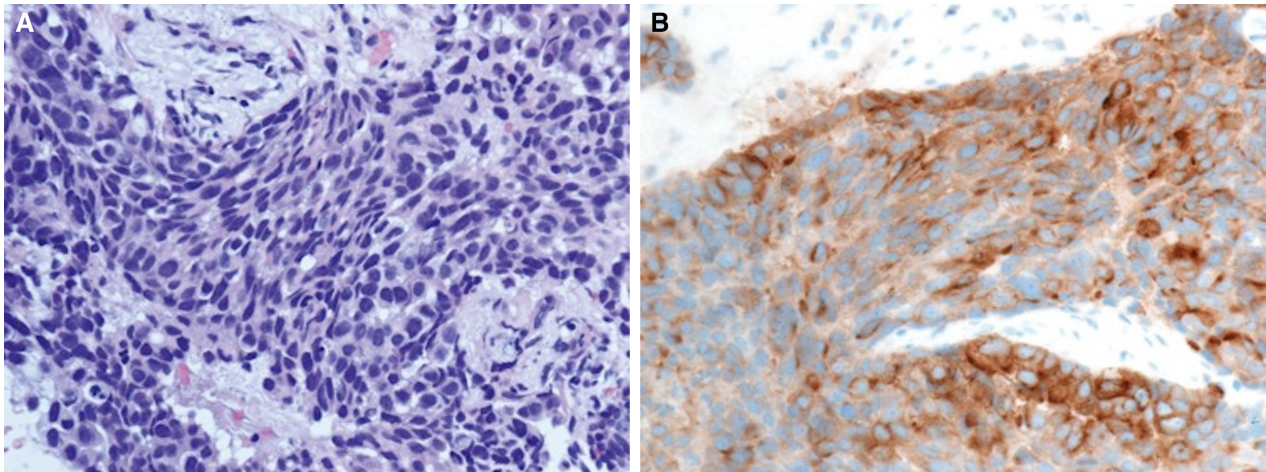
## Discussion

Although most lung cancers harbouring EGFR mutations achieve drastic response to treatment with EGFR-TKI, developing drug resistance after long-term use is inevitable. Recently, the mechanisms of resistance to EGFR-TKI are becoming well known. Acquiring an EGFR T790M mutation is a major cause of EGFR-TKI resistance [1,2]. An EGFR T790M mutation is detected in about half of patients who previously underwent EGFR-TKI treatment [1,2]. Transformation to SCLC is another resistance

mechanism. It is observed in  $<20\%$  of cases and is less common than the EGFR T790M mutation [3].

It is known that EGFR-TKI-resistant patients often have SCLC transformation and a sensitive EGFR mutation in recurrent tumours [3]. This phenomenon suggests the existence of a shared origin for cancer stem cells in the tumours. It is also known that different resistance factors have reciprocal relationships with each other [5]. Recently, Suda *et al.* mentioned a reciprocal relationship between the SCLC transformation and the EGFR T790M mutation [4]. Compared to these previous reports, our case was unique for having different resistance mechanisms in the same cancer cells. Because the treatment of erlotinib had maintained a response for 16 months and SCLC retaining the EGFR exon 19 deletion was identified, the present case





**Figure 2.** Second biopsy (after acquired epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) resistance developed) specimens showing diffuse proliferation of small- to intermediate-sized cells with scant cytoplasm and round to oval hyperchromatic nuclei. Immunohistochemical analysis demonstrated positive staining for synaptophysin (A,  $\times 400$ ) and chromogranin (B,  $\times 400$ ), which are markers of small-cell carcinoma.

was not likely to have had SCLC initially but suggested to share the origin of cancer stem cells. In addition to having initial morphological and immunohistological features of adenocarcinoma, our case also showed positive staining of synaptophysin, suggesting neuroendocrine differentiation (Fig. 1D). Immunohistological specificity may influence this unique result. Because we identified the T790M mutation, we challenged osimertinib for our patient. Osimertinib is the oral, third-generation EGFR-TKI, which is designed to target the EGFR T790M mutation while sparing wild-type EGFR. Phase I and II studies of osimertinib have shown good clinical activity [6,7].

In conclusion, this is the first case of concomitant T790M mutation and SCLC transformation after a patient acquired resistance to EGFR-TKI. Learning point from our case is that it might be helpful to consider checking the T790M mutation even when SCLC transformation is confirmed at re-biopsy. Compilation of more such cases and further analysis of similar cases are required.

### Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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