A patient with simultaneously appearing adenocarcinoma and small-cell lung carcinoma harbouring an identical EGFR exon 19 mutation

Mutations in the epidermal growth factor receptor (EGFR) gene occur in ~10%–20% of non-small-cell lung carcinoma (NSCLC) patients, specifically adenocarcinoma, and are associated with response to EGFR tyrosine kinase inhibitors (TKI) such as erlotinib and gefitinib. In contrast to NSCLC, EGFR mutations have rarely been reported in small-cell lung carcinoma (SCLC) [1]. The identification of a patient with combined SCLC and adenocarcinoma harbouring an identical mutation in EGFR exon 21 (L858R) in both histologies gave rise to the hypothesis that SCLC may originate from adenocarcinoma with an EGFR mutation [2].

A 42-year-old Caucasian female with no history of smoking was diagnosed with CT2N2M1b (stage IV) adenocarcinoma of the right upper lobe lung in March 2008. Diagnosis was made by cytology from a bronchial lavage of the RUL. A specimen for histological diagnosis was not procured at the time of diagnosis. The patient was subsequently treated with cisplatin–gemcitabine resulting in a partial response. For a single cerebellar metastasis, which was detected at a MRI scan after she complained about dizziness, she was treated with stereotactic radiotherapy.

In August 2008 the tumour relapsed and based on favourable clinical features (female, non-smoker, adenocarcinoma) treatment with erlotinib was started, resulting in a partial response lasting 10 months. As third-line treatment she received four courses of carboplatin–pemetrexed. At completion of this schedule, a CT scan demonstrated progressive disease, and it was decided to restart treatment with erlotinib. However, after 4 weeks of treatment, the tumour progressed and docetaxel treatment was initiated. After two cycles, a surgical biopsy was taken from a, not previously enlarged, supraclavicular lymph node which demonstrated SCLC (Figure 1B). EGFR mutation analysis using high-resolution melting analysis followed by Sanger sequencing disclosed a classical activating EGFR exon 19 deletion (c.2235-2249del15, p.delE746-A750) (Figure 2A). At the same time a transthoracic biopsy from an intrapulmonary metastasis in the left lung was obtained. Pathology demonstrated an adenocarcinoma (Figure 1A) harbouring two EGFR mutations: a mutation in exon 20 (c.2369C>T, p.T790M) and the identical exon 19 deletion detected in the SCLC containing supraclavicular lymph node (Figure 2B). Between March 2010 and September 2010, the patient received several chemotherapy schedules aimed at SCLC and/or adenocarcinoma. In addition, she received radiotherapy for new cerebral metastases and bone metastases. She passed away in December 2010.

To our knowledge, this is the first report that describes a patient with simultaneously appearing adenocarcinoma and SCLC harbouring an identical EGFR exon 19 deletion mutation. Recently, Sequist et al. reported five patients with a fundamental histology transformation from NSCLC to SCLC at the time of TKI resistance [3]. In all five patients, the original EGFR mutation was maintained, supporting the hypothesis of transformation rather than developing a second primary tumour. None of the SCLC specimens demonstrated a T790M mutation. However, apparently none of these patients had both adenocarcinoma and SCLC components at the time of these repeated biopsies. Other case reports describe never-smoking patients presenting with EGFR-mutant stage IV adenocarcinoma transforming into SCLC after developing TKI resistance [4].

It could be argued that from the beginning our patient had combined SCLC and adenocarcinoma, as primarily only a cytological diagnosis was obtained [2]. However, more recent histological biopsies demonstrated no mixed type tumours and, in addition, a T790M mutation was found only in the adenocarcinoma.

The fact that we identified identical EGFR mutations in both tumours at roughly the same time point and only a T790M mutation in the adenocarcinoma seems to support the hypothesis of transformation at the time of acquired resistance to TKI. The background of such a transformation is unknown at this time but of great interest. This case also demonstrates that distinct mechanisms of resistance to EGFR TKI (i.e. T790M mutation and histological transformation) may be operative within the same tumour. A report containing a small series of patients rebiopsied at progression after treatment with EGFR TKI suggested that resistance can be conveyed through cMET amplification simultaneously with the occurrence of T790M mutations [5]. Heterogeneity in resistance mechanisms, be it from initial diagnosis or arising de novo, might therefore be
more common than previously appreciated. This case report underlines the need for repeated biopsies for histological and molecular analysis at the time of progression in patients treated with EGFR-TKI. Furthermore, never-smoking patients developing SCLC after a previous diagnosis of adenocarcinoma should be investigated for EGFR mutations.

Figure 1. Histology. Biopsy of pulmonary tumour showed adenocarcinoma (A, H&E ×40) and of lymph node metastases SCLC (B, H&E ×40). Immunohistochemistry of adenocarcinoma was TTF1 + and CD56 – (C, TTF1 ×40) and of SCLC TTF1- and CD56+ (D, CD56 ×40).

Figure 2. EGFR mutational analysis. Direct sequencing of HRM PCR products showing (A) EGFR exon 19 deletion (c.2235-2249del15, p.delE746-A750) in SCLC and (B) EGFR exon 19 deletion (c.2235-2249del15, p.delE746-A750) and exon 20 point mutation (c.2369C>T, p.T790M) in adenocarcinoma.

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references

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