Small Cell Transformation and T790M Mutation as Coresistance Mechanisms for First-line Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) Therapy Failure

To the Editor:

Discovery of the activating *EGFR* mutation gene has revolutionized the treatment of patients with NSCLC. Nevertheless, resistance to first-line EGFR tyrosine kinase inhibitors (TKIs) develops in most patients with *EGFR*-mutant NSCLC after a period of 9 to 13 months. Here, we reported a case of first-line EGFR TKI failure attributed to SCLC transformation and T790M mutation.

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A 43-year-old male never-smoker presented with dyspnea in November 2015. Contrasted chest computed tomography (CT) scan showed a 20 × 25 × 17-mm enhancing nodule in the right upper lobe with multiple smaller nodules and ipsilateral pleural effusion (Fig. 1*A*). These lesions and a left parietooccipital brain lesion were 18F-fluorodeoxyglucose–avid on positron emission tomography/CT scanning. The brain lesion measured 21 × 23 × 24 mm on brain magnetic resonance imaging. CT-guided needle biopsy of the right upper lobe lung lesion revealed thyroid transcription factor-1–positive adenocarcinoma. Exon 19 deletion *EGFR* mutation was detected in the biopsy specimen by cobas v2 real-time polymerase chain reaction (RT PCR) (Roche Molecular Diagnostics, Pleasanton, CA). He began receiving gefitinib, 250 mg daily, and underwent stereotactic radiosurgery for his brain metastasis. His dyspnea diminished. Repeat CT scan and magnetic resonance imaging of the brain at 1 month and 3 months after commencement of gefitinib showed partial response (Fig. 1*B*). However, CT scan examination in May 2016 showed increased size of the primary right upper lobe lesion, with the appearance of three new lung nodules (Fig. 1*C*). A repeat biopsy was not performed because the patient was asymptomatic. Treatment was switched to the second-generation EGFR TKI afatinib at 40 mg daily. Further asymptomatic increase in size of the primary lung lesion and lung nodules was noted on CT scan a

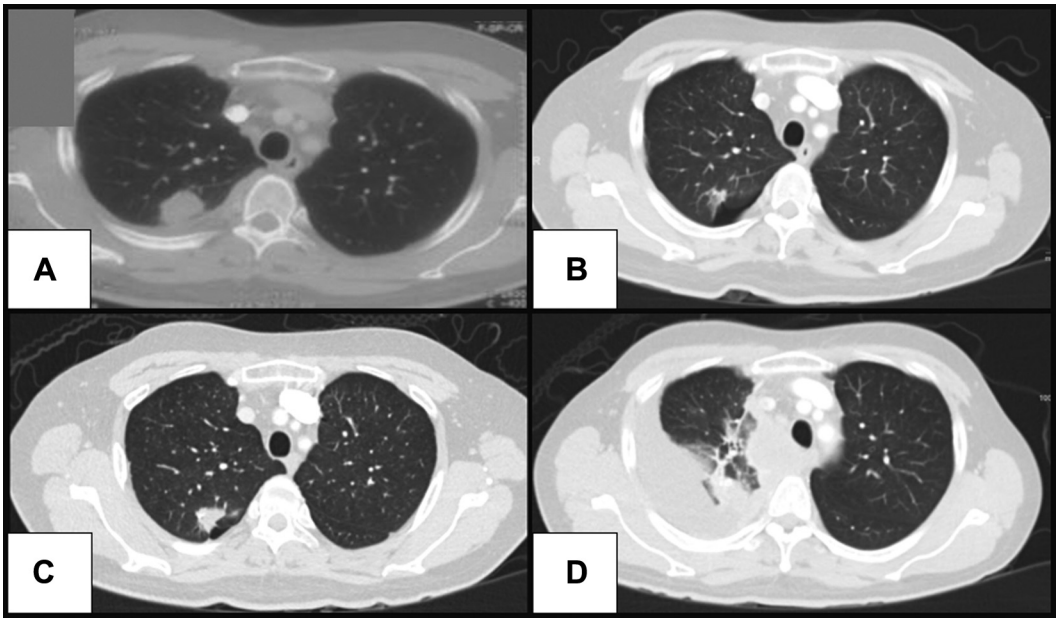

Figure 1. Serial contrasted computed tomography scan of the patient's thorax. (*A*) November 2015: nodule in the right upper lobe with ipsilateral pleural effusion at diagnosis. (*B*) February 2016: significant reduction in size of the primary tumor and complete resolution of the right pleural effusion after 3 months of gefitinib therapy. (*C*) May 2016: increase in size of the primary lung lesion and appearance of new lung nodules. (*D*) February 2017: marked increase in size of the primary tumor and recurrence of right pleural effusion prompting liquid and repeat tissue biopsies.

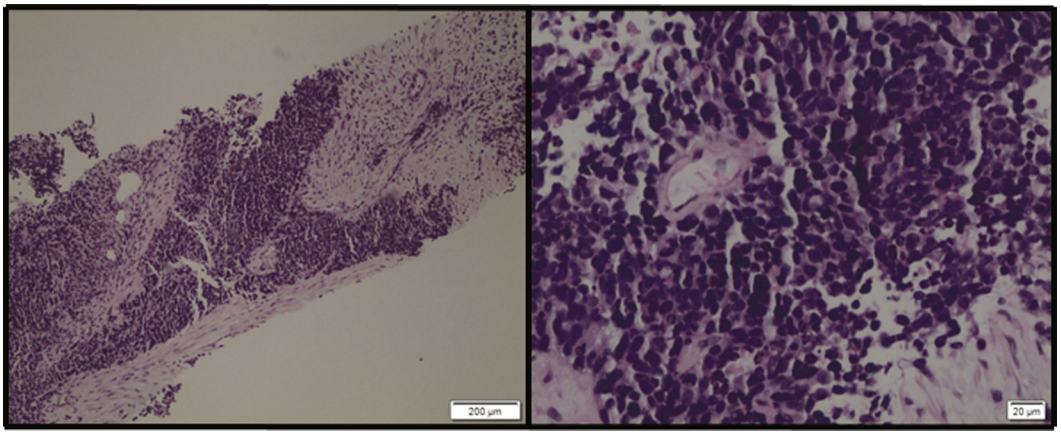

Figure 2. (*left*) Biopsy specimen shows tumor cells infiltrating in a diffuse manner against a fibrotic background (hematoxylin and eosin stain; original magnification, ×240). (*right*) Higher-power view of the tumor showed dark cells with high nuclear-to-cytoplasmic ratios, nuclear molding, and frequent mitosis (hematoxylin and eosin; original magnification, ×200).

month later. Afatinib was continued, and the patient's disease was stable on further CT examination 3 months later.

In February 2017, dyspnea developed. CT scan examination showed further increase in size of the right upper lobe primary lung lesion and a large right pleural effusion (Fig. 1*D*). Droplet digital PCR (Sanomics, Hong Kong) of cell-free plasma tumor DNA detected exon 19 deletion and exon 20 T790M mutations. CT-guided needle biopsy of the rapidly enlarging primary right upper lobe lesion showed SCLC that was strongly positive for CD56 and chromogranin, with some tumor cells exhibiting positivity for p63 and thyroid transcription factor-1 (Figs. 2 and 3). Exon 19 deletion but not T790M

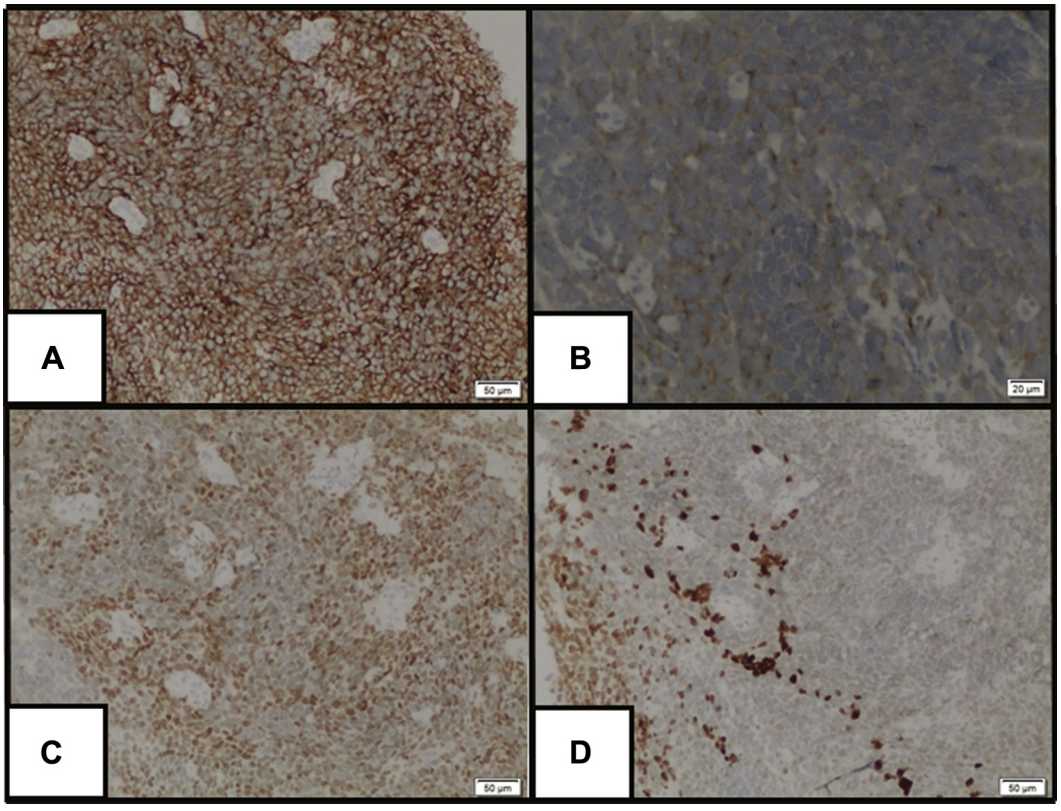

Figure 3. Tumor cells are diffusely and strongly positive for CD56 (original magnification, ×100) (*A*), weakly positive for chromogranin (original magnification, ×200) (*B*), and positive for p63 (original magnification, ×100) (*C*) and show focal expression of thyroid transcription factor-1 (original magnification, ×100) (*D*).

mutation was detected in the SCLC biopsy specimen by cobas v2 RT PCR. The patient then began receiving carboplatin/etoposide chemotherapy three times weekly.

Several cases of both SCLC transformation and T790M mutation in patients with *EGFR*-mutant lung adenocarcinoma who failed EGFR TKI therapy have been reported.[1–3] In these cases, SCLC transformation and T790M mutation were detected in different sites of tumor progression without coexisting. Such findings support the concept of a reciprocal relationship between SCLC transformation and T790M mutation.[4] So far, there has been only one case report on the presence of T790M mutation in the primary lung adenocarcinoma that had transformed to SCLC.[5] Because adenocarcinoma and SCLC originate from the same stem cell, such rare transformation that preserves the EGFR TKI resistance property of adenocarcinoma is possible.

In our patient, SCLC transformation in the primary tumor and T790M mutation detected in the plasma but not in the transformed SCLC are the resistance mechanisms accounting for failure of first-line EGFR TKI therapy. If only the tumor specimen from repeat biopsy or cell-free plasma tumor DNA had been analyzed, coexistence of the two resistant mechanisms would have been missed. Our patient demonstrates the heterogeneity of acquired resistance during EGFR TKI treatment and highlights the importance of performing repeat tissue biopsy even when T790M mutation is detected in the plasma, especially when there is rapid disease progression. The ability to detect different resistance mechanisms will translate into clinic benefit because SCLC is responsive to cytotoxic chemotherapy whereas T790M mutation needs targeted therapy with a third-generation T790M mutant–specific EGFR TKI. In conclusion, whenever possible, a repeat biopsy specimen and plasma T790M mutation should be tested upon failure of first-line EGFR TKI therapy.

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