A Case of Small Cell Lung Cancer Transformation from *EGFR*-Mutant Lung Adenocarcinoma with Primary Resistance to Gefitinib

To the Editor:

Transformation of SCLC from lung adenocarcinoma (LADC) was regarded as a rare mechanism for acquired resistance to EGFR tyrosine kinase inhibitors (TKIs),[1–4] which occurs months (range 10–58 months) after effective TKI treatment.[1,2] A predisposition toward divergence of SCLC from LADC clones was shown at the early stages of LADC before any treatment[4]; therefore, non-TKI treatment may also trigger SCLC transformation. Here, we present a case of LADC-to-SCLC transformation with primary resistance to gefitinib despite harboring of the *EGFR* exon 19 deletion.

A 58-year-old female never-smoker presented with coughing and was referred to our hospital. Computed tomography revealed a 3-cm lump in the right lower pulmonary lobe (Fig. 1); percutaneous biopsy indicated LADC, whereas the results of brain magnetic resonance, bone scintigraphy, and abdomen ultrasonography were negative. The patient underwent a right lower lobectomy with systematic mediastinal and hilar lymph node (LN) dissection. Pathologic examination showed LADC without LN metastasis (T2aN0M0 according to the seventh edition of the American Joint Committee on Cancer staging system) (Fig. 2). The patient received no adjuvant therapy and was subjected to routine surveillance.

Forty-two months later, the patient exhibited dyspnea and cough. Computed tomography revealed a subcarinal lesion compressing the left main bronchus but no evidence of other metastases (see Fig. 1). She declined biopsy and immediately received pemetrexed plus carboplatin to constrain her rapidly progressing symptoms. In parallel, amplification refractory mutation system analysis revealed *EGFR* exon 19 deletion in the primary LADC. Her symptoms were greatly relieved after one cycle of chemotherapy, so she received two more cycles and subsequent radiotherapy to this lesion (60 Gy in 30 fractions), followed by pemetrexed consolidation (see Fig. 1).

An enlarged mediastinal LN in her right tracheoesophageal groove was discovered at the completion of two cycles of pemetrexed treatment (see Fig. 1). She immediately received gefitinib but achieved no response. At 2 weeks after initiation of gefitinib therapy, the tumor had progressed to the left adrenal gland and left supraclavicular LN (see Fig. 1), and it further progressed to the liver by 2 months (see Fig. 1).

We performed fine needle aspiration on the left supraclavicular LN. Immunohistochemistry was performed on cell block sections and revealed SCLC cells that were positive for synaptophysin, chromogranin A, and CD56 (see Fig. 2). The patient subsequently received two cycles of etoposide plus cisplatin. Her supraclavicular and right tracheoesophageal groove lesions recessed significantly (see Fig. 1); however, she presented evident fatigue, nausea, and multiple new lesions in the liver, and her adrenal lesions progressed. Her condition deteriorated rapidly and she was transferred to palliative care.

To the best of our knowledge, this is the first report of SCLC transformation from *EGFR*-mutant LADC with primary resistance to TKIs. We consider it a case of bona fide SCLC transformation rather than a case with mixed histologic type or a second primary SCLC for several reasons. First, the resected primary LADC lesion was uniformly LADC without any SCLC components in the post hoc analysis (see Fig. 2). Second, there were 42 months between the initial diagnosis and recurrence, which was inconsistent with the aggressive behavior of SCLC (see Fig. 1). Lastly, the primary and transformed lesions shared the same *EGFR* driving mutation (exon 19 deletion E746-A750), which was double-confirmed by amplification refractory mutation system analysis and targeted sequencing.

Inactivation of the tumor suppressors Rb and p53 has been shown to predict SCLC transformation in patients with EGFR TKI–treated LADC.[4] In the present case, concurrent Rb and p53 inactivation was also found in both primary LADC and transformed SCLC cells (see Fig. 2), which is consistent with the findings in the aforementioned report.

The presented evidence implies that SCLC transformation does not exclusively depend on EGFR TKI treatment and may be induced by chemotherapy and/or radiotherapy. Clinicians should be wary of SCLC transformation in LADCs that have relapsed after any treatments, and the importance of prompt rebiopsy should be emphasized in cases of suspected transformation.

Disclosure: The authors declare no conflict of interest.

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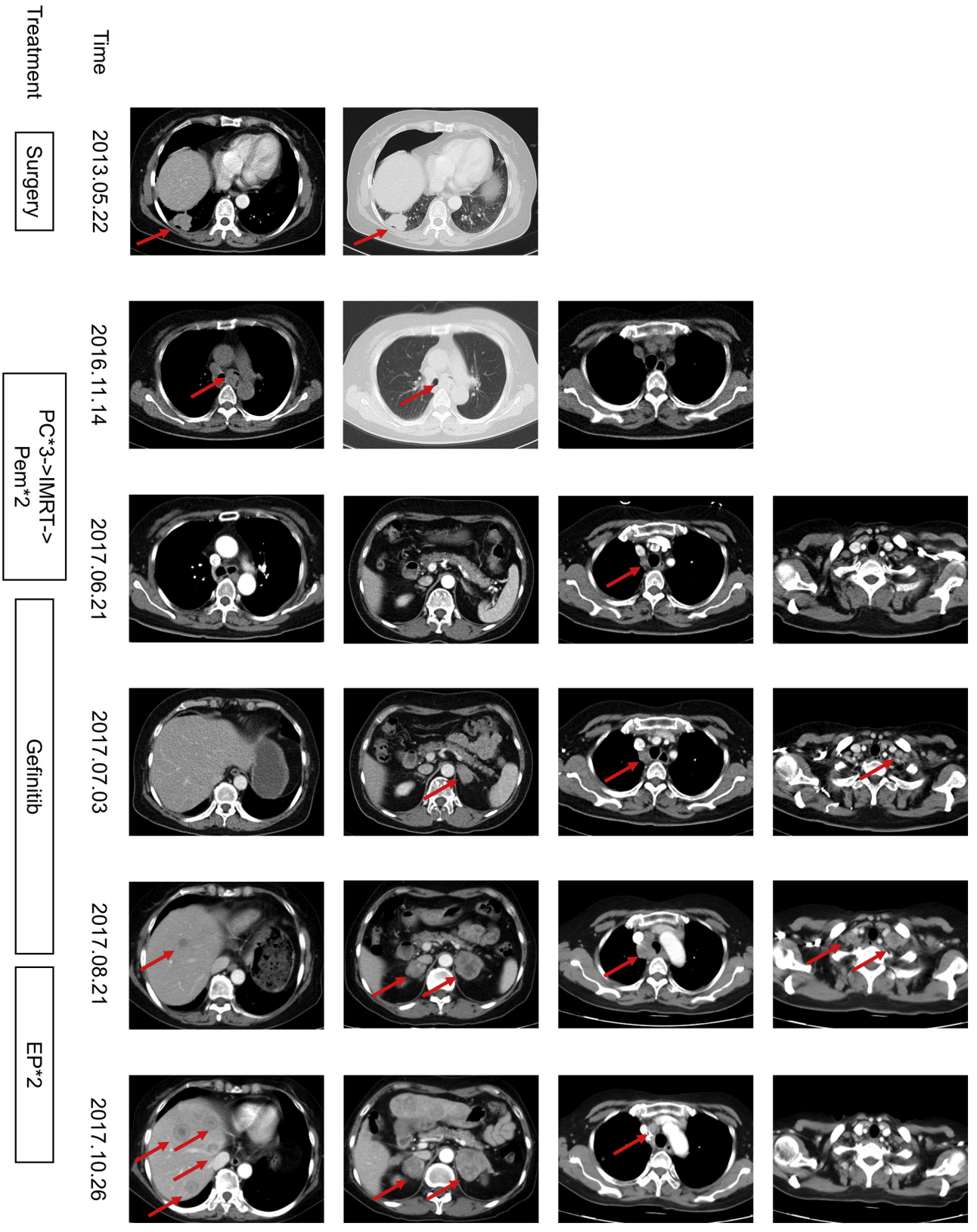

Figure 1. Follow-up schematic diagram. Serial computed tomography axial sections showing disease development. Red arrows indicate tumor lesions. Treatments and time line are presented to the left of the scans.