Heterogeneity or transformation? A whack-a-mole case of EGFR-mutant lung adenocarcinoma and small cell carcinoma: A case report

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Abstract
Histological transformation from adenocarcinoma to small cell lung cancer (SCLC) occurs ~10% after acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors. Transformed SCLC generally responds well to chemotherapy regimens for SCLC such as platinum plus etoposide. After the response, histological nature and clinical course could be complicated by possible heterogeneity or transformation. Therefore, monitoring rebiopsy is desirable to seize its histological nature at that moment. We report a case of EGFR-mutated adenocarcinoma, where histological transformations from adenocarcinoma and SCLC alternated. In this case, first rebiopsy after gefitinib revealed adenocarcinoma, but second rebiopsy after osimertinib identified SCLC transformation. After failure of platinum plus etoposide, adenocarcinoma-induced leptomeningeal metastases were controlled by osimertinib reintroduction. Optimal therapies could be provided according to the result of monitoring rebiopsy.

Keywords
EGFR-TKI, leptomeningeal metastases, osimertinib, small cell transformation

INTRODUCTION
Histological transformation to small cell lung cancer (SCLC) is one of the resistance mechanisms to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in EGFR-mutant non–small cell lung cancer (NSCLC) patients. Transformed SCLC responds favorably to chemotherapy such as platinum plus etoposide as in de novo SCLC. However, after treatment of SCLC, residual clones of NSCLC could re-emerge and progress. Tumors of different histological characteristics could co-exist in one patient. Monitoring rebiopsy is desirable to recognize dominant histology and to select suitable therapies. We report a case of EGFR-mutated NSCLC, where pathological diagnosis alternated between adenocarcinoma to SCLC.

CASE REPORT
A 59-year-old woman with a past smoking history was diagnosed with metastatic EGFR-mutant (exon 19 deletion) lung adenocarcinoma (Figure 1(a)). Gefitinib was administered as first-line therapy. After 14 months, right mediastinal lymph node enlarged, and biopsy detected T790M-positive adenocarcinoma (Figure 1(b)). Osimertinib was administered as second-line therapy. Twenty-four months after osimertinib initiation, primary lesion progressed. Afatinib plus bevacizumab was administered as third-line therapy. We, then, performed rebiopsy from the primary lesion, and the biopsy samples were positive for synaptophysin (Figure 1(c,i)) and chromogranin A (Figure 1(c,ii)), by which we confirmed transformation to SCLC. Pro-gastrin releasing peptide (pro-GRP) was as elevated as 109 pg/mL. As primary lesion exhibited enlargement after two cycles of afatinib plus bevacizumab (Figure 2(a)), we administered cisplatin plus etoposide for SCLC. After one cycle of chemotherapy, chest X-ray revealed remarkable response (Figure 2(b)). Pro-GRP greatly decreased to 58.8 pg/mL. Although primary lesion remained stable after four cycles of chemotherapy, she had difficulty moving the fingers of her right hand. Magnetic resonance imaging (MRI) revealed leptomeningeal metastases...
and atypical cell suspected of adenocarcinoma was detected in cerebrospinal fluid (Figure 1(d)). We reintroduced osimertinib and her symptoms improved immediately. Follow-up MRI showed favorable response (Figure 3(b)). Two months after osimertinib reintroduction, chest X-ray showed increased pleural fluid, whose cytology

**Figure 1** (a) Initial biopsy tissue sample from lung stained with H&E: adenocarcinoma. (b) First rebiopsy tissue sample from mediastinal lymph node stained with H&E: adenocarcinoma. (c) Second rebiopsy tissue sample from lung: SCLC. Stained with (i) synaptophysin and (ii) chromogranin a. (d) Third rebiopsy cytology sample from cerebrospinal fluid stained with Papanicolaou: atypical cell. (e) Fourth rebiopsy cytology sample from pleural fluid stained with Papanicolaou: adenocarcinoma. (f) Fifth rebiopsy tissue sample from liver stained with H&E: SCLC. H&E, hematoxylin and eosin; SCLC, small cell lung cancer.

**Figure 2** (a) Chest X-ray before cisplatin plus etoposide therapy. (b) Chest X-ray after one cycle, exhibiting a remarkable response.

**Figure 3** (a) Brain magnetic resonance imaging (MRI) before osimertinib reintroduction showed several metastatic lesions along sulci, suggesting leptomeningeal metastases. (b) One month after osimertinib reintroduction, brain MRI showed a favorable response.
revealed adenocarcinoma (Figure 1(e)). We started carboplatin plus pemetrexed, while continuing osimertinib simultaneously, fearing LM flare. Although pleural fluid diminished after one chemotherapy cycle, we switched to gemcitabine because of renal dysfunction and next switched to nab-paclitaxel, with continuous osimertinib. After one cycle of nab-paclitaxel, liver metastases progressed rapidly. Biopsy from liver revealed SCLC (Figure 1(f)). Pro-GRP level elevated again to 498 pg/mL. We immediately switched to amrubicin, while still continuing osimertinib. Although response was obtained for ∼4 months, LM further progressed, leading to convulsion and impaired mental status. We could no longer continue osimertinib nor amrubicin by performance status deterioration. She passed away 5 years after initial diagnosis. Detailed radiological change is presented in Figures 4 and S1.

**DISCUSSION**

Our case exhibited pathological diagnosis alternated between adenocarcinoma and SCLC (Figure 4), as recently reported by Wysota et al.\(^5\) SCLC transformation occurs in 3% to 14% of EGFR-mutant cases after EGFR-TKI.\(^1,2\) First rebiopsy after gefitinib detected adenocarcinoma, but second rebiopsy after osimertinib found SCLC transformation. After osimertinib resistance, rebiopsy is not clinically recommended because osimertinib resistant mechanisms are variable without any specific targeted therapies.\(^2\) However, efficacies of platinum plus etoposide and amrubicin were reported after SCLC transformation\(^3,4\) and were indeed effective in our case. This suggests importance of rebiopsy even after osimertinib failure to confirm SCLC transformation.

Osimertinib was reintroduced and continued after LM confirmation. Notable efficacy of osimertinib was demonstrated for LM by preclinical and clinical studies.\(^6,7\) Although combination therapy with EGFR-TKI and cytotoxic chemotherapy is not generally recommended, we decided on osimertinib continuation with sequential cytotoxic chemotherapies to prevent LM flare. Frequent disease flare was reported in brain metastases, including LM.\(^8\) Continuous osimertinib possibly contributed to survival over 1 year after LM diagnosis. Additionally, although no significant survival benefit was obtained, combination therapy with cytotoxic chemotherapy and EGFR-TKI could improve response rate and progression free survival after transformation from EGFR-mutated adenocarcinoma to SCLC.\(^9\) To maximize patients’ benefit, combination therapy could be one of treatment options, especially those with LM.\(^10\)

Two hypotheses were proposed as the mechanism of transformation.\(^11\) According to one hypothesis, EGFR-mutated NSCLC and SCLC are initially mixed in the tumor, and by responding to EGFR-TKI, EGFR-mutated NSCLC will decrease in number and SCLC component will increase. Another hypothesis is that type II alveolar cells have the capacity to differentiate into both adenocarcinoma and SCLC. The inactivation of RB1 and TP53 plays a role in transformation from adenocarcinoma to SCLC.\(^12\) In our case, we did not identify SCLC cells at initial rebiopsy, although we cannot exclude the possibility that this may be because of limited tissue collection. Considering that 24 months had already passed after osimertinib when SCLC was detected from the primary lesion, it is unlikely that adenocarcinoma and SCLC were mixed in the tumor. When adenocarcinoma was detected from CSF, re-introduction of osimertinib improved LM associated symptoms, which signifies EGFR-mutated adenocarcinoma resurgence. Several months after cessation of SCLC treatment, SCLC was detected in liver, this suggests SCLC recurrence. This clinical course implies that SCLC and adenocarcinoma clones coexisted in one patient. Rebiopsy is important to promptly seize dominant histological characteristics. Further studies are warranted to avoid playing “whack-a-mole” for SCLC transformation patients.

In conclusion, we experienced a case of EGFR-mutated adenocarcinoma, where pathological diagnosis alternated between adenocarcinoma and SCLC. Monitoring rebiopsy can be useful to identify dominant histological characteristics and provide timely/optimal therapies.
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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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