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Case report

Histologic transformation of *EGFR* mutant lung adenocarcinoma without exposure to EGFR inhibition

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ABSTRACT

Resistance to EGFR kinase inhibitors appears to be invariable in the treatment of non-small cell lung cancer. Several mechanisms have been described. Here, we report the first case of histologic transformation of *EGFR* mutant lung adenocarcinoma without prior exposure to EGFR inhibition.

1. Introduction

Despite initial marked response to EGFR kinase inhibitors in patients with non-small cell lung cancer (NSCLC) harboring activating *EGFR* mutations, drug resistance develops within a median of 12 months. Described resistance mechanisms include secondary mutations within *EGFR* (e.g. T790M), *MET* amplification, PI3K pathway hyperactivation, *HER2* amplification, AXL overexpression, and epithelial-to-mesenchymal transition. Additionally, in rare cases, *EGFR* mutant lung adenocarcinoma may undergo histologic transformation to small cell lung cancer and squamous cell cancer after EGFR inhibitor treatment [1,2]. Here, we report the first case of histologic transformation of *EGFR* mutant lung adenocarcinoma without prior exposure to EGFR inhibition.

2. Case report

During radiographic evaluation of a stage 3A invasive ductal carcinoma of the right breast, a 79-year old woman with no smoking history was found to have a right middle lobe mass (Fig. 1A). Biopsy demonstrated a TTF-1- and Napsin A-positive primary lung adenocarcinoma (Fig. 2A–C) harboring a classic *EGFR* exon 19 deletion (Fig. 3). She underwent right middle lobe lobectomy and mediastinoscopy, with a final diagnosis of stage 2 (T2N1M0) disease. The patient received three cycles of adjuvant carboplatin-pemetrexed chemotherapy (Fig. 1C). Subsequently she underwent partial right mastectomy, breast and axillary radiation therapy, and started tamoxifen.

Approximately 13 months after completing adjuvant chemotherapy, surveillance chest CT demonstrated an enlarging nodule at the right cardiophrenic angle (Fig. 1D). Biopsy revealed squamous cell carcinoma (Fig. 2E–F) with no evidence of adenocarcinoma histology. Molecular analysis demonstrated the original *EGFR* exon 19 deletion and no evidence of T790M mutation (Fig. 3). Immunohistochemical analysis of both the original and subsequent lung tumors demonstrated Rb expression (images not shown), suggesting absence of small cell histology. For both the original and subsequent lung tumors, all available tissue underwent histologic review. The patient initiated erlotinib, with partial response lasting six months (Fig. 1E).

3. Discussion

To our knowledge, this is the first reported case of histologic transformation of *EGFR* mutant lung adenocarcinoma without prior

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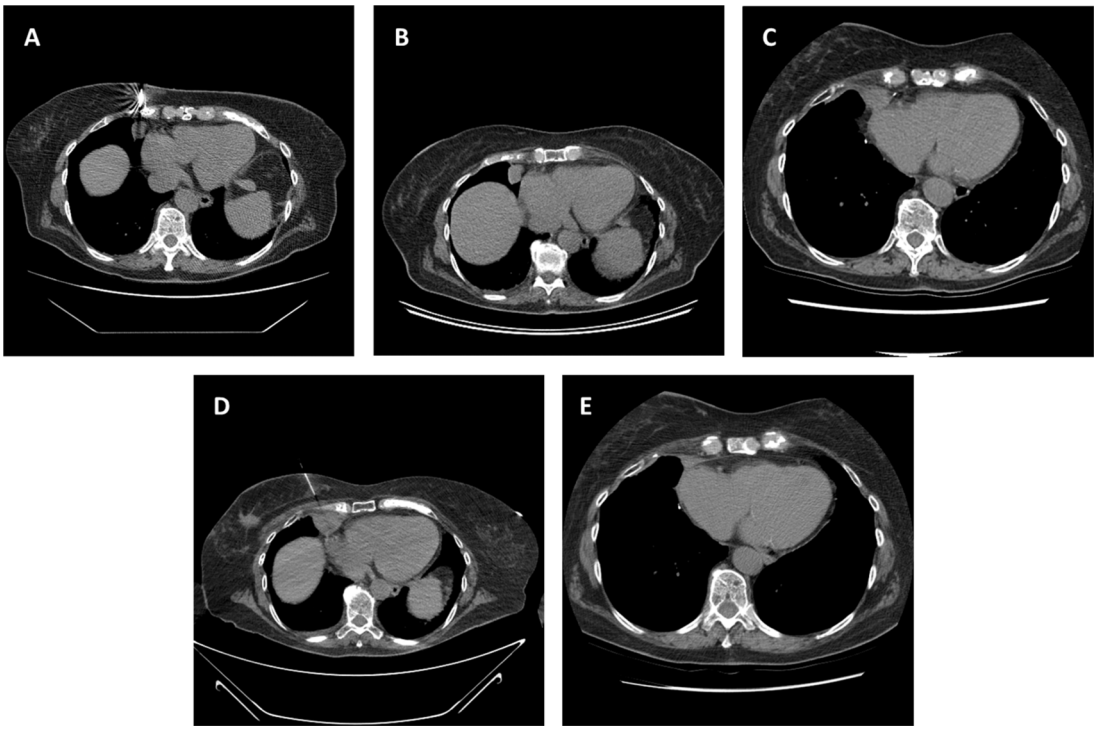

Fig. 1. A. Images from computed tomography (CT)-guided biopsy of adenocarcinoma lung lesion at the time of diagnosis. B. Chest CT before right middle lobectomy and adjuvant carboplatin-pemetrexed. C. Chest CT 5 months after right middle lobectomy and 1 month after last cycle of carboplatin-pemetrexed. D. CT-guided biopsy of squamous cell lung cancer progression. E. Images from chest CT 1 month after initiation of erlotinib with lesion now 1.9 × 0.8 cm, previously 2.4 × 2.0 cm.

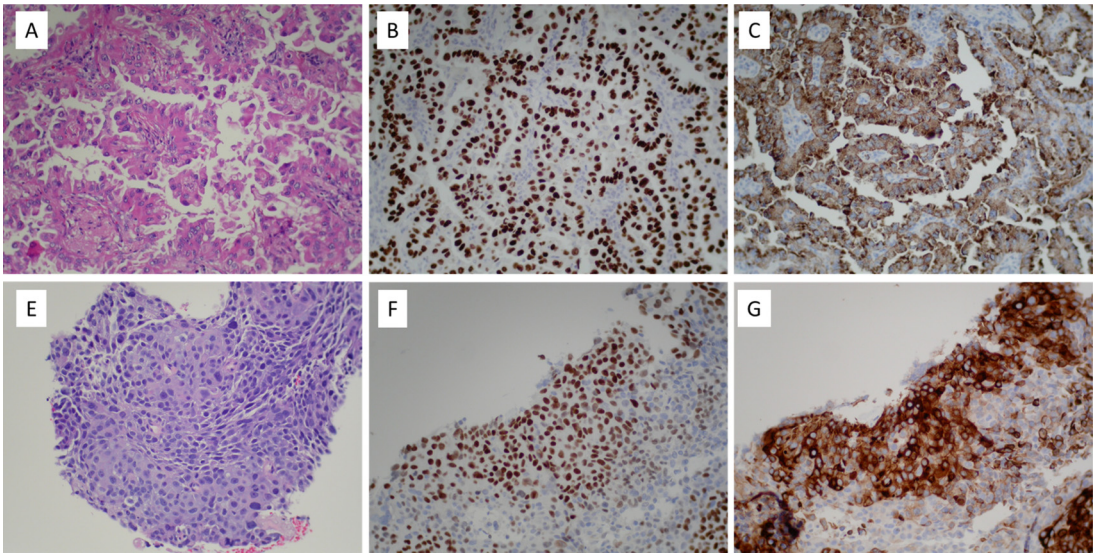

Fig. 2. A. Pulmonary adenocarcinoma, right middle lobe, H&E (200X). B. Pulmonary adenocarcinoma positive for TTF-1 (200X). C. Pulmonary adenocarcinoma positive for Napsin A (200X). Immunohistochemical stains for p63 and CK5/6 were negative (not shown). E. Squamous cell carcinoma, right cardiophrenic angle, H&E (200X). F. Squamous cell carcinoma positive for p63 (200X). G. Squamous cell carcinoma positive for CK5/6 (200X). An immunohistochemical stain for TTF-1 was negative (not shown).

exposure to EGFR inhibition. Potential explanations for the histologic transformation described in this case include (1) metaplastic transformation, (2) co-existence of both squamous and adenocarcinoma cells in the original tumor mass, or (3) development of a second primary cancer (unlikely given the maintenance of the original *EGFR* mutation). This phenomenon may suggest a population of pluripotent *EGFR* mutant cancer stem cells as the source of resistance. Although we observed morphological and immunohistochemical differences between the initial and recurrence specimens, we cannot rule out the possibility of a mixed tumor because needle biopsies provide limited sampling.

In this case, interval therapies included platinum-pemetrexed chemotherapy, breast irradiation, and the estrogen receptor modulator tamoxifen. Of these, pemetrexed seems the most likely to be associated with selective histologic pressure. Multiple clinical trials have demonstrated preferential efficacy of this agent against non-squamous tumors, which has been attributed to relatively greater expression and activity of thymidylate synthase in squamous cancers. The six-month duration of clinical benefit from EGFR inhibitor