Case report

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

Tri Le\textsuperscript{a}, Joseph Sailors\textsuperscript{b}, Dwight H. Oliver\textsuperscript{b, c}, Melissa Mayer\textsuperscript{c}, Sharon Hoskin\textsuperscript{c}, David E. Gerber\textsuperscript{a, c, *}

\textsuperscript{a} Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, United States
\textsuperscript{b} Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, United States
\textsuperscript{c} The Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, United States

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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.

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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 \cite{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...
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
treatment of the squamous lung cancer in this case—approximately half the median duration observed in adenocarcinoma cases—is characteristic of EGFR mutant squamous cancers [3].

Recently, histologic transformation has also been reported in anaplastic lymphoma kinase (ALK)-positive NSCLC after ALK inhibitor treatment [4]. The present case suggests that lung cancers harboring driver mutations may undergo histologic transformation independent of exposure to kinase inhibitors. Whether these cases have greater propensity than pan-wild type tumors, or their molecular characterization permits a clearer distinction from second primaries, is not clear.

Conflict of interest statement

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2017.01.005.

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