CE Case Report

EGFR-Mutated Lung Cancer With *T790M*-Acquired Resistance in the Brain and Histologic Transformation in the Lung

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Abstract

This case report describes the rare occurrence of a *T790M* resistance mutation found in a central nervous system (CNS) parenchymal metastasis. A concomitant squamous histology transformation in a lung non–*T790M*-resistant metastasis is also described. The authors hypothesize that this CNS resistance and histology transformation may have resulted from intermittent use of erlotinib treatment. This case report emphasizes the complexities of using erlotinib in the induction setting. (*JNCCN* 2013;11:1040–1044)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Explain a potential resistance mechanism to EGFR-TKI therapy when used to treat adenocarcinoma of the lung
- Discuss CNS metastases in patients receiving TKI therapy

Targeted epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have altered the treatment paradigm for patients with non–small cell lung

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cancer.[1,2] Although the initial response to these targeted agents among *EGFR*-mutated patients is dramatic, the response is often short-lived. Resistance mechanisms have been identified, including the *T790M* mutation, a point mutation involving a threonine to methionine amino acid change at position 790.[3] These secondary mutations are now frequently seen in non–central nervous system (CNS) tissue of patients who have been treated with EGFR-TKIs. However, almost one-third of patients treated with TKIs develop CNS metastases[4] without a documented resistance secondary mutation. Progression outside of the CNS is hypothesized to be from drug resistance, whereas CNS metastases are from inadequate penetration of initial drug treatment.[5,6]

Case Report

A 58-year-old woman with a 5 pack-year smoking history presented with cough and hemoptysis in January 2010. CT revealed a 5.5 × 4.5 × 5.5-cm right upper lobe mass abutting the pleura and superior vena cava without encasement. She was also found to have enlarged right hilar, paratracheal, subcarinal, and subcentimeter supraclavicular lymph nodes. CT-guided biopsy results of the lung mass indicated moderately differentiated adenocarcinoma (Table 1). PET scan showed increased fluorodeoxyglucose uptake in the right upper lobe mass and the right hilar and subcarinal regions. MRI of the brain in February 2010 was negative. She underwent an endobronchial ultrasound biopsy of a subcarinal node, which was positive for adenocarcinoma. Concurrent chemotherapy and radiation with carboplatin and pemetrexed was initiated for her T2b,N2,Mx non–small cell lung adenocarcinoma.

The patient received 1 dose of concurrent chemotherapy and radiation, at which time *EGFR* mutational status became available, revealing an exon 19 deletion. After extensive discussion with the patient and her informed family, the patient's neoadjuvant therapy was changed to erlotinib at 150 mg/d in mid-February 2010. She tolerated the therapy well, with minimal rash and fatigue. CT scan after 4 weeks of therapy showed an excellent response, with an approximate 30% reduction of the right upper lobe mass, and a reduction of all previously enlarged lymph nodes. The patient continued on erlotinib therapy for an additional 4 weeks. CT scan after 8 weeks of erlotinib showed continued significant decrease in the right upper lobe mass and mediastinal lymphadenopathy.

In April 2010, the patient underwent right pneumonectomy with lymph node dissection. Pathology results showed a moderately differentiated adenocarcinoma without evidence of squamous histology in any of the specimens. Margins were focally positive at the hilar and perivascular soft tissue margin. Of the 10 sampled lymph nodes, 5 were involved with adenocarcinoma (3 hilar nodes, 1 level 10 node, and 1 subcarinal node). The tumor size was 4.1 × 2.5 × 1.8 cm; posttreatment staging was ypT2a,N2,M0.

Given the persistence of nodal disease, the patient was reinitiated on concurrent chemotherapy and radiation. She received 3 additional cycles of cisplatin and pemetrexed with 5940 cGy of radiation completed in July 2010. In January 2011, the patient was noted to have prominent left-sided pulmonary nodules, the largest being 8 mm. She was therefore reinitiated on erlotinib therapy at a reduced dose of 100 mg/d to minimize toxicity in the postoperative setting. Repeat imaging in April 2011 showed a decreased size of the 3 pulmonary nodules but a new 1.3 × 2.5-cm osteoblastic lesion in the left iliac bone. This was confirmed through bone scan, which also revealed a new 5-mm lytic lesion in the left L5 lami-

Table 1 Tissue Biopsy Characteristics

Date	Biopsy Site	Histology	Exon 19 Mutation	*T790M*
1/2010	FNA: lung mass	Adenocarcinoma	Present	Absent
2/2010	EBUS: subcarinal node	Adenocarcinoma	Present	Absent
4/2010	Pneumonectomy: right lung, hilar, level 7, and subcarinal nodes	Adenocarcinoma	Present	Absent
9/2011	Cerebellar mass	Adenocarcinoma	Present	Present
10/2011	FNA: anterior lingula nodule	Squamous	Present	Absent

Abbreviations: EBUS, endobronchial ultrasound; FNA, fine-needle aspiration.

na. An MRI scan of the brain was negative. Erlotinib was continued and monthly denosumab was started.

In September 2011, the patient experienced acute nausea, malaise, and loss of balance. MRI scan of the brain revealed a 2.9 × 2.4 × 2.4-cm enhancing cerebellar mass with surrounding vasogenic edema. Erlotinib was held and the patient underwent surgical resection of the mass followed by stereotactic radiosurgery. Pathology results were consistent with metastatic lung adenocarcinoma. *EGFR* mutation analysis of the resected cerebellar lesion showed a heterozygous deletion in exon 19 of the *EGFR* gene and a *T790M* mutation in exon 20 of the *EGFR* gene, consistent with acquired resistance.

In October 2011, the patient underwent repeat CT imaging of the chest, revealing slightly increased nodules in the left lung: a 7-mm nodule in the anterior lateral lingula abutting the pleural surface, a 3-mm nodule in the lateral left lower lobe, and a previously noted 5-mm pleural-based nodule, which was unchanged. Biopsy results of the anterior lingula nodule showed p63-positive, CK5/6-positive, and TTF-1–negative squamous cell carcinoma (Figure 1). *EGFR* mutational analysis showed an exon 19 deletion, consistent with her previous lung pathology results, without evidence of a *T790M* mutation.

Discussion

This case describes a CNS parenchymal metastasis from a lung adenocarcinoma expressing the *T790M* resistance mutation. Only 3 cases of a *T790M* mutation seem to have been reported in the CNS.[7,8] Jackman et al[5] and Ruppert et al[6] previously described patients with CNS metastatic disease found to have *T790M* mutations in peripheral tissues but absent in the CNS. With decreased bioavailability of EGFR-TKIs in the CNS, the development of resistance in the brain was previously thought to be unlikely. This patient received approximately 2 months of standard-dose TKI therapy followed by withdrawal of the drug for 8 months before it was resumed at a reduced dose. Documented resistance developed 9 months after reinitiation of TKI therapy. The time to resistance is consistent with previous analyses documenting non-CNS resistance.[5,9,10]

Because of the efficacy of TKIs in the metastatic setting, studies are being performed to understand the role of TKIs in adjuvant and neoadjuvant treatment.[11–13] A prospective trial evaluating EGFR-TKIs delivered to unselected patients in the adjuvant settings has led to disappointing results.[12] However, a retrospective analysis of adjuvant TKI use in patients with an *EGFR* mutation has shown an improved

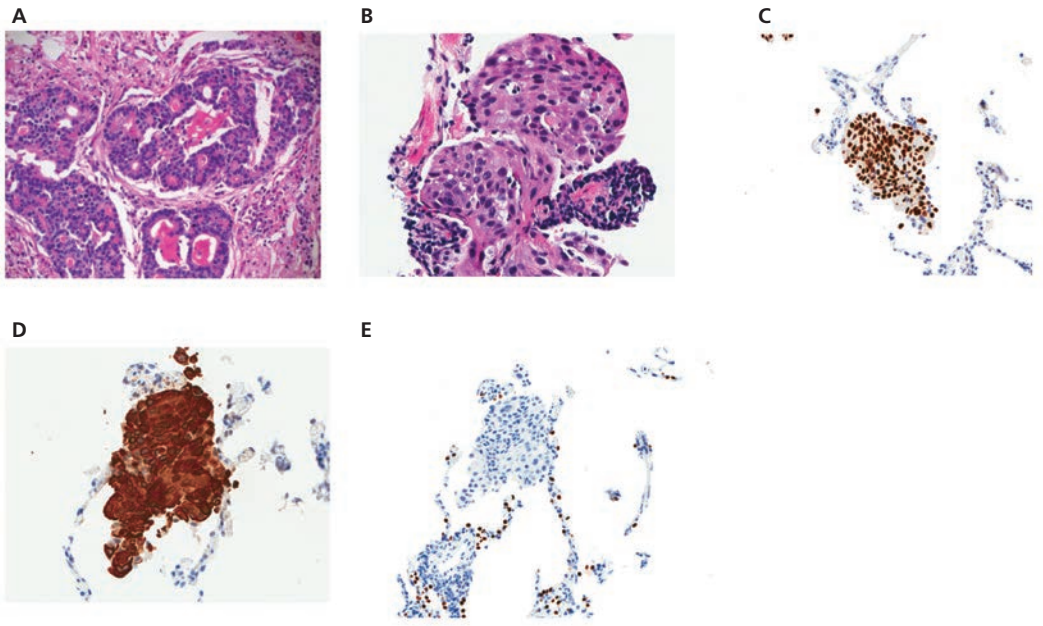

Figure 1 Transformation of lung tumor to squamous cell carcinoma with del19. A) Original adenocarcinoma (hematoxylin and eosin [HE], original magnification x400); B) squamous cell transformation (HE, original magnification x400); C) squamous cell, p6- positive (original magnification x200); D) squamous cell, cytokeratin 5/6-positive (original magnification x400); and E) squamous cell, TTF-1–negative (original magnification x200).

2-year disease-free survival.[13] Several case reports have described the use of erlotinib in neoadjuvant therapy with limited success.[14,15] Larger prospective studies are underway to evaluate the adjuvant and neoadjuvant use of TKIs in lung cancer treatment (ClinicalTrials.gov identifiers: NCT01410214 and NCT01407822).

This patient's course was unique in that she received interrupted TKI therapy: neoadjuvant for 2 months and then 8 months later for metastatic disease. Intermittent use of TKI therapy in mouse models has been hypothesized to lead to increased tumor resistance.[16] Evolutionary mathematical models reveal that dosing strategies contribute to resistance patterns.[17] Factors contributing to decreased time to secondary resistance have been studied in gastrointestinal stromal tumors (GIST). Although imatinib interruption has been shown to lead to rapid progression in GIST, the data are inconclusive regarding the impact of treatment interruption on time to secondary resistance.[18,19] The authors question whether the interrupted use of erlotinib may have altered selection pressure and led to this unique situation of a central *T790M* mutation. The unique properties of the blood–brain barrier combined with intermittent TKI use (both leading to inconsistent drug levels in the CNS) may explain the central *T790M* mutation without acquired resistance in the lung.

The evolution of the patient's lung tumor histology from adenocarcinoma to squamous cell carcinoma is also of interest. Tumor heterogeneity leading to cancer evolution is a complex process, as shown in renal cell carcinoma,[20] and this case highlights a divergent process of adaptation to therapy at separate metastatic sites. Sequist et al[21] previously described the evolution in histology from adenocarcinoma to small cell lung cancer. They hypothesized the existence of a pluripotent population of *EGFR*-mutant cancer stem cells. The transformation in histology with maintenance of *EGFR* mutation may be a consequence of TKI treatment. This alteration in the biology of the disease may complicate the use of TKIs in the neoadjuvant and adjuvant settings.

This patient highlights the complexities of using TKI therapy in the nonmetastatic setting. Although the use of induction TKIs may result in downstaging or eradiation of N2 disease, this is at the expense of increased TKI use and the potential for earlier development of resistance. With SWOG S0023 showing a potential harm in using consolidation TKI versus placebo after definitive chemoradiotherapy, one must question whether TKIs alter the biology of the disease (as evidenced by histology transformation) and even subsequent response to chemotherapy.[22] This patient's case underscores the need for further studies examining the neoadjuvant and adjuvant roles for TKIs. Elucidating mechanisms of tumor transformation and resistance will provide better data on how to use TKIs in a multimodality setting incorporating surgery, radiation, and chemotherapy.

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Instructions for Completion

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Posttest Questions

1. Intermittent erlotinib therapy is hypothesized to be a reason the CNS resistance and histology transformation in the lung may have occurred.
   a. True
   b. False
2. What percentage of patients treated with TKI's develop CNS metastases without a documented resistance secondary mutation?
   a. 20%
   b. 33%
   c. 50%
   d. 67%
3. Patients receiving TKI therapy often become resistant to therapy. Which of the following is an acquired secondary mutation associated with the development of resistance to TKI therapy?
   a. *T790M*
   b. Deletion in exon 19