Epidermal Growth Factor Receptor Exon 19 Deletions Predict Complete Regression of Multiple Intracranial Metastases in Two Cases of Non-small Cell Lung Cancer Treated with Erlotinib

To the Editor:

The incidence of intracranial metastases in non-small cell lung cancer (NSCLC) is increasing as a result of both advances in neuroimaging and increased survival, and a synchronous presentation with the primary lung disease is not uncommon. Whole-brain radiation therapy (WBRT) can prolong the median survival by only 1 to 3 to 6 months, and chemotherapeutic regimens have response rates below 20%, with median survivals of 4 to 6.5 months.[1] Recently, Caucasian patients treated with Gefitinib or Erlotinib have experienced unexpected activity against brain metastases, revealing the ability of small-molecule tyrosine kinase inhibitors (TKIs) to cross the blood brain barrier. Phase II trials using Gefitinib or Erlotinib for NSCLC harboring epidermal growth factor receptor (EGFR) mutations have recently shown a higher response rate for metastases to all sites, included multiple intracranial lesions.[2] The Spanish Lung Cancer Group monitored a subgroup of chemotherapy-naive, EGFR-mutated NSCLC patients with intracranial lesions who were treated with erlotinib: four complete responses and three partial responses were reported.[3] Fekrazad et al.[4] published a case of a nonsmoking native American woman who had a complete and continued regression of the brain metastases from a lung adenocarcinoma using Erlotinib, whereas WBRT had failed to control the same lesions. The primary lung tumor mass was partially controlled. However, these authors did not analyze EGFR mutations.

Numerous studies have analyzed the prognostic and predictive significance of the mutational spectrum of EGFR. Murray et al.[5] described an analytical database of 12,244 patients with 3381 somatic EGFR mutations They catalogued mainly the somatic mutational spectrum of exons 18–21 of EGFR, with 50% of the mutations being exon 19 deletions or deletional insertions. A clear association between EGFR mutations and a response to TKIs was confirmed, but no specific behavior regarding intracranial metastases was identified. Moreover, there is no specific analysis that correlates treatment with TKIs and the response at a particular disease site, although observations of this phenomenon are accumulating.

Here, we report two cases of NSCLC in which the EGFR exon 19 deletion predicted complete regression of multiple intracranial metastases treated with Erlotinib.

Case 1 was a 44-year-old, nonsmoking man who underwent total body computed tomography (CT) because he developed sudden right hemiplegia. A 2.7-cm tumor in the left lung with concomitant bilateral parenchymal metastases and synchronous multiple intracranial metastases (MIMs) ranging in size from 1 to 3.3 cm were found (Figure 1*A*). Adenocarcinoma of the lung was diagnosed after a transbronchial biopsy. The patient refused WBRT, and the cisplatin and etoposide chemotherapy was stopped at the second cycle because of an anaphylactic reaction. At that time, both the lung and intracranial lesions persisted unchanged, as shown by CT. A new sample of tumor tissue was obtained, and the molecular analysis identified the L747-P753 deletion of EGFR exon 19. Erlotinib 150 mg/d was administered orally with no clinically relevant side effects, except a mild skin rash. After 6 months, all of the intracranial lesions had disappeared, although a fibrotic image remained in the left lung on positron emission tomography-CT (Figures 1*A*, *B*). The patient died 15 months later from a relapse and disease progression. No data were available regarding a possible T790M EGFR gene mutation.

Case 2 was a 48-year-old, Caucasian woman who smoked and presented with a lung neoplasm, synchronous metastases to the liver, spleen, and bones, and MIMs. Histologically, a transbronchial fine-needle aspiration showed large cell carcinoma of the lung. The patient was treated with four cycles of cisplatin plus fotemustine, followed by WBRT. Stable disease was obtained. However, 3 months later, disease progression was documented on CT scan, and the levels of the serological tumor markers CEA and CA-125 were 115 μg/ml and 494 U/ml, respectively. Molecular analysis of a tumor sample showed an EGFR deletion in exon 19 (K745_E749del). Subsequently, the patient was given Erlotinib 150 mg/d orally beginning in February 2007. Four months later, the MIMs had disappeared completely, and the lung, bone, liver, and spleen metastases had regressed partially. The CEA and CA-125 fell to normal levels. The disease had remained stable at the last follow-up visit, after 24 months of Erlotinib treatment.

These experiences confirm that intracranial NSCLC metastases can regress completely and for long time after treatment with Erlotinib in cases in which standard systemic chemotherapy and radiation therapy were useless. This is striking, because until now the central nervous system has been considered a sanctuary limiting the activity of all medical oncology strategies. Moreover, Erlotinib seems to be site specific for intracranial metastases harboring EGFR exon 19 deletions. Perspective studies in selected patients are needed to confirm these observations. In addition, it would

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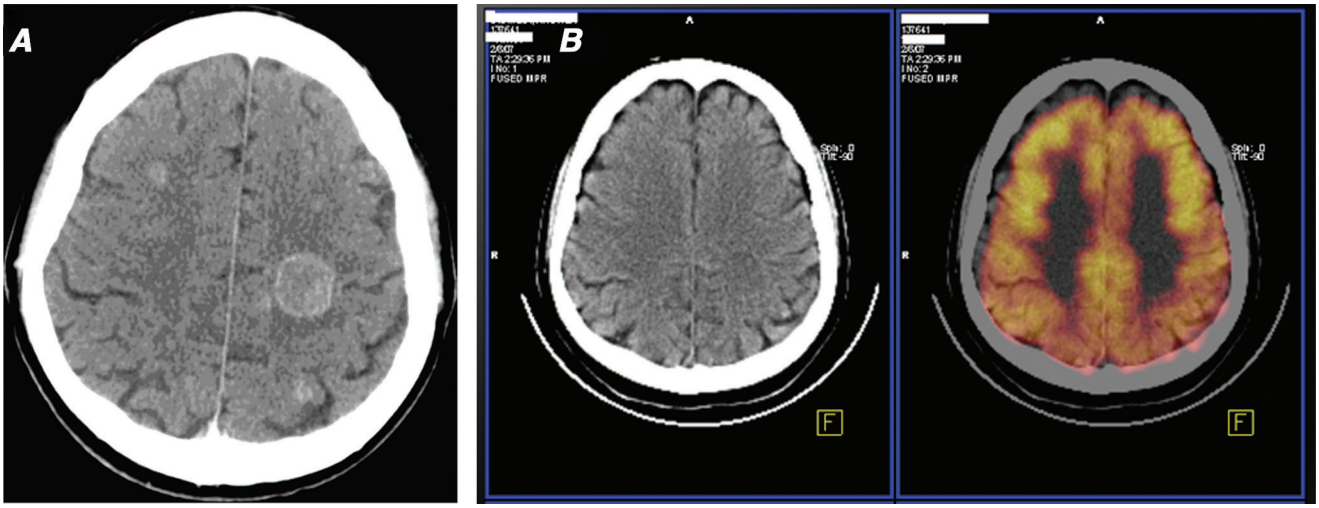

FIGURE 1. *A*, Case 1: Computed tomography (CT) images of synchronous multiple intracranial metastases in a non-small cell lung cancer (NSCLC) patient before erlotinib treatment. *B*, Case 1: Positron emission tomography-CT showing dimensional and functional complete remission of multiple intracranial metastases (MIMs) after 8 months of erlotinib treatment.

be useful to analyze the penetration of erlotinib into the central nervous system and the development of resistance, to possibly explain differences in responses and relapses.

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Asymptomatic Air Embolism After Computed Tomography-Guided Lung Needle Marking

To the Editor:

Computed tomography (CT)-guided lung needle marking has become a frequently used method to localize a small lung nodule before video-assisted thoracoscopic surgery (VATS). Although the procedure is associated with various complications, air embolism is extremely rare and sometimes fatal. As most of air embolism is diagnosed by clinical symptoms, its frequency might be underestimated in patients without cardiac or cerebral symptoms. Here, we report a case of asymptomatic air embolism after CT-guided lung needle marking.

The patient was 65-year-old man with no symptoms. Chest CT showed a small nodule in the segment 6 of the right lower lobe. CT-guided lung needle marking was performed to identify the tumor for planned VATS resection. The patient was placed in a prone position. After the local anesthesia, a 21-gauge marking needle (Guiding-Marker System, Hakko, Tokyo, Japan) was inserted into the right lower lobe and a hook wire marker was placed under intermittent CT guidance (Figure 1). Although the patient did not complain of any symptoms, postprocedural CT showed air in the right inferior pulmonary vein and left atrium (Figure 2). Twenty minutes later, the air disappeared

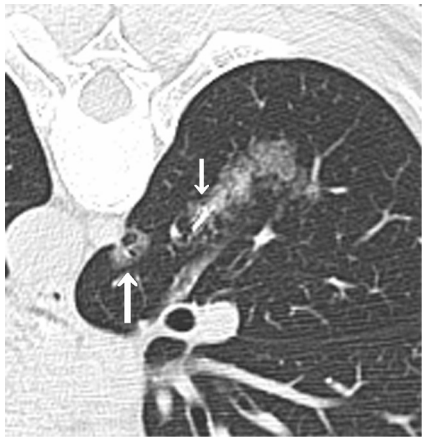

FIGURE 1. Postprocedural computed tomography (CT) scan shows the hook wire marker (small arrow) placed near the pulmonary nodule (large arrow).

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