Miliary Never-Smoking Adenocarcinoma of the Lung

Strong Association with Epidermal Growth Factor Receptor Exon 19 Deletion

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Abstract: Miliary pattern of pulmonary metastases is a rarity in patients with lung cancer. We report five cases of patients with a never-smoking adenocarcinoma of the lung with such a pattern of metastases. In the tumor cells of all five patients, epidermal growth factor receptor (*EGFR*) mutation gene sequencing identified a deletion in exon 19 of the *EGFR* gene, and all five patients had a dramatic response to EGFR tyrosine kinase inhibitors. No echinoderm microtubule-associated protein-like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) translocation was detected. We believe that the miliary never-soking adenocarcinoma of the lung is a distinct clinically relevant subgroup of the never-smoking non-small cell lung cancer. Physician should recognize this subgroup of patients with lung cancer when facing a picture of miliary pulmonary metastases in chest x-ray or computed tomography scan in patients with a history of never smoking and consider upfront therapy with EGFR tyrosine kinase inhibitors.

Key Words: Adenocarcinoma of the lung, *EGFR* exon 19 deletion, EGFR tyrosine kinase inhibitor, Miliary lung metastases, Never smoker.

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Miliary pattern of pulmonary metastases is a rarity in patients with lung cancer. Five of our patients with lung cancer had a never-smoking adenocarcinoma with such a pattern of metastases.

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CASE 1

A woman from Thailand, aged 40 years, was diagnosed in 2007 with a moderately differentiated acinar adenocarcinoma of the lower lobe of the right lung and miliary pulmonary metastases in both lungs (>100 metastases per side) and a brain metastasis. A deletion in exon 19 of the epidermal growth factor receptor (*EGFR*) gene (p.E746_A750del) was detected in the tumor cells of the brain metastasis (Figure 1). Patient was treated with the EGFR-tyrosine kinase inhibitor (EGFR-TKI) erlotinib as first-line therapy. Seven weeks later, computed tomography (CT) scan demonstrated a complete remission of the primary tumor and of the miliary lung metastases (Figures 2*A*, *B*). Patient was 19 months in complete remission before the tumor progressed.

CASE 2

A woman from Germany, aged 70 years, was diagnosed in 2008 with a moderately differentiated acinar adenocarcinoma of the upper lobe of the right lung, with involved ipsilateral and contralateral lymph nodes of the mediastinum, malignant pleural effusion, and miliary pulmonary metastases in both lungs. Tumor progression was observed after two cycles of first-line chemotherapy carboplatin and etoposide. *EGFR* mutations gene sequencing identified a deletion in exon 19 of the *EGFR* gene (Figure 1). Therefore, we started second-line therapy with erlotinib. One month later, chest x-ray showed an extremely rapid response of the miliary lung metastasis and a partial remission of the primary tumor and the malignant pleural effusion (Figure 3), which was confirmed by CT scan (Figures 2*C*, *D*). Most of the miliary pulmonary metastases were no longer detectable. Patient was 19 months in partial remission before the tumor progressed.

CASE 3

A young woman from Germany, aged 42 years, was diagnosed in 2008 with a moderately differentiated acinar adenocarcinoma of the lung, which was localized in the upper lobe of the right lung. At the time of diagnosis, she had extensive disease with metastases in liver, bone, mediastinal lymph nodes, and a malignant pericardial effusion and the picture of miliary

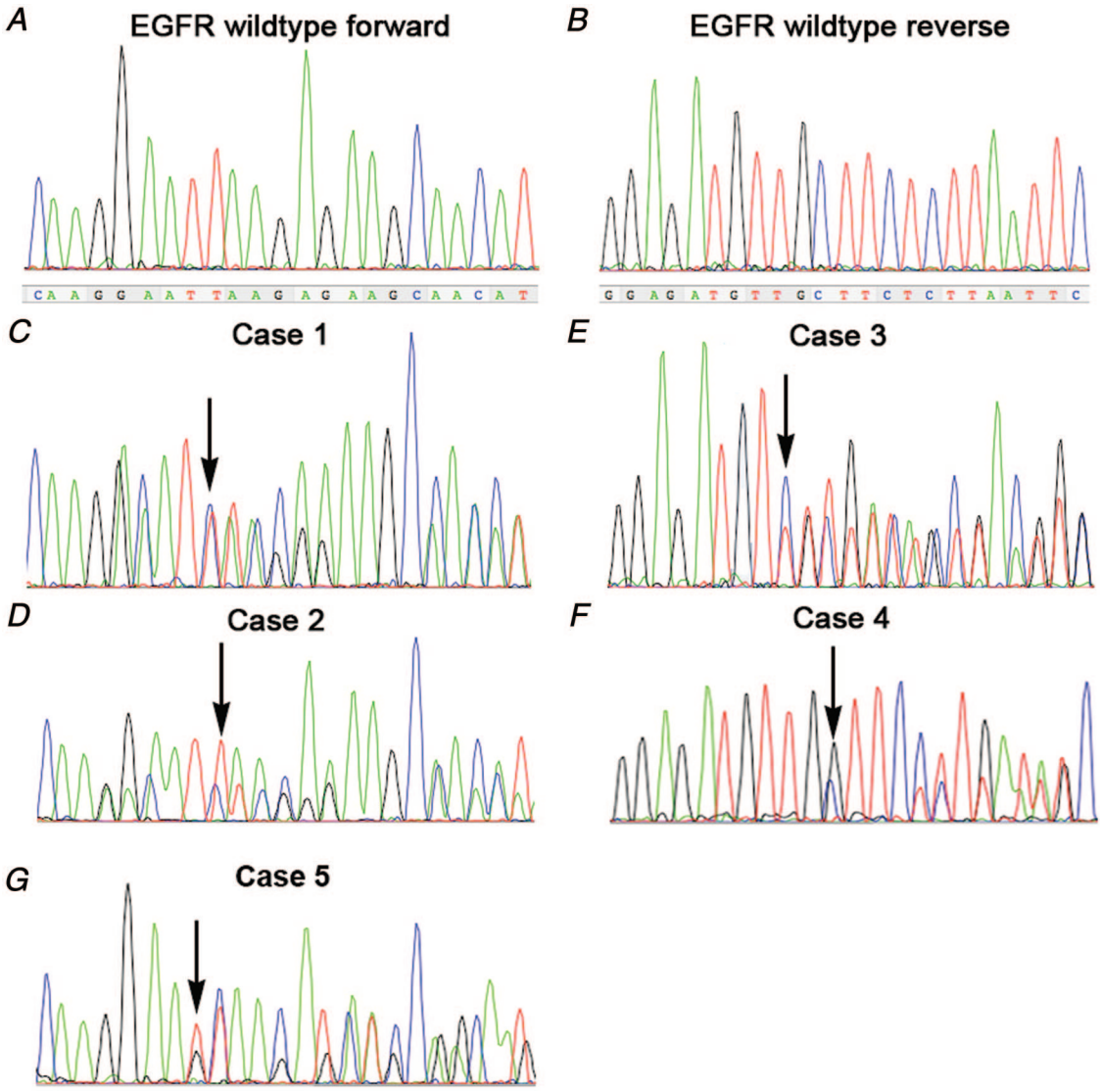

FIGURE 1. Epidermal growth factor receptor (*EGFR*) sequence analysis results of exon 19. *A* and *B*, *EGFR* wild-type sequence by forward and reverse sequencing. *C–E*, Sequence analysis results of cases 1, 2, 3, 4, and 5 by forward (*C*, *D*, and *G*) or reverse (*E* and *F*) sequencing. Case 1: c.2238_2252del; case 2: c.2237G>A and c.2238_2252del; case 3: c.2238_2252del; case 4: c.2238_2252del; and case 5: c.2238_2252del (an arrow point out the mutation for each case).

pulmonary metastases. The patient was treated with first-line chemotherapy containing carboplatin and paclitaxel. After three cycles of chemotherapy, the CT scan demonstrated progressive disease. Erlotinib was started as second-line therapy. Four months later, the CT scan revealed a partial remission of all tumor lesions, and the miliary lung metastases had almost disappeared (Figures 2*E*, *F*). Patient was 8 months in partial remission before the tumor progressed in the liver, whereas the lung metastases were still in remission. Also, in this patient, a deletion in exon 19 of the *EGFR* gene (p.E746_A750del) was detected in the tumor cells (Figure 1).

CASE 4

A man from Germany, aged 63 years, was diagnosed in 2004 with a moderately differentiated acinar adenocarcinoma of the lung, which was localized in the lower lobe of the right lung. At the time of diagnosis, he had involved mediastinal lymph nodes and miliary pulmonary metastases in both lungs. Patient was treated with two cycles of cisplatin and gemcitabine as first-line chemotherapy and with three cycles of pemetrexed as second-line chemotherapy, whereby the patient had progressive disease after both therapies. Erlotinib was started as third-line treatment. Two, 4, 6, and 8 months later, the CT scan revealed a dramatic response of all tumor lesions. Altogether, the patient was 12 months in remission before tumor progressed. The latest performed EGFR mutation analysis also detected a deletion in exon 19 of the *EGFR* gene (p.E746_A750del) in the tumor cells (Figure 1).

CASE 5

A man from Germany, aged 68 years, was diagnosed in 2008 with a moderately differentiated acinar adenocarcinoma of the upper lobe of the left lung, with involved lymph nodes of the mediastinum, malignant pleural effusions, bone metastases, one liver metastasis, and miliary pulmonary metastases in both lungs. We analyzed tumor tissue for harboring EGFR gene mutations. *EGFR* mutations gene sequencing also identified a deletion in exon 19 of the *EGFR* gene (Figure 1). Therefore, we started first-line therapy with erlotinib per day. CT scans showed an extremely rapid response of the miliary lung metastasis and the primary tumor and a complete remission of the liver metastasis, the malignant pleural effusions, and the involved lymph nodes. Patient was 18 months in complete remission before the tumor progressed.

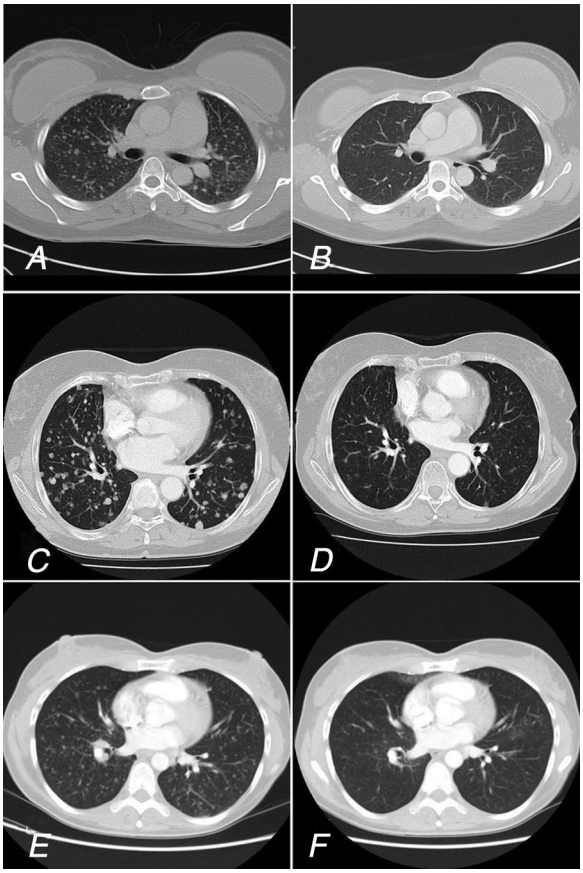

FIGURE 2. Transverse computed tomography (CT) images (window center/window width: 450/1800 Houndsfield units) represents the three patients before treatment (*A*: case 1, *C*: case 2, and *E*: case 3) and horizontally corresponding images of the same patients (*B*: 7 weeks later, *D*: 8 weeks later, and *F*: 17 weeks later) after treatment with EGFR tyrosine kinase inhibitor erlotinib. The right column of images demonstrates a clearly visible reduction of metastasis in size and number.

All five patients presented in this study were lifelong never smokers, had the radiologic picture of miliary pulmonary metastases, and in all five cases, the pathologic assessment of tumor biopsies showed acinar adenocarcinoma of the lung. Neither of them had histologic or radiologic features of bronchioloalveolar carcinoma.[1] In the tumor cells of all five patients, *EGFR* mutation gene sequencing identified a deletion in exon 19 of the *EGFR* gene, thus all five patients had a dramatic response to EGFR TKIs.[2] In cases 1 and 5, erlotinib was given as first-line treatment, in cases 2 and 3 as second-line treatment, and in case 4 as third-line treatment.

Further, to identify *ALK* rearrangements, fluorescence in situ hybridization analysis was performed in the tumor cells of all five patients. However, no *EML4-ALK* translocation was detected.

DISCUSSION

Lung cancer can metastasize in each organ and region of the body, but typically, lung cancer spreads into locoregional lymph nodes and favors liver, bone, brain, and adrenal glands as sites of distant metastases. Sometimes, few pulmonary metastases or satellite tumors in the lung are observed. A miliary pattern of lung metastases, which is characterized by hundreds of small metastases scattered throughout the entire lung, is a rarity in patients with lung cancer. We had never observed this pattern of metastases in our patients with lung cancer with a history of smoking nor has this miliary pattern of lung metastases in current, recent, or former smokers been reported in the literature.

Our patient cohort shows striking similarities to five patients with adenocarcinomas of the lung with miliary metastases to the lung reported in 1993 by Umeki.[3] Umeki identified five cases in a consecutive cohort of 630 patients, suggesting that the prevalence of miliary phenotype may approximately 1% in Japanese patients.[3] The author reported a short survival time after appearance of the miliary lung

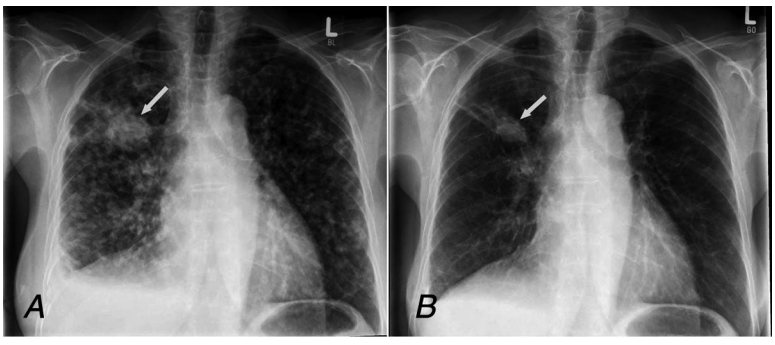

FIGURE 3. Case 2: conventional chest x-rays prior (*A*) and 4 weeks posttreatment with epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor erlotinib (*B*) illustrate not only a fulminant decrease of the miliary lung metastases but also a reduction of size of the primary tumor side of the right upper lobe (arrows) and of the pleural effusion.

metastases and suggested that the unique pattern of multiple pulmonary metastases was secondary to bone metastases, because all his five patients also had had bone metastases.[3] In contrast, three of our five patients with a miliary never-smoking adenocarcinoma of the lung had no bone metastases. A specific molecular phenotype facilitating tumor cell homing to the lungs may represent an alternative explanation to the unique metastatic traits of the miliary never-smoking adenocarcinoma of the lung. Our finding of identical exon 19 deletions (p.E746_A750del) and of negative *EML4-ALK* rearrangements in the tumors of all five patients argues for a common molecular signature of these tumors. Additionally to our five patients, Sebastian et al.[4] reported the case of a 37-year-old man from Germany, who had never smoked and had also such a miliary pulmonary metastases of an adenocarcinoma of the lung. In this study, we report the miliary never-smoking adenocarcinoma of the lung as one distinct subtype of never-smoking non-small cell lung cancer characterized by a unique (miliary) pattern of lung metastases in combination with a specific histologic (adenocarcinoma) and genetic (*EGFR* exon 19 deletions and no *EML4-ALK* rearrangements) phenotype.

The miliary never-smoking adenocarcinoma of the lung occurred in women and in men and in whites and in Asians. Although being rare, this finding has high clinical relevance, and physicians should be aware of this entity and the need for early treatment with EGFR TKIs after detection of activating *EGFR* gene mutations.

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