

# 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-smoking 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

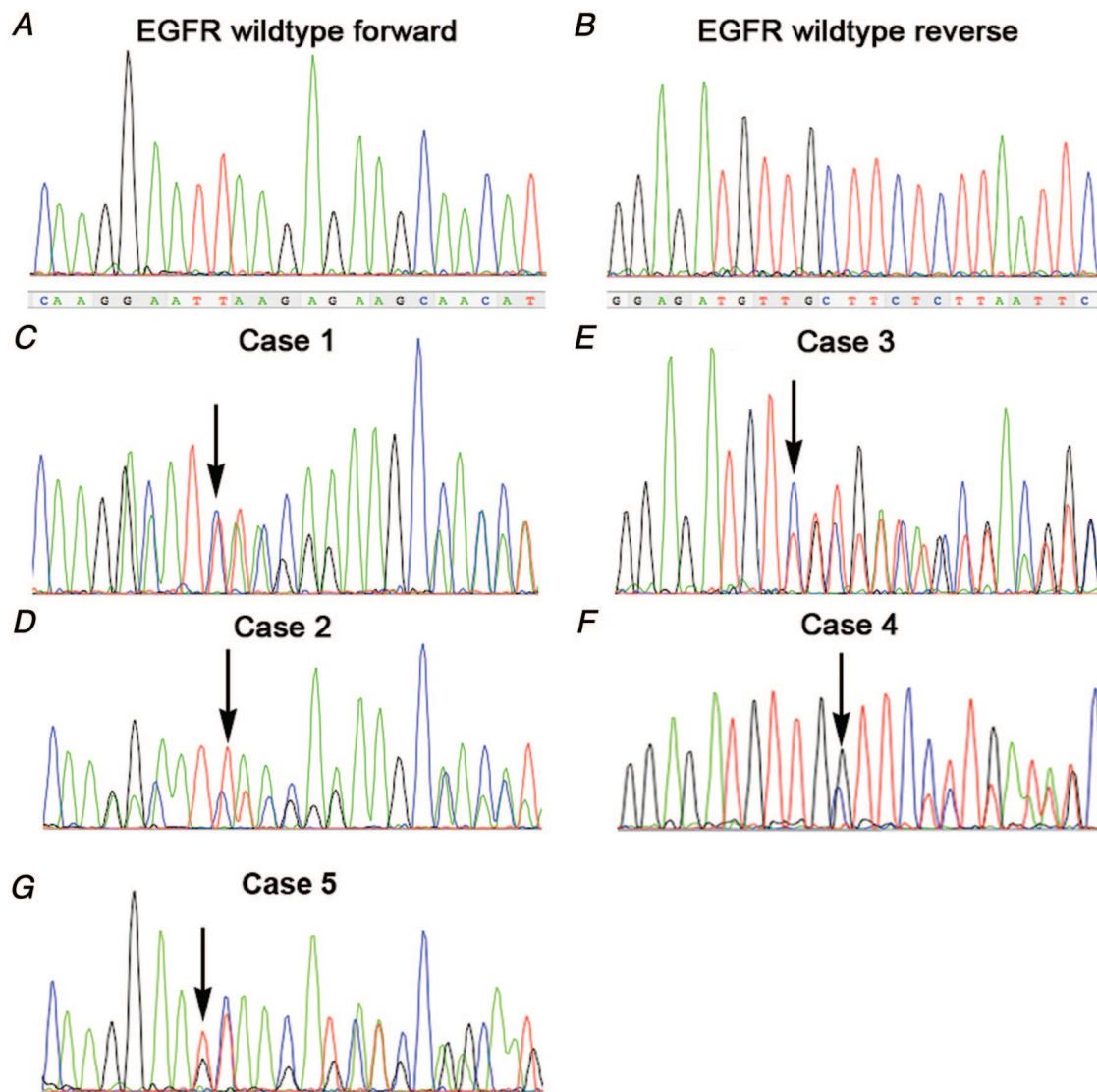
A woman from Thailand, aged 40 years, was diagnosed in 2007 with a moderately differentiated acinar adenocarcinoma of the lower lobe of the right lung and miliary pulmonary metastases in both lungs (>100 metastases per side) and a brain metastasis. A deletion in exon 19 of the epidermal growth factor 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 2A, 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 2C, 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).

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