

[CASE REPORT]

An Acquired Epidermal Growth Factor Receptor T790M Mutation after the Addition of Bevacizumab to Preceding Erlotinib Monotherapy in a Lung Cancer Patient with Leptomeningeal Metastases

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Abstract:

A 53-year-old man with advanced lung adenocarcinoma harboring epidermal growth factor receptor (*EGFR*) exon 19 deletion received erlotinib. After 12 months of disease control with erlotinib monotherapy, leptomeningeal metastases (LM) occurred. A cerebrospinal fluid examination demonstrated a pre-existing *EGFR* exon 19 deletion. Bevacizumab was combined with erlotinib, and the LM improved. After six months of combination therapy, however, the LM was exacerbated. A re-examination of the cerebrospinal fluid revealed a T790M mutation and exon 19 deletion. Osimertinib was administered, and the LM improved. The combination of bevacizumab and erlotinib was effective for erlotinib-resistant LM and resulted in the expression of a newly acquired T790M mutation, which enabled successful treatment with osimertinib.

Key words: leptomeningeal metastases, lung cancer, *EGFR*, bevacizumab, osimertinib

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Introduction

Leptomeningeal metastasis (LM) is a severe complication that occurs in 1-3.8% of lung cancer patients (1, 2). Conventional cytotoxic therapies demonstrate only limited effectiveness for LM, and the prognosis is poor, with an overall survival of only 1 to 4.3 months (3-6). Patients with LM harboring epidermal growth factor receptor (*EGFR*) mutations can be treated with *EGFR* tyrosine kinase inhibitors (TKIs), one of the most successful anti-cancer drugs among recent lung cancer therapies (7, 8). The median survival time of LM patients treated with *EGFR*-TKIs is 8 to 19.2 months (3, 4, 9, 10). However, despite the initial success of *EGFR*-TKIs, acquired resistance occurs after a certain period. Osimertinib, a third-generation *EGFR*-TKI, demonstrates remarkable efficacy for lung cancer with the *EGFR*

T790M mutation that is resistant to first- and second-generation *EGFR*-TKIs (11). However, the T790M mutation only occurs in up to 50% of patients after *EGFR*-TKI therapy (12), and thus approximately half of patients are excluded from the benefit of osimertinib. Overcoming acquired resistance that is not due to the T790M mutation and/or inducing the T790M mutation, thereby enabling osimertinib treatment, remains a challenge.

We herein report a case of *EGFR*-mutant lung cancer with LM that was resistant to erlotinib monotherapy and improved by the addition of bevacizumab. Furthermore, the T790M mutation was eventually acquired after the combination therapy with erlotinib and bevacizumab, which enabled the recurrent LM to be successfully treated by osimertinib.

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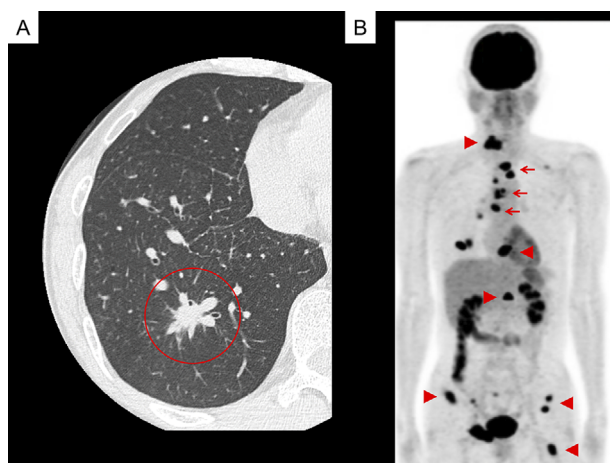


Figure 1. Chest computed tomography (CT) on admission (A) revealed a tumor in the right lower lung lobe (circle). Positron emission tomography-CT (B) demonstrated mediastinal lymph node (arrow) and multiple bone metastases (arrow-head).

Case Report

A 53-year-old man was admitted to our hospital for the evaluation of a nodule shadow in the right lower lobe of the lungs. He also had right coxalgia that had persisted for eight months. He had a 35-pack-year history of smoking with no other remarkable medical history. Computed tomography (CT) of the chest revealed a tumor in the right lower lobe of the lungs (Fig. 1A). Positron emission tomography-CT demonstrated mediastinal lymph node metastases and multiple bone metastases (Fig. 1B). There was no central nervous system (CNS) metastasis according to brain magnetic resonance imaging (MRI). A transbronchial biopsy of the lung tumor revealed adenocarcinoma with an *EGFR* mutation of exon 19 deletion as assessed by the peptide nucleic acid (PNA)-locked nucleic acid (LNA) polymerase chain reaction (PCR) clamp method. His Eastern Cooperative Oncology Group performance status was 0, and he had a normal hematopoietic, renal and hepatic function, except for elevated serum alkaline phosphatase (684 IU/L) due to bone metastases.

First-line chemotherapy with carboplatin (AUC=6), pemetrexed (500 mg/m²) and bevacizumab (15 mg/kg) at day 1 in a 21-day cycle was administered, in addition to palliative radiotherapy for right pubic metastasis. After four cycles of chemotherapy, he had partial response and received maintenance therapy with pemetrexed and bevacizumab. After 27 cycles (21 months) of the maintenance therapy, he had progressive disease with an increase in the primary lung tumor. Daily erlotinib (150 mg) was administered as the second-line therapy, and he achieved a good response.

After 13 months of erlotinib, he developed headaches and nausea. An examination of the cerebrospinal fluid detected adenocarcinoma, and brain MRI demonstrated enhanced LM

(Fig. 2A). A PNA-LNA PCR clamp analysis of the cerebrospinal fluid demonstrated an *EGFR* mutation of exon 19 deletion without a T790M mutation. He received bevacizumab (15 mg/kg) in addition to the preceding erlotinib. The symptoms were relieved, and the leptomeningeal enhancement on brain MRI was improved after one month of additional bevacizumab (Fig. 2B).

Six months after the addition of bevacizumab, he developed headaches and nausea again. Brain MRI showed worsening of the LM (Fig. 2C). A re-examination of the cerebrospinal fluid showed a newly acquired *EGFR* T790M mutation, in addition to the pre-existing exon 19 deletion (Table). He received daily osimertinib (80 mg), and the symptoms immediately improved. Brain MRI at two months after osimertinib treatment demonstrated an improvement in the leptomeningeal enhancement (Fig. 2D).

Discussion

Bevacizumab, in combination with preceding erlotinib monotherapy, was effective for the erlotinib-resistant LM of lung cancer without the T790M mutation. The combination therapy also resulted in the expression of a newly acquired *EGFR* T790M mutation, which enabled the recurrent LM to be successfully treated by osimertinib. Combination therapy with erlotinib and bevacizumab may be a promising approach to treating lung cancer patients with LM harboring an *EGFR* mutation.

Anti-angiogenesis therapy combined with chemotherapy is well known to enhance the efficacy of anti-tumor agents (13, 14). A previous clinical trial demonstrated the improved efficacy of the EGFR-TKI erlotinib combined with bevacizumab (3, 15). The enhancement of anti-tumor activity by anti-angiogenesis therapy is mainly explained by the improvement in the drug delivery system due to vascular normalization (16). Previous studies have also shown that the blockade of the EGFR pathway induces the suppression of the VEGF pathway and vice versa (17-19), which could synergistically improve the antitumor effects. In addition, the VEGF pathway is associated with resistance to erlotinib monotherapy, and bevacizumab, in combination with erlotinib, exerts anti-tumor activity for erlotinib-refractory tumors *in vivo* (20). Vandetanib, a multitarget TKI of EGFR, VEGFR-2 and RET, demonstrated greater anti-tumor activity than gefitinib, a first-generation EGFR-TKI, in a xenograft model with the T790M mutation, which also indicated that the inhibition of the VEGF pathway plays an important role in EGFR-TKI therapy (21). In the current case, bevacizumab was sequentially administered to erlotinib-refractory LM and successfully achieved a clinical response.

Bevacizumab also has clinical benefits for metastases in the CNS. The combination of chemotherapy and bevacizumab improves existing CNS metastases (22, 23) and decreases newly developed CNS metastases in lung adenocarcinoma (24, 25). In addition, bevacizumab improves peritumoral brain edema (26-29), which may lead to the relief of

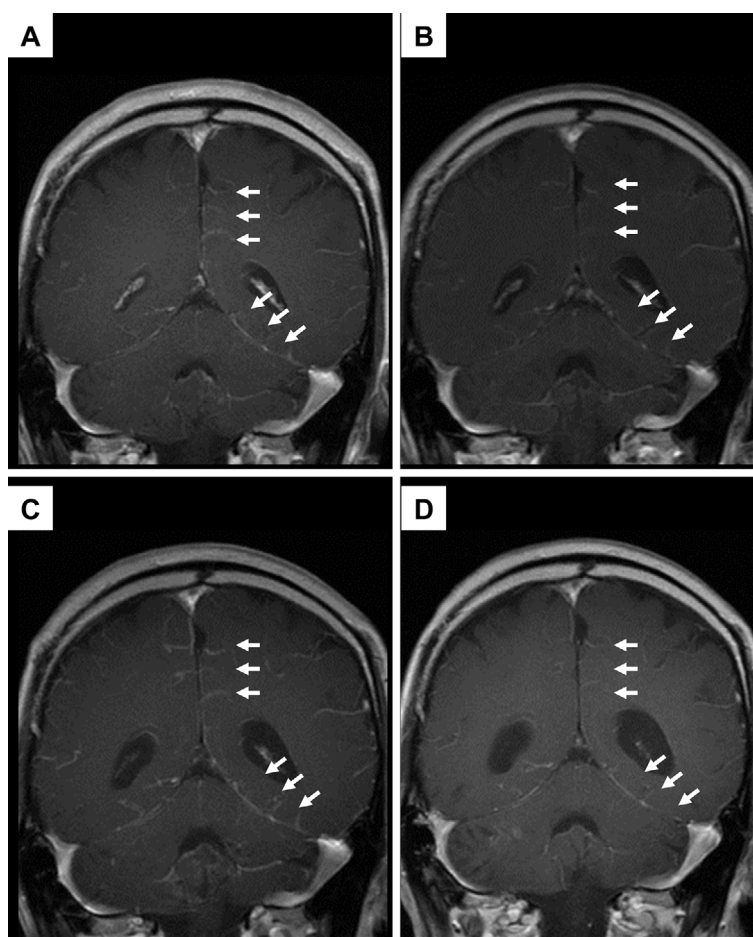


Figure 2. Coronal images of magnetic resonance imaging (MRI) of the brain demonstrated leptomeningeal metastasis (LM; enhanced area of the surface of brain, arrow) after 13 months of erlotinib monotherapy (A), which was improved after 1 month of combination therapy with erlotinib and bevacizumab (B). The LM was exacerbated again after six months of the combination therapy (C) and then improved after two months of osimertinib monotherapy (D).

Table. Changes in the *EGFR* Mutation Status after Treatment.

The time of the evaluation	Sample	<i>EGFR</i> mutation status
At the diagnosis	Primary lung tumor	Exon 19 deletion
After erlotinib treatment	Cerebrospinal fluid	Exon 19 deletion
After erlotinib and bevacizumab treatment	Cerebrospinal fluid	Exon 19 deletion+exon 20 T790M

EGFR: epidermal growth factor receptor

symptoms induced by CNS metastases. The concentrations of VEGF in the cerebrospinal fluid are increased in lung cancer patients with LM (30), thus underscoring the fact that VEGF inhibition is particularly beneficial in lung cancer with LM.

The development of the T790M mutation is a clinical concern in the therapy of lung cancer with *EGFR* mutations. One study showed that chronic exposure to *EGFR*-TKIs induces the T790M mutation in cancer cells *in vitro* (31). In other studies, the T790M mutation was detected in 3.5% to 36.4% of *EGFR*-TKI-naïve patients using a highly sensitive PCR analysis of peripheral blood (32, 33), which suggests that a certain amount of cancer cells with the T790M muta-

tion already exist in a heterogeneous cancer cell population (31). Whether the development of T790M is dependent on the *de novo* expression or the selective survival of residual cells harboring T790M (or both) is unknown. Some studies have shown that patients with a longer duration of *EGFR*-TKI treatment were more likely to acquire the T790M mutation (34, 35). Nanjo et al. reported that *EGFR* mutation-positive lung cancer patients with LMs after *EGFR*-TKI failure less frequently had the T790M mutation than those with extracranial metastases. They also demonstrated in a mouse model of acquired resistance to gefitinib that LMs harboring the *EGFR* mutation of exon 19 deletion demonstrated *MET* copy number gain and *MET* activation

but not the T790M mutation (36). In contrast, a subcutaneous metastases model developed T790M. The authors therefore suspected that exposure to a low concentration of gefitinib in CSF may induce resistance due to *MET* copy number gain but not T790M.

The findings in the current case suggest that prolonged and enhanced treatment of erlotinib by adding bevacizumab might contribute to the development of the T790M mutation, thereby enabling successful osimertinib treatment.

The authors state that they have no Conflict of Interest (COI).

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