Remarkable response to Osimertinib plus Gumarontinib for EGFR mutation and concomitant MET exon 14 skipping in a patient with lung adenocarcinoma: A case report

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Abstract. The evaluation of individuals with lung cancer for the presence of oncogenic mutations and the subsequent administration of personalized targeted therapies are of significance in clinical practice. Epidermal growth factor receptor (EGFR) mutation and mesenchymal-epithelial transition (MET) exon 14 skipping mutation were previously found to be mutually exclusive. The co-occurrence of these mutations in individuals diagnosed with adenocarcinomas signifies a distinctive and uncommon molecular subtype of non-small cell lung cancer. A 70-year-old man was admitted to Shandong Cancer Hospital and Institute (Jinan, Chian) with a 1-month history of chest pain. The CT scanning findings indicated the presence of a 5.8x5.6 cm mass in the left lower lobe, accompanied by enlarged mediastinal and hilar lymph nodes, as well as metastases in both lungs and bones. Analysis of a biopsy specimen showed lung adenocarcinoma. Gene examination revealed EGFR Del19 mutation and concomitant MET exon 14 skipping mutation. Osimertinib and Gumarontinib were administered for 8 months and the efficacy was determined to be a partial response. The present study marks the initial discovery of MET exon 14 skipping and EGFR Del19 in a single patient, who achieved partial response through a treatment plan involving Osimertinib and Gumarontinib. These findings provide valuable perspectives on treatment approaches for individuals sharing similar genetic profiles.

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Introduction

Lung cancer remains the primary cause of cancer-related mortality on a global scale (1). The discovery of driver mutations in lung cancer has revolutionized treatment by enabling personalized targeted therapies. As a result, the screening of patients with lung cancer for oncogenic drivers and the subsequent administration of tailored targeted treatments hold great importance (2). Tyrosine kinase inhibitors (TKIs) are currently considered the primary initial treatment choice for patients with advanced non-small cell lung cancer (NSCLC) who have a known driver mutation (3).

Epidermal growth factor receptor (EGFR) mutations are prevalent genetic alterations, constituting ~10-15% of NSCLC incidences in individuals of European heritage and ~30% in those of East Asian ancestry (4). Osimertinib, a third generation, irreversible EGFR-TKI, is approved as a first-line drug for the treatment of patients with metastatic EGFR-mutated NSCLC based on the results of the FLAURA trial (5).

The mesenchymal-epithelial transition (MET) exon 14 skipping mutation, a splice-site oncogenic mutation, is found in 2-3% of patients with NSCLC (6). Patients with this condition exhibit a good response to MET-TKIs, such as gumarontinib, which garnered approval from the Food and Drug Administration of the P.R. China based on the findings of the GLORY study (7).

Previous research has shown that EGFR mutation and MET exon 14 skipping mutation were mutually exclusive (8). The simultaneous presence of these mutations in a patient with adenocarcinoma represents a unique and rare molecular subtype of NSCLC (8). The present study reported on the case of a patient with NSCLC harboring EGFR Del19 and MET exon 14 skipping, who achieved significant remission through the administration of two corresponding TKIs. The case is presented in accordance with the CARE reporting checklist (9).

Case report

In December 2023, a 70-year-old man was admitted to Shandong Cancer Hospital and Institute (Jinan, Chian) with

a 1-month history of chest pain. The patient had no previous history of smoking or alcohol consumption and no family history of malignancy. A chest computed tomography (CT) scan revealed a left lower lobe mass measuring ~5.8x5.6 cm, along with multiple enlarged mediastinal and hilar lymph nodes, bilateral lung metastasis and bone metastasis (Fig. 1A). Magnetic resonance imaging of the brain showed no malignant metastases. A biopsy specimen taken by endoscopic ultrasound-guided transbronchial needle aspiration showed lung adenocarcinoma (Fig. 2A). The histology protocol is provided in the Supplemental methods. The patient was clinically diagnosed with lung adenocarcinoma, with a clinical stage of cT3N2M1c (pulmonary and bone metastases), cStage IVB according to the 8th Edition of TNM in Lung Cancer (10) and Eastern Cooperative Oncology Group Performance Status 1 (11). Amplification refractory mutation system-polymerase chain reaction technology (ADx-ARMS kit; Amoy Diagnostics, Co., Ltd.) examination performed according to the manufacturer's instructions revealed the known EGFR Del 19 mutation (Fig. 2B), but also a concomitant MET exon 14 skipping mutation (MET gene fusion between exon 13 and exon 15) (Fig. 2C). Immunohistochemical analysis of the tumor (protocol is provided in the Supplemental methods) showed that programmed cell death ligand 1 expression was negative (Fig. 2D). Therefore, the patient commenced a combination therapy regimen consisting of Osimertinib (80 mg, oral, daily) and gumarontinib (300 mg, oral, twice daily) (12). A significant reduction in the primary mass and all lymph nodes was observed after 1 month, and the efficacy was evaluated as a partial response based on the Response Evaluation Criteria In Solid Tumors (13) (Fig. 1B-D). Continuous monitoring of chest CT scans revealed a gradual reduction in tumor size. During subsequent treatment, the patient developed a first-degree rash, which was managed with topical corticosteroids and resolved within 7 days. Concurrently, the patient was diagnosed with Grade 2 pneumonia based on clinical symptoms and radiographic findings. This was managed with a course of oral corticosteroids (prednisone 0.5 mg/kg/day), temporary withholding of the anticancer therapy and supportive care. The pneumonia and associated symptoms subsided completely within 7 days and a follow-up chest X-ray confirmed resolution. The patient passed away due to cerebral infarction.

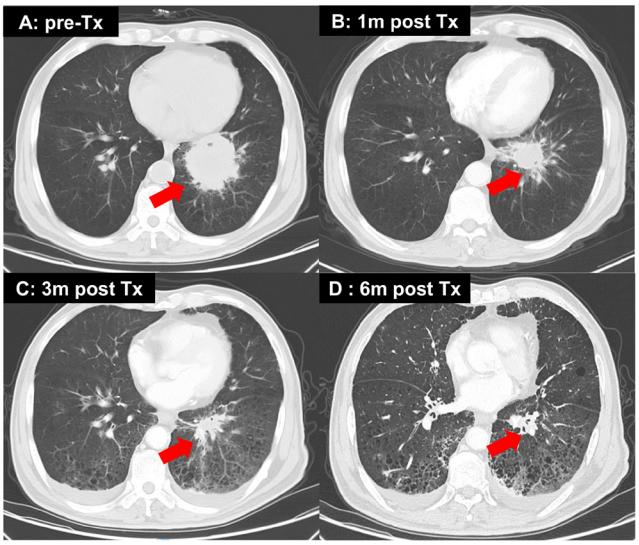

Figure 1. CT scans of the patient showing a left lower lobe nodule (A) prior to treatment with osimertinib and gumarontinib and at (B) one month, (C) 3 months and (D) 6 months follow-up. CT imaging indicated a partial response according to the Response Evaluation Criteria In Solid Tumors.

Discussion

The present study reported a rare case of a patient with lung adenocarcinoma with co-occurrence of EGFR mutations and MET exon 14 skipping. The co-existing of EGFR Del 19 and MET exon 14 skipping is relatively rare (~0.2%) (14). To the best of our knowledge, this is the first case that has been documented.

Resistance to EGFR TKI therapy in EGFR-mutant lung adenocarcinoma often involves the modification of the MET signaling pathway (15). MET is essential for regulating cell growth, survival and migration. The presence of MET alterations has been linked to a less favorable prognosis in patients with EGFR-mutant lung adenocarcinoma, serving as a potential biomarker for predicting resistance to EGFR-TKI therapy (16). Research indicates that individuals with EGFR-mutant lung adenocarcinoma and MET alterations are less likely to respond to EGFR-TKI treatment and experience shorter progression-free survival than those without MET alterations (17).

Other research findings indicate that simultaneous blocking of EGFR and MET is necessary for achieving tumor regression (18). MET exon 14 skipping has been recognized by Kauffmann-Guerrero *et al* (19) as a significant factor contributing to the development of resistance to EGFR TKI among patients with sensitizing EGFR mutations. Gumarontinib, an oral MET inhibitor, is highly selective. It has shown a favorable safety profile in preclinical and preliminary clinical investigations (20,21). The National Medical Products Administration of China has granted conditional approval for Gumarontinib in the treatment of locally advanced or metastatic NSCLC with MET exon 14 skipping mutation. Gumarontinib currently serves as an available therapeutic agent in China specifically tailored to address MET exon 14 skipping mutations (7).

The combination therapy of osimertinib and gumarontinib in this patient resulted in a partial response, demonstrating the potential benefits of targeting multiple pathways simultaneously. The observed reduction in tumor size suggests that this approach may be effective in overcoming resistance mechanisms associated with the MET mutation. It also raises important questions regarding the optimal sequencing and combination of therapies in the context of advanced lung cancer. Despite the initial success, the patient's eventual demise due to cerebral infarction highlights a critical aspect of managing patients with lung cancer: The intricate interplay between cancer treatment and the risk of thromboembolic events.

Several reports and early-phase studies have documented a clinical benefit from dual targeted therapy in patients with concurrent EGFR mutations and MET alterations, most often using osimertinib in combination with MET inhibitors such asor capmatinib, leading to partial responses or disease stabilization despite limited evidence from small series and case reports (12,19,22,23). However, the feasibility

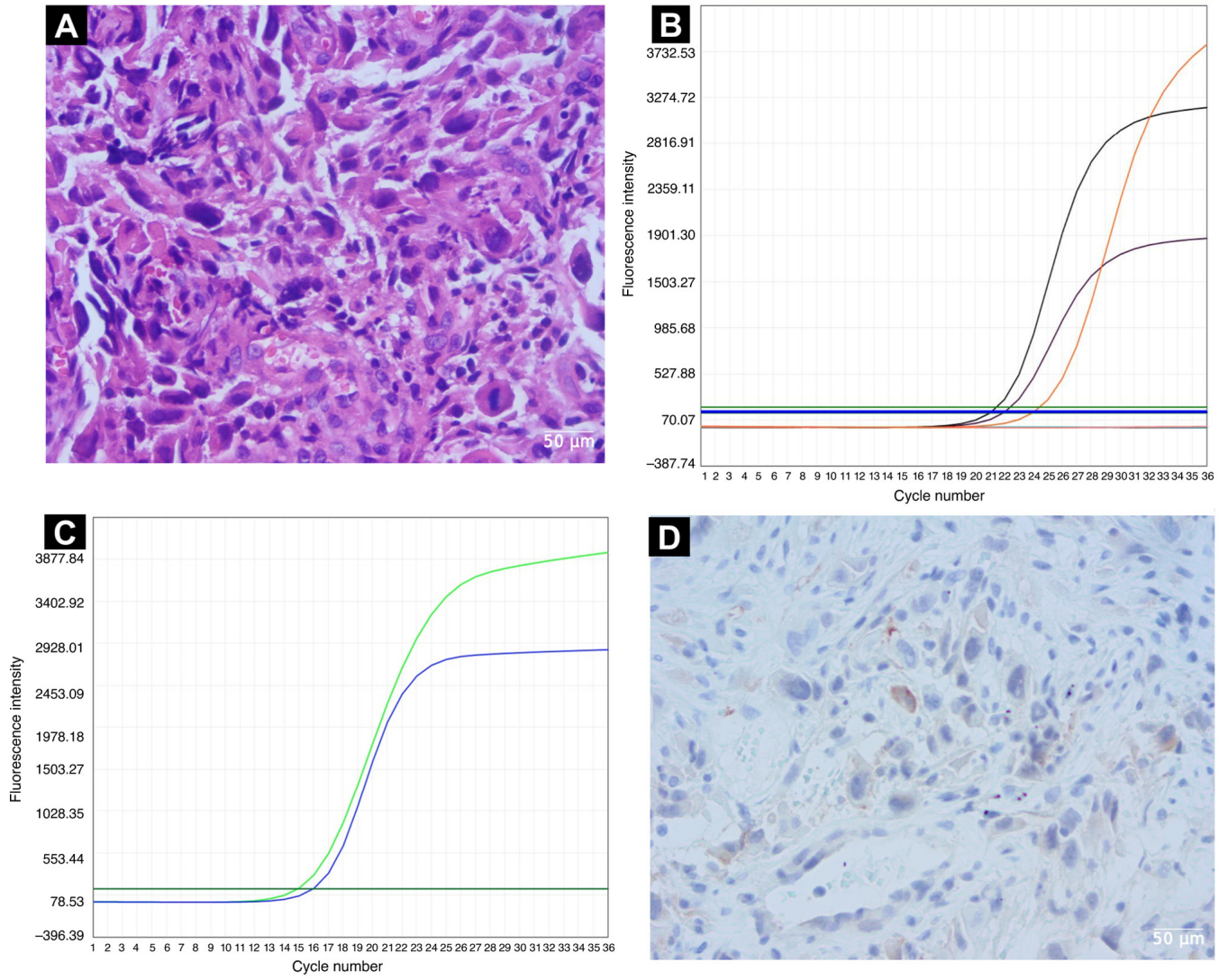

Figure 2. (A) H&E staining of the lung biopsy showed lung adenocarcinoma (scale bar, 50 μm; original magnification, x400). (B) Mutation of EGFR exon 19 deletion. (C) Mutation of MET exon 14 skipping. (D) Immunohistochemical analysis of programmed cell death ligand 1 (PD-L1) expression. Representative photomicrograph shows negative PD-L1 staining in tumor cells. Note the positive brown membranous staining in adjacent infiltrating immune cells, which serves as an positive control. Tissue sections were counterstained with hematoxylin (scale bar, 50 μm; original magnification, x400).

of such approaches varies considerably across regions due to differences in regulatory approval, reimbursement policies and clinical guideline recommendations (24-26). In resource-limited settings or under restrictive insurance systems, the high cost of targeted agents, limited availability of molecular testing and lack of trial infrastructure represent major barriers to the real-world implementation of combination strategies, underscoring the need for global efforts to bridge disparities in access to precision oncology (27).

It is noteworthy that the patient succumbed to a cerebral infarction approximately 11 months after commencing treatment. Given the patient's advanced age (70 years), which is a primary risk factor for cerebrovascular events, this occurrence was carefully evaluated. While the patient was on a combination of osimertinib and gumarontinib, there is no established direct evidence linking either agent, or their combination, to a significantly increased incidence of cerebral infarction. Therefore, after comprehensive assessment, the cerebral infarction may be considered to be most likely unrelated to the anticancer therapy and attributable to the patient's underlying age-related vascular risk.

In the present case, the concurrent presence of EGFR and MET mutations was detected in the biopsy specimen. Should osimertinib monotherapy be employed, its efficacy in suppressing the growth of EGFR-positive neoplastic cells may be limited (28). Consequently, it was chosen to employ a combination therapy incorporating gumarontinib. The choice of combining gumarontinib or other inhibitors is still under exploration (29-31). The present study reported the first detection of MET exon 14 skipping and EGFR Del19 in a patient, to the best of our knowledge. This patient achieved remission with osimertinib combined with gumarontinib treatment. The present findings provide valuable evidence for the subsequent treatment of such patients.

In conclusion, this case emphasizes the importance of understanding the genetic landscape of lung adenocarcinoma and the implications of concurrent mutations in treatment response and patient outcomes. Future clinical strategies should include

thorough genetic testing and possibly a shift towards combination therapies that address multiple pathways to enhance treatment efficacy while managing adverse effects. Continued research is essential to refine therapeutic approaches and improve the prognosis for patients with complex lung cancer profiles.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XJ and HZ conceptualized the study and wrote the original manuscript. LL and SL searched the literature and obtained case-related data. SL and XZ analyzed data and relevant literature. HZ reviewed and edited the final draft, and was responsible for project administration and funding acquisition. XJ and HZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the Shandong Cancer Hospital and Institute (Jinan, China; approval no. SDTHEC2024001026).

Patient consent for publication

Written informed consent for publication was obtained from the patient and his family prior to the study.

Competing interests

The authors declare that they have no competing interests.

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