

Challenges associated with the treatment of E709K and L858R double mutation in lung adenocarcinoma: A case report and literature review

JIANGQIN SONG^{1,2*}, QIN WU^{3*}, LILIN HE⁴, LIAN DONG⁴, LAMEI CHEN⁵,
HUASHUN LI⁶, KAIYUAN DIAO⁷ and HUABING YUAN⁸

¹Department of Medical Laboratory, The First People's Hospital of Tianmen City (Tianmen Hospital Affiliated to Wuhan University of Science and Technology), Tianmen, Hubei 431700, P.R. China; ²Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Science and Technology, Wuhan, Hubei 430065, P.R. China;

³Department of Hematologic Oncology, The People's Hospital of Yingcheng City, Xiaogan, Hubei 432400, P.R. China;

⁴Department of Oncology, The First People's Hospital of Tianmen City, Tianmen, Hubei 431700, P.R. China;

⁵Department of Radiology, The First People's Hospital of Tianmen City, Tianmen, Hubei 431700, P.R. China;

⁶Department of Pathology, The First People's Hospital of Tianmen City, Tianmen, Hubei 431700, P.R. China;

⁷Department of Solid Tumor Testing Laboratory, Guangzhou KingMed Center for Clinical Laboratory Company Limited, Guangzhou, Guangdong 510000, P.R. China; ⁸Department of Pharmacy, The First People's Hospital of Tianmen City (Tianmen Hospital Affiliated to Wuhan University of Science and Technology), Tianmen, Hubei 431700, P.R. China

Received February 20, 2025; Accepted July 25, 2025

DOI: 10.3892/ol.2025.15255

Abstract. Non-small-cell lung cancer (NSCLC) frequently harbors EGFR mutations, with the L858R and exon 19 deletions being the most prevalent. Rare EGFR exon 18 mutations, such as E709K, account for a small proportion but may significantly influence treatment response. The coexistence of E709K and L858R mutations presents unique therapeutic challenges and opportunities. This report describes a 64-year-old Chinese woman diagnosed with advanced lung adenocarcinoma harboring concurrent EGFR mutations (exon 18 p.E709K and exon 21 p.L858R). Initial treatment with osimertinib achieved partial response with a progression-free survival of 8 months, followed by disease progression. The patient was subsequently treated with afatinib, which

showed transient efficacy but was discontinued due to poor tolerance. Combination therapies involving chemotherapy (paclitaxel-platinum and pemetrexed), bevacizumab, radiotherapy and the third-generation EGFR TKI amitinib were sequentially administered, resulting in sustained symptomatic relief and clinical benefit. Leptomeningeal metastasis was later managed with intrathecal pemetrexed and ongoing amitinib therapy. In conclusion, this case highlights the complex clinical course of NSCLC with dual EGFR mutations, including E709K. While first- and second-generation TKIs offer variable efficacy, third-generation TKIs like amitinib may provide a durable benefit in selected patients. Comprehensive genomic profiling and individualized therapeutic strategies are essential for optimizing outcomes, particularly in cases involving rare EGFR mutations.

Correspondence to: Dr Qin Wu, Department of Hematologic Oncology, The People's Hospital of Yingcheng City, 69 Puyang Boulevard, Yincheng, Xiaogan, Hubei 432400, P.R. China
E-mail: 123061479@qq.com

Dr Jiangqin Song, Department of Medical Laboratory, The First People's Hospital of Tianmen City (Tianmen Hospital Affiliated to Wuhan University of Science and Technology), 1 East Renmin Avenue, Jingling, Tianmen, Hubei 431700, P.R. China
E-mail: mainx@qq.com

*Contributed equally

Key words: E709K and L858R, double mutation, lung adenocarcinoma

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small-cell lung cancer (NSCLC) accounting for 80-85% of all cases (1). Somatic activating mutations in the EGFR gene are the most frequent oncogenic driver mutations in Asian patients with NSCLC, with a prevalence of ~47% (2). Mutations in EGFR exons 18-21 notably predict responses to targeted therapies (3).

Among these mutations, the L858R substitution in exon 21 is one of the most common, alongside exon 19 deletions, together representing ~85-90% of all EGFR mutations in NSCLC. These mutations are typically sensitive to first-generation tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib (4). By contrast, mutations in exon 18, including G719X, E709X and exon 18 deletions, are found in 3-4% of all EGFR

mutations in NSCLC (5). The most frequent point mutations in exon 18 are G719X and E709X, which together account for 84% of mutations in this exon. DelE709_T710insX, the most frequent exon 18 deletion, accounts for ~2.4%. For patients with these rare mutations, afatinib is considered a first-line treatment option (6), which demonstrates moderate efficacy even against mutations that confer resistance to osimertinib.

E709X mutations, although rare, are notable for their sensitivity to targeted therapies. This mutation represents ~1.5% of all EGFR mutations and includes several variants, such as E709K, E709A, E709G, E709V, E709H, E709D and E709Q. Among these, E709K, E709A and E709G are the most common (7,8). However, due to the low incidence of E709X mutations and their occurrence in combination with other EGFR mutations, systematic studies on the efficacy of TKIs for E709X mutations remain limited. The co-occurrence of E709K and L858R mutations, in particular, has garnered notable attention due to their impact on disease progression and treatment response.

The present study reported a patient with both E709K and L858R mutations, treated sequentially with osimertinib, afatinib and ametinib. A literature review was also conducted on the rare E709X mutation in exon 18 and its implications for treatment strategies.

Case report

A 64-year-old Chinese woman, a non-smoker with no family history of cancer, was admitted to The People's Hospital of Yingcheng City (Yincheng, China) in March 2022. The patient experienced swelling, numbness and limited movement in the right hip and knee for >10 days. Pelvic MRI indicated multiple abnormal lesions in the right iliac crest, pubic bone, ischium, upper right femur, bilateral femoral heads, L5 vertebra and bilateral sacrum. CT scans of the neck revealed enlarged lymph nodes in the left neck and left supraclavicular region. Chest and upper abdomen CT revealed a tumor in the left lower lobe (3.1x1.7 cm) with enlarged left hilar and mediastinal lymph nodes, bilateral lung nodules and some irregular ground-glass opacities. Cranial MRI indicated multiple brain metastases in both the frontal and temporal lobes.

A percutaneous lung biopsy was performed under CT guidance, which revealed invasive adenocarcinoma (solid + acinar type) (Fig. 1A and B). Hematoxylin and eosin staining was performed according to standard histopathological protocols routinely used in our pathology department. Programmed cell death-ligand 1 (PD-L1) expression was positive with 30% tumor cell interpretation, the test was performed on a biopsy specimen using Ventana SP263 reagent and the Ventana BenchMark Ultra platform (Fig. 1C). Immunohistochemistry revealed that tumor cells were positive for thyroid transcription factor 1 [TTF-1 (+)] (Fig. 1D), Napsin A (+) (Fig. 1E), cytokeratin (CK)7 (+) (Fig. 1F), Ki-67 (LI 10%) (Fig. 1G) and negative for P40 (Fig. 1H). Marker selection followed the International Association for the Study of Lung Cancer 2021 consensus guidelines (9). Formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples were prepared using 10% neutral-buffered formalin at room temperature for 24 h. Tissue sections were cut to a thickness of 4 μ m using a microtome. For antigen retrieval and intracellular epitope exposure, slides

were permeabilized with 0.2% Triton X-100 (Merck KGaA; Sigma-Aldrich) in PBS for 10 min at room temperature. To reduce nonspecific binding, tissue sections were blocked with 5% normal goat serum (Abcam) in PBS for 30 min at room temperature. Immunohistochemical staining was then performed using the following primary antibodies: Anti-TTF-1 (1:200 dilution; cat. no. M3575; Dako; Agilent Technologies, Inc.), anti-Napsin A (1:100 dilution; cat. no. 760-4867; Roche Diagnostics), anti-CK7 (1:300 dilution; cat. no. M7018; Dako; Agilent Technologies, Inc.), anti-Ki-67 (1:100 dilution; cat. no. M7240; Dako; Agilent Technologies, Inc.) and anti-P40 (1:200 dilution; cat. no. 760-4863; Roche Diagnostics). Primary antibodies were incubated at 4°C overnight. Secondary antibody incubation was performed using the EnVision+ System-HRP Labeled Polymer Anti-Mouse/Rabbit (cat. no. K4007; Dako; Agilent Technologies, Inc.) at room temperature for 30 min. Diaminobenzidine was used as the chromogen, followed by counterstaining with hematoxylin. All slides were examined using a Nikon Eclipse E200 light microscope at x200 and x400 magnifications.

Emission CT scan demonstrated clear body bone imaging with strong distribution of radioactivity in the parietal, right shoulder, left humerus, left clavicle, multiple ribs, T2-4 vertebrae, sacrum, right sacroiliac joint, right iliac, bilateral hips and right femur, with physiological distribution elsewhere (Fig. 1I). Next-generation sequencing (NGS) of the transthoracic lung biopsy tissue identified EGFR exon 21 p.L858R mutation (15.59%) and EGFR exon 18 p.E709K mutation (21.2%) (Table I; Fig. 1J and K). Genomic DNA was extracted from FFPE lung biopsy tissue using a commercial DNA extraction kit (Auto-Pure 96; Hangzhou Allsheng Instruments Co., Ltd). The quality and integrity of the extracted DNA were assessed using standardized procedures, and the sample passed internal quality control metrics (average sequencing depth: 1191.02x; Q30: 94.25%). NGS was conducted using a hybrid capture-based 26-gene panel targeting lung cancer-related genes (WuHan Kingmed Center for Clinical Laboratory Co., Ltd). Paired-end sequencing was performed using the Illumina NovaSeq platform, with a read length of 150 bp (2x150 bp). Library preparation and enrichment were performed according to the manufacturer's protocols (KM Miniseq-DX; Guangzhou Jinqi Rui Biotechnology Co., Ltd). The final library was quantified using a Qubit fluorometer and normalized to a loading concentration of 2.0 nM, calculated using standard molar concentration formulas. Variant calling and visualization were performed using Integrative Genomics Viewer software [analytical software 1: bcl2fastq (v2.19.0.316); analytical software 2: fastp (v0.23.2); analytical software 3: BWA (v0.7.17-r1188); analytical software 4: Mutect 2 (v4.2.3.0); Analytical software 5: annovar (v2020-06-08); Analytical software 6: msisensor-pro (v1.0.2); Analytical software 7: manta (v1.6.0); Analytical software 8: Delly (v0.9.1); and Analytical software 9: cnvkit (v0.9.10)]. For bioinformatic analysis, the laboratory used proprietary pipelines and quality standards validated under ISO15189 guidelines. The serum tumor biomarker CEA level was 17.82 ng/ml, above the normal range (<5.0 ng/ml) (Fig. 1L). Based on these findings, the patient was diagnosed with stage IV left lower lung adenocarcinoma with lymphatic, intracranial and extensive bone metastasis (TNM staging, cT2N3M1; according to the

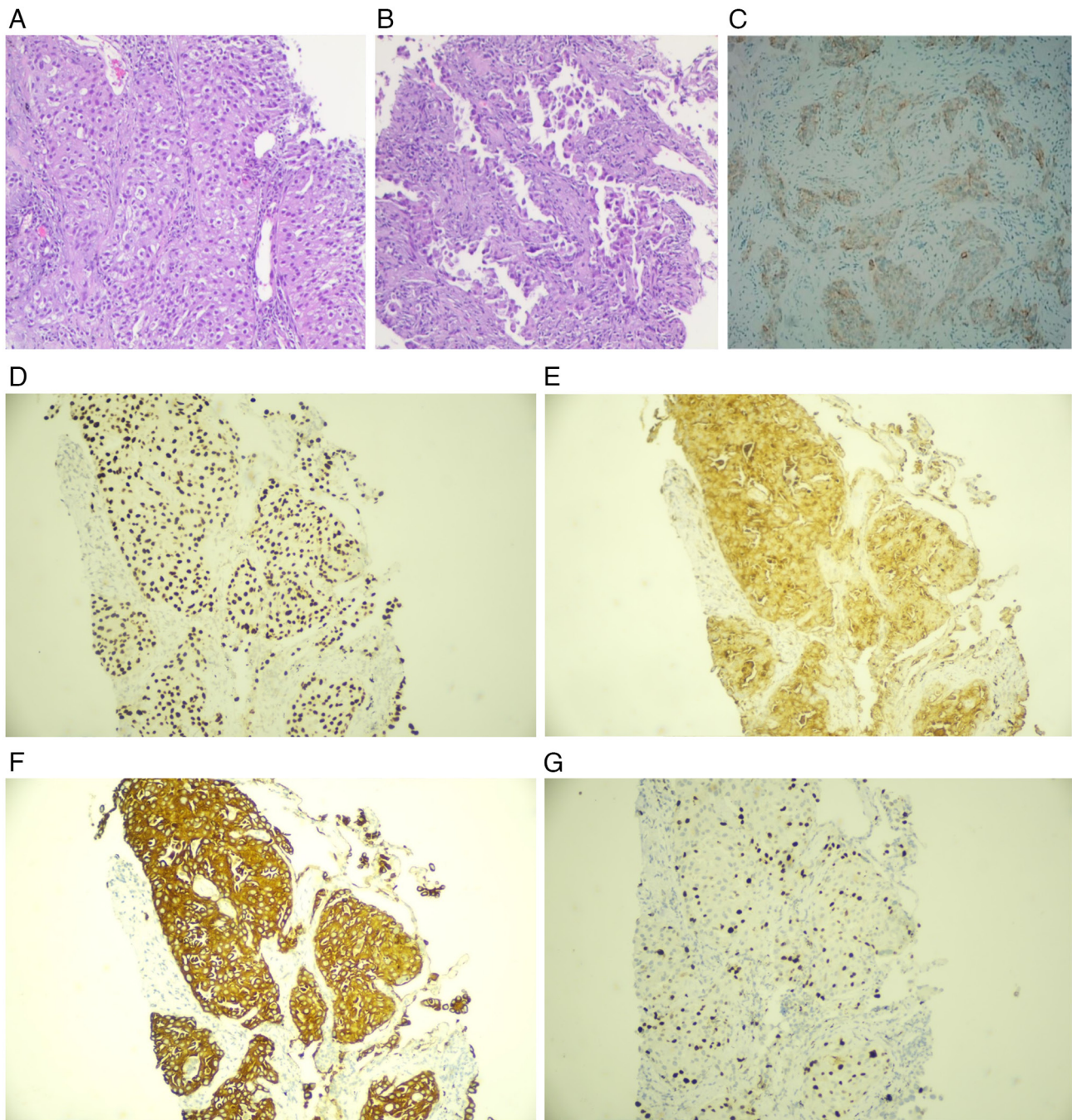


Figure 1. Continued.

guidelines from the International Association for the Study of Lung Cancer, 9th edition) (10). Osimertinib targeted therapy was recommended in accordance with the National Comprehensive Cancer Network guidelines (11).

In March 2022, the patient initially reported improvement in right hip pain, the chest CT and head MRI of the patient at that time are shown in Fig. S1A. Oral osimertinib therapy was initiated in March 2022 (80 mg, once daily). After 10 days, the patient experienced notable relief from lower back pain. A follow-up in April 2022, 1 month after starting osimertinib, indicated partial response (PR) (Fig. S1B). A 3-month follow-up in July 2022 also indicated PR (Fig. S1C).

However, by November 2022, after 8 months of osimertinib treatment, progression of disease (PD) was observed (Fig. S1D).

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) performed at Tongji Hospital (Wuhan, China) confirmed non-small cell carcinoma with pathology consistent with lung adenocarcinoma (Fig. 1M and N). NGS of the EBUS-TBNA biopsy tissue revealed EGFR exon 21 p.L858R (12.4%) and exon 18 p.E709K (12.5%) mutations and PD-L1 expression was again 30% (Fig. 1C).

In December 2022, the patient tested positive for COVID-19 and was admitted to the First People's Hospital of Tianmen City (Tianmen, China). The patient received 50 Gy/25 fractions of radiotherapy to the lower left lung and 1 month of oral afatinib therapy during the radiation (40 mg, once daily). However, afatinib was discontinued due to poor tolerance and osimertinib was resumed. In February 2023, following

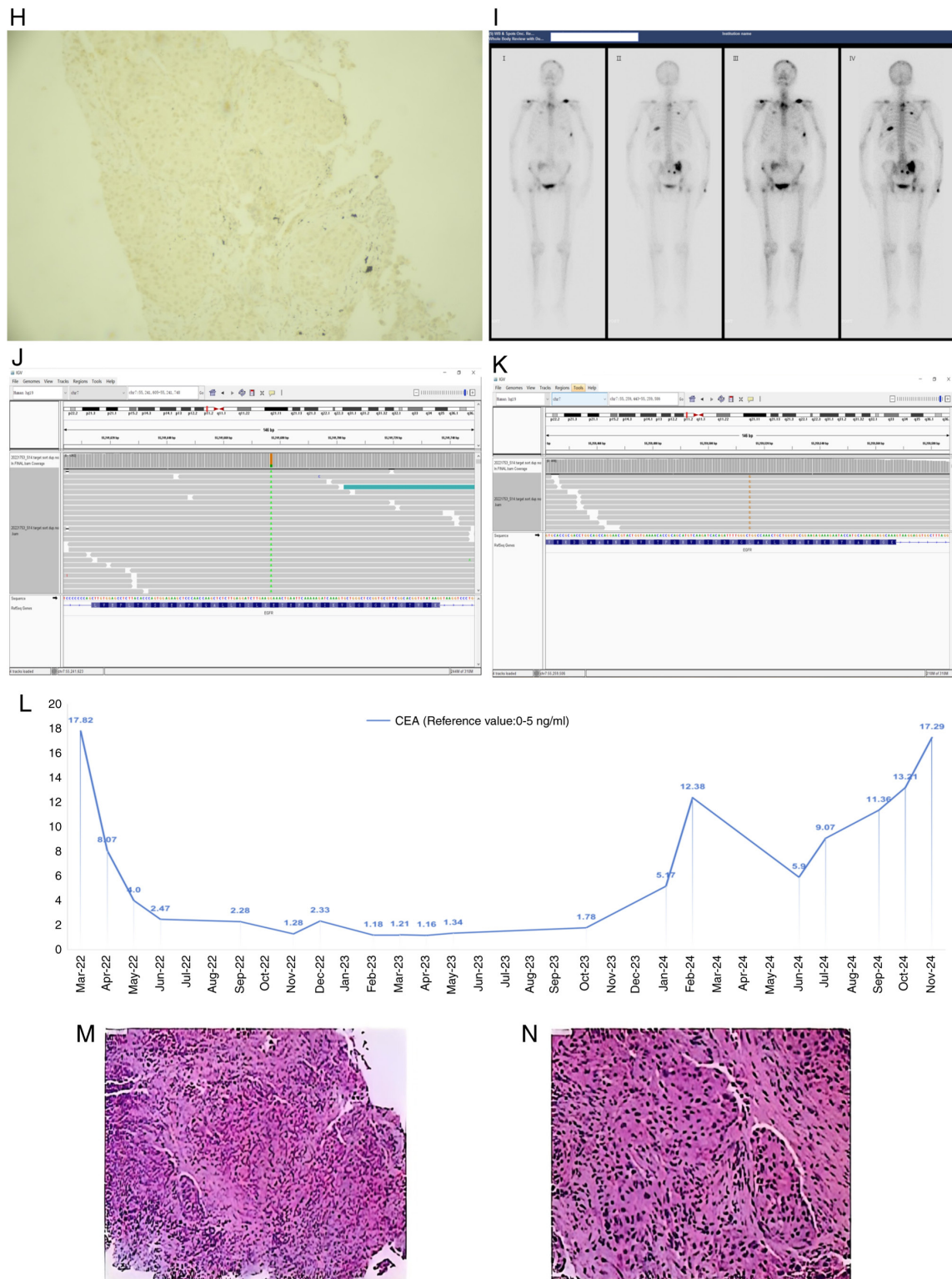


Figure 1. The percutaneous lung biopsy tissue in the lower lobe of the left lung was observed by H&E staining and magnifications at (A) x50 and (B) x400. (C) Programmed cell death ligand 1 test result: Positive, with tumor cell interpretation indicating 30%. Quality control demonstrated an assessable tumor cell count of 50%. Both positive and negative controls were successful. Combined with the results of immunohistochemistry [(D) thyroid transcription factor-1 (+) (nuclear staining). (E) Napsin A (+) (cytoplasmic granular staining). (F) Cytokeratin 7 (+) (diffuse cytoplasmic staining). (G) Ki-67:10% (labeling index). (H) P40 (-) (no nuclear staining) (magnification, x200)], and the pathological diagnosis was non-small cell lung cancer, which was consistent with the type of pulmonary adenocarcinoma. (I) Emission CT bone scintigraphy. Four panels show whole-body bone scans from different views. Panel I (far left, anterior view): Increased radioactivity in the parietal bone, right shoulder joint and left humerus. Panel II (left middle, posterior view): Increased radioactivity in the left clavicle, multiple ribs, and T2-T4 vertebrae. Panel III (right middle, anterior view): Increased radioactivity in the sacrum, right sacroiliac joint, and right ilium. Panel IV (far right, posterior view): Increased radioactivity in the bilateral hip joints and right femur. Remaining bones and joints show normal physiological distribution. (J) NGS results: The EGFR p.L858R mutation, with a frequency of 15.5% in the transthoracic lung biopsy tissue. (K) NGS results: The EGFR p.E709K mutation, with a frequency of 21.2% in the transthoracic lung biopsy tissue. (L) Serum tumor marker levels: A line chart depicting changes in serum CEA levels during the course of treatment (reference range, 0-5 ng/ml). Endobronchial ultrasound-guided transbronchial needle aspiration biopsy was performed to obtain tissue in the lower lobe of the left lung was observed by H&E staining at magnifications of (M) x50 and (N) x400. PCK, phosphoenolpyruvate carboxykinase; INSM1, insulinoma-associated protein 1; NGS, next-generation sequencing.

Table I. Results of NGS of tissue or peripheral blood samples.

Date (month and year)	Sample	Gene	Cytoband	Chr	Ref	Variant	AAchange.refgene add exons	Exons	Mutant frequency, % (total reads)	Other inspection
March 2022	Transthoracic lung biopsy tissue	EGFR	7p11.2	7	G	A	NM_005228:c.2125G>A (p.E709K) exon18;	18	15.5 (4536X)	/
			7p11.2	7	T	G	NM_005228:c.2573T>G (p.L858R) exon21;	21	21.2 (4595X)	
December 2022	EBUS-TBNA biopsy tissue	EGFR	7p11.2	7	G	A	NM_005228:c.2125G>A (p.E709K) exon18;	18	12.5 (4536X)	PD-L1 TC:30%
			7p11.2	7	T	G	NM_005228:c.2573T>G (p.L858R) exon21;	21	12.4 (4595X)	
March 2023	Cardiac puncture fluid	EGFR	7p11.2	7	G	A	NM_005228:c.2125G>A (p.E709K) exon18;	18	25.2 (4536X)	i) ARID2 p.S1309*, ii) MAP2K4 c.634-2A>G; and iii) FGFR4 chr5q35.1 duplication
			7p11.2	7	T	G	NM_005228:c.2573T>G (p.L858R) exon21;	21	23.6 (4595X)	BCL2L1 (BIM) intron 2 deletion
March 2024	Peripheral blood	EGFR	7p11.2	7	G	A	NM_005228:c.2125G>A (p.E709K) exon18;	18	1.18 (4536X)	
			7p11.2	7	T	G	NM_005228:c.2573T>G (p.L858R) exon21;	21	0.92 (4595X)	

NGS, next-generation sequencing; Chr, chromosome; Ref, reference nucleotide; Variant, mutant nucleotide; AAchange.refgene, amino acid change according to reference gene; PD-L1 TC, programmed death-ligand 1 tumor cell proportion; X, coverage depth; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

radiotherapy, afatinib was reintroduced for 1 month and the patient was again reviewed, which indicated PR (Fig. S1E).

In March 2023, the patient's condition progressed again and the patient developed intermittent cough, dizziness, nausea and vomiting. A CT scan indicated pericardial effusion and cancerous lymphangitis (Fig. S1F), with PD observed. In January 2023, 75 ml of bloody pericardial effusion was drained and pathological examination confirmed metastatic lung adenocarcinoma. Immunohistochemistry results were positive for PCK, CK7, TTF-1 and Napsin A, and negative for P40, CK5/6 and P40, with Ki-67 expression at ~40% (Anti-PCK: 1:150 dilution; cat. no. M3515; Dako; Agilent Technologies, Inc. Other antibody information is the same as stated above). NGS of the pericardial effusion revealed the same EGFR mutations (L858R and E709K). Given disease progression and suspected resistance to targeted therapy, cisplatin chemotherapy (cavum pericardii: 40 mg; vein: 60 mg, once) was administered in March 2023. Systemic chemotherapy with the paclitaxel-platinum (PP) (cisplatin: 100 mg; pemetrexed: 750 mg, once a month) regimen was continued, which led to PR after one cycle (Fig. S1G). After one cycle, bevacizumab (400 mg, once a month) was added to the PP regimen, which resulted in another PR (Fig. S1H).

In August 2023, after four cycles of the PP regimen, the treatment was switched to a combination of pemetrexed (750 mg, once a month) and bevacizumab (400 mg, once a month). After one cycle, a SD was achieved (Fig. S1I). However, after three cycles in November 2023, PD was observed and compliance with chemotherapy in the patient was suboptimal. Because the patient's self-perceived tolerance was poor, treatment intervals were extended to 45 days (Fig. S1J).

In February 2024, after six cycles of pemetrexed and bevacizumab, brain MRI revealed sporadic nodular enhancement and CT scans demonstrated worsening left lower lobe tumor and metastasis (Fig. S1K). The patient reported occasional dizziness and headaches and PD was confirmed. Whole-brain radiotherapy (WBRT) was initiated. NGS of peripheral blood indicated EGFR exon 21 p.L858R (0.92%) and exon 18 p.E709K (1.18%), with Bcl-2-like protein 11 interacting mediator of cell death intron 2 deletion (Table I). In May 2024, treatment with ameritinib (110 mg, once daily) and bevacizumab (400 mg, once a month) was started and after 1 month of WBRT, the patient demonstrated PR (Fig. S1L). The reexamination in August 2024 showed SD (Fig. S1M).

By November 2024, after 6 months of combined treatment with ameritinib and bevacizumab, the patient developed proteinuria (3+) and marked blood pressure fluctuations ($\leq 170/120$ mmHg), suspected to be side effects of bevacizumab. Consequently, bevacizumab was discontinued and intravenous pemetrexed chemotherapy (750 mg, once a month) was started. The patient subsequently developed symptoms of dizziness, headache, vomiting, somnolence, decreased vision, hearing loss, reduced appetite, lower limb weakness and unsteady gait. Brain MRI revealed slight enlargement of ventricles and cisterns, mild widening of sulci and possible leptomeningeal metastasis (Fig. S1N).

Following the confirmation of leptomeningeal metastasis, an Ommaya reservoir implantation (Fig. 2A) was performed and cerebrospinal fluid examination confirmed the presence of tumor cells (Fig. 2B). Intrathecal administration of pemetrexed

(30 mg, once a month) via the Ommaya reservoir, in combination with oral ameritinib (220 mg, once daily), led to notable improvement in the symptoms of the patient. The treatment regimen is ongoing and the patient receives an intrathecal injection once a month. The timeline of the diagnosis and treatment of the patient is displayed on the left side of Fig. S1.

Discussion

The treatment of EGFR mutations has undergone notable advancements, with targeted therapies serving a key role in the improvement of patient outcomes. Among the various mutations in the EGFR gene, the E709X mutation, including the E709K mutation, has gained attention due to its implications for treatment response to different generations of EGFR TKIs. A comprehensive summary of previous studies on the E709X mutation is provided in Table II.

Mutations such as E709K and L858R have demonstrated varying responses to different generations of EGFR TKIs: i) First-generation TKIs: Both L858R and E709K mutations exhibit sensitivity to first-generation TKIs, although E709K generally exhibits a slightly lower response compared with L858R. Previous studies indicated that while first-generation TKIs are initially effective, resistance typically develops over time (7,12,13); ii) second-generation TKIs: Afatinib and dacomitinib, as second-generation EGFR TKIs, irreversibly bind to the EGFR receptor. Clinical data suggested that afatinib is particularly effective in treating E709K mutations, offering a notable progression-free survival (PFS) advantage. Afatinib is also highly efficacious for L858R mutations and is often preferred due to its potency and broader mutation coverage (5); and iii) third-generation TKIs: Osimertinib, a third-generation TKI, is typically reserved for patients with acquired T790M resistance mutations but has also demonstrated efficacy in L858R mutation cases after resistance to earlier-generation TKIs. However, the effectiveness of osimertinib and other third-generation TKIs in the treatment of E709K mutations remains elusive and warrants further investigation (12).

Previous studies reported three lung cancer cases with dual EGFR mutations (L858R and E709K) treated using afatinib: 1 patient achieved PR and 2 patients had stable disease (SD) (14). The E709 amino acid alteration in the EGFR gene is relatively rare in NSCLC and is often associated with other sensitive EGFR mutations (e.g., G719X and L858R) (15,16). A study suggested that the E709K mutation may be sensitive to afatinib-targeted therapy but demonstrates reduced sensitivity to gefitinib and erlotinib (6), a finding confirmed by a retrospective case-control study conducted by Kuiper *et al* (17). Furthermore, patients with uncommon EGFR mutations (e.g. S768I and exon 20 insertion mutation) (18,19) tend to have shorter PFS and overall survival (OS) on EGFR-TKI treatment compared with those with classic EGFR mutations (e.g. Del19 and L858R point mutation) (20), although there is considerable variability depending on the specific mutation.

A previous study by Wu and Shih (21) offers the largest sample size for evaluating the efficacy of first-generation TKIs in patients with NSCLC with E709X mutations. Their results indicated that, such as G719X mutations, E709X mutations exhibit moderate sensitivity to first-generation TKIs. In a cohort of 18 patients with the E709X mutation, treated

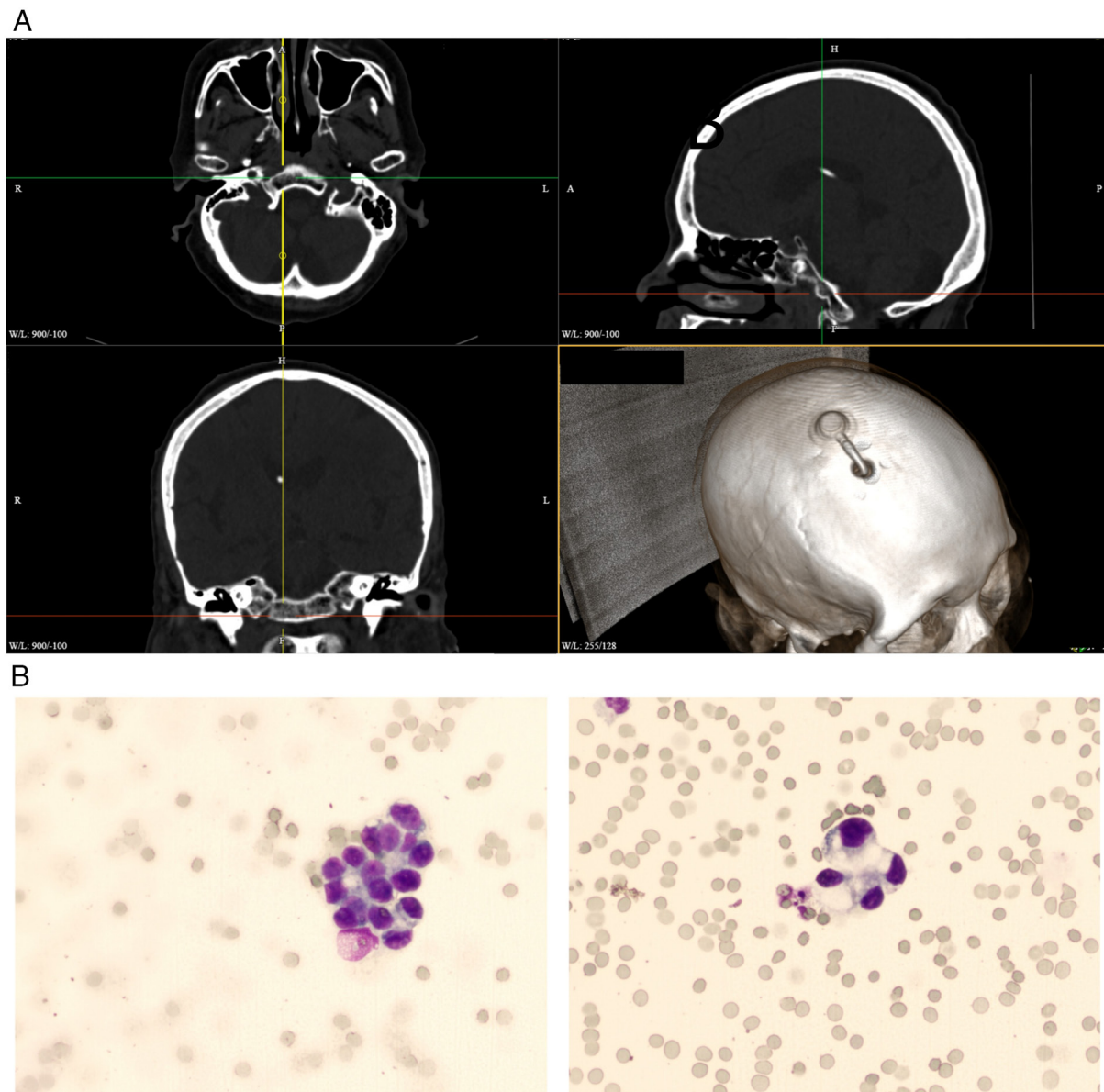


Figure 2. Results following leptomeningeal metastasis confirmation. (A) CT examination: Post-implantation of the Ommaya reservoir. (B) CSF cytology: During surgery, CSF was drained and examined using liquid-based cytology after concentration and centrifugation. A small number of tumor cells were identified, which confirmed leptomeningeal metastasis. CSF, cerebrospinal fluid.

with gefitinib or erlotinib, the response rate was 50.0% for E709X mutations, compared with 16.5% for wild-type EGFR and 74.1% for classic EGFR mutations. The median PFS was 6.2 months for E709X mutations, compared with 2.0 months for wild-type EGFR and 9.1 months for classic mutations. The initial OS for self-medication was 29.3 months for E709X mutations, compared with 11.8 months for wild-type EGFR and 19.1 months for classic mutations. Despite these findings, larger clinical studies are required to confirm whether second-generation TKIs offer greater survival advantages over first-generation TKIs for patients with the E709X mutation.

The E709_T710delinsX mutation is a deletion/insertion mutation occurring at position 709 of exon 18, which accounts for ~0.16% of all EGFR mutations. This includes several variants, with the E709_T710delinsD mutation being the most common, which represents ~70% of cases (16,22,23). There is limited systematic research on the sensitivity of the

E709_T710delinsX mutation to first-generation TKIs. In a study by Wu *et al* (24), 5 patients with the E709_T710delinsD mutation, treated with gefitinib, had a poor response, with 2 cases of SD and 3 cases of progressive disease (PD) and a median PFS of 2.3 months. Another previous study including 2 patients with the E709_T710delinsD mutation treated with gefitinib or erlotinib also reported 1 case with PD and 1 with SD, which further suggested that this mutation may confer resistance to first-generation TKIs (12).

A previous study by Kobayashi *et al* (5) compared the inhibitory effects of various EGFR TKIs on Ba/F3 cells expressing the E709K/E709_T710delinsD mutation. The results indicated that second-generation TKIs, such as afatinib, were more potent in inhibiting the E709K/E709_T710delinsD Ba/F3 cell line compared with first-generation TKIs. This suggested that second-generation TKIs may be more effective in the treatment of patients with NSCLC with the E709_T710delinsD

Table II. All reported cases of the EGFR E709X (E709A, E709G, E709V, E709K) and E709-T710delinsX mutation in patients with lung adenocarcinoma treated with EGFR TKIs.

First author, year	Age, years	Sex, M/F	Mutations	Incorporation of other mutations	Smoker	Stage	Cancer type	Treatment	Response to TKI (time)	PFS, months	OS, months	(Refs.)
Wu <i>et al.</i> , 2011	61	F	E709-T710delinsX	No	No	IV	ADC	Gefitinib ^a	SD	5.1	79.0	(24)
	65	M	E709-T710delinsX	No	Yes	IV	ADC	Gefitinib	PD	0.9	11.1	
Wu <i>et al.</i> , 2016	57	F	E709-T710delinsX	No	No	IV	ADC	Gefitinib	PD	6.0	24.1	(21)
	79	M	E709-T710delinsX	No	Yes	IV	ADC	Gefitinib	O	6.2	6.2	
	68	M	E709-T710delinsX	No	Yes	IV	ADC	Gefitinib	PD	2.3	29.5	
	59	F	E709A	G719C	No	IV	ADC	Gefitinib	SD	7.3	12.1	
	58	F	E709A	G719C	No	IV	ADC	Erlotinib ^a	PR	14.9	29.3	
	76	M	E709A	L858R	No	IV	ADC	Erlotinib	SD	3.9	5.4	
	48	F	E709A	L858R	No	IV	ADC	Gefitinib	PR	13.6	32.0	
	69	M	E709G	G719C	No	IV	ADC	Erlotinib	PD	1.4	8.3	
Ackerman <i>et al.</i> , 2012	57	F	E709G	Del exon 19	No	IV	ADC	Gefitinib	PR	77.4	104.6	
	85	M	E709G	L858R	Yes	IIIB	ADC	Erlotinib	PR	8.6	13.2	
	48/	F	E709G	L858R	No	IV	ADC	Gefitinib	PD	2.4	6.8	
	55	F	E709G	L858R	No	IV	ADC	Gefitinib	PR	18.4	75.3	
	64	F	E709K	G719S	No	IV	ADC	Gefitinib	PR	11.1	11.1	
	71	M	E709K	L858R	No	IV	ADC	Gefitinib	PR	6.5	6.5	
	69	M	E709K	L858R	Yes	IV	ADC	Gefitinib	PR	8.6	8.6	
	66	M	E709V	L858R	Yes	IV	ADC	Gefitinib	PR	9.2	9.5	
Isaksson <i>et al.</i> , 2020	88	F	E709-T710delinsX	Wild-type KRAS	No	IV	NSCLC	Erlotinib	PR (4 months)	NA	NA	(23)
		NA	E709-T710delinsX	No	NA	IV	NA	Erlotinib	PD	8.0	NA	(29)
	66	F	E709-T710delinsX	No	Yes	IV	ADC	Gefitinib	PD	3.0	24.0	(30)
	46	F	E709-T710delinsX	No	Former heavy	IV	ADC	Erlotinib	DD	4.0	26.0	
Klughammer <i>et al.</i> , 2016	57	F	E709-T710delinsX	No	No	IV	ADC	Erlotinib	PD	3.0	18.0	
	50	F	E709-T710delinsX	No	No	II or IV	NSCLC	Erlotinib	PD	1.3	1.7	(31)
	58	M	E709A	G719S	Yes	NA	NA	Erlotinib	SD	253	509	
	50	M	E709K	G719A	No	NA	NA	Erlotinib	PD	42	259	
Kobayashi <i>et al.</i> , 2015	63	M	E709-T710delinsX	No	NA	IV	ADC	Erlotinib	SD	NA	NA	(5)
		F						Afatinib ^a	Tumor shrinkage (1 month)	NA	NA	
Ibrahim <i>et al.</i> , 2017	52	F	E709-T710delinsX		No	IV	ADC	Afatinib	2 months	NA	NA	(32)
D'Haene <i>et al.</i> , 2019	57	M	E709-T710delinsX		No		ADC	Afatinib	PR (12 months); PD	12.0	36.0	(33)

Table II. Continued.

First author, year	Age, years	Sex, M/F	Mutations	Incorporation of other mutations	Smoker	Stage	Cancer type	Treatment	Response to TKI (time)	PFS, months	OS, months	(Refs.)
Martin <i>et al</i> , 2019	60	F	E709-T710delinsX		No	IV	ADC	Erlotinib	PD	1.0	3.0	(34)
Wei <i>et al</i> , 2021	70	F	E709-T710delinsX	Amplification, M246_T256del, E545K, E542K etc.	No	II	NSCLC	Afatinib	PD	23.0	Ongoing	(12)
		M						Almonertinib ^a	SD	NA		
Liu <i>et al</i> , 2022	30	F	E709K	G724S, V689I	No	IV	NSCLC	Afatinib	PR (2 months)	3	13.5	(35)
Frega <i>et al</i> , 2016	70	F	E709K	L833V, H835L	Yes	IV	ADC	Afatinib	PR (2 months)	2	Ongoing	(36)
Present case	64	M	E709K	L858R	No	IV	NSCLC	Osimertinib ^a	PR (8 months)	8	Ongoing	-
								Afatinib	NA	NA		
								Almonertinib	PR (>4 months)	NA		

^a Afatinib, gefitinib, erlotinib, osimertinib and almonertinib refer to EGFR tyrosine kinase inhibitors. NGS, next-generation sequencing; F, female; M, male; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; ADC, lung adenocarcinoma; NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available; delins, deletion-insertion; Del exon 19, deletion of exon 19.

mutation. However, clinical evidence confirming the efficacy of second-generation TKIs in patients with E709_T710delinsX mutations remains sparse.

The findings of the present study align with those of previous studies (5,8,18), which demonstrated moderate to good responsiveness of dual EGFR mutations (E709K and L858R) to targeted EGFR-TKIs, notably afatinib and osimertinib. Similar to Wu *et al* (24), the present study observed initial sensitivity followed by the development of resistance. By contrast, while Kobayashi *et al* (5) and Wei *et al* (12) reported a notable clinical benefit with afatinib for exon 18 mutations, the present patient exhibited limited tolerance to afatinib, which necessitates a treatment switch to third-generation TKI amitinib.

The novel insight provided by the present study is the clinical efficacy and tolerability of sequential treatment involving osimertinib, afatinib and amitinib, including comprehensive radiotherapy and chemotherapy management strategies. These findings suggest individualized therapeutic strategies and highlight the importance of real-time genomic monitoring to promptly manage resistance mechanisms. However, notable gaps remain, particularly regarding standardized treatment protocols for rare EGFR mutations, mechanisms underlying acquired resistance and the optimal sequencing and combination of TKIs in clinical practice. Future large-scale studies are key to filling these knowledge gaps.

A notable case study reported a patient with lung adenocarcinoma with the rare E709_T710delinsD mutation who responded well to afatinib, which achieved a PFS of 23 months (12). The present case highlighted the potential of second-generation TKIs, such as afatinib, in the management of mutations involving exon 18. Additionally, broader analyses suggested that patients with E709K and other exon 18 mutations exhibited an improved response to afatinib or neratinib compared with first-generation TKIs (5,25,26).

Functional studies using transfected cell models (Ba/F3 and NIH/3T3) have demonstrated that the E709K mutation, similar to G719X, induces oncogenic transformations. These mutations exhibit greater sensitivity to second-generation TKIs, such as afatinib and neratinib, compared with first-generation TKIs. These findings underscore the importance of precise molecular diagnostics in guiding optimal treatment strategies for patients with rare EGFR mutations (6).

The present case included a patient with EGFR mutations, specifically E709K and L858R, who was treated with multiple targeted therapies, including osimertinib (8 months), afatinib (1 month) and amitinib (ongoing). Due to the complexity of the treatment regimen, which combined targeted therapies with radiation for the primary lesions, it was difficult to assess the efficacy of the treatment. However, both osimertinib (PFS, 8 months) and amitinib (ongoing therapy) demonstrated favorable responses, which resulted in remission. The present case highlighted the potential effectiveness of third-generation EGFR TKIs in the treatment of the rare E709K mutation. Although resistance ultimately developed, these treatments markedly alleviated the condition of the patient and produced tolerable side effects, rendering them a promising therapeutic option for similar cases in the future.

Resistance mechanisms to third-generation EGFR TKIs, such as osimertinib, include secondary mutations such as C797S, MET amplification and histological transformations (e.g., small

cell transformation). The patient of the present case study eventually demonstrated progression on osimertinib, which suggested potential activation of such resistance pathways. Future treatment strategies should integrate comprehensive genomic monitoring to promptly identify and target these resistance mechanisms.

Additionally, the patient began chemotherapy in April 2023, which included a combination of bevacizumab, the PP regimen, pemetrexed chemotherapy, whole-brain radiotherapy and continued targeted therapy with amitinib and intrathecal injections. Xu *et al* (27) also suggested that continuing EGFR-TKI therapy in combination with bevacizumab is a rational strategy for patients with NSCLC who experience gradual progression after initial EGFR-TKI treatment. Clinical studies have reported that the addition of bevacizumab to standard chemotherapy (carboplatin/paclitaxel) notably increases survival in patients with NSCLC. In the pivotal Phase III study (ECOG 4599), chemotherapy plus bevacizumab resulted in improved OS (12.3 vs. 10.3 months) and longer PFS (6.2 vs. 4.5 months) (28).

The present case underscores the value of incorporating targeted therapies and bevacizumab into treatment regimens for advanced NSCLC, particularly for patients with rare mutations such as E709K, where conventional therapies may offer limited efficacy. Further studies are warranted to optimize these combination therapies and enhance the understanding of their long-term impact on patient survival and quality of life.

The present case study demonstrated the complex treatment process for a patient with advanced lung adenocarcinoma. Through multidisciplinary collaboration, the patient received effective symptomatic treatment and an improvement in quality of life. The present case underscores the importance of individualized treatment plans in oncology.

The treatment of patients with EGFR mutations, particularly the E709X and E709_T710delinsX mutations, poses notable challenges due to their unique properties and varying responses to different EGFR TKIs. While first-generation TKIs exhibit certain efficacy, second-generation TKIs, particularly afatinib, appear to offer a more favorable therapeutic option for patients with these mutations, the literature on E709X and E709_T710delinsX mutations was searched and their views seem to support this conclusion (29-36). However, further clinical studies with larger sample sizes are required to validate these findings and optimize treatment strategies for these patients. Furthermore, the role of third-generation TKIs, such as osimertinib, in the treatment of these mutations remains to be elucidated in future research.

The E709K and L858R mutations in EGFR are key factors in the pathogenesis and treatment response of NSCLC. While the L858R mutation is well-characterized and commonly targeted with established treatment protocols, the E709K mutation, although less frequent, demonstrates promising responses to second-generation EGFR TKIs, particularly afatinib. Ongoing research and clinical trials are necessary to refine therapeutic strategies and improve patient outcomes for those with these mutations. For clinicians, understanding the specific EGFR mutation profile is essential for the selection of the most effective targeted therapies, which ultimately enhances both survival and quality of life for patients.

The limited number of cases including rare or complex mutations poses challenges for the design of large-scale prospective trials. Therefore, translational studies and the establishment of

national and international biobanks will be key to addressing several of the unresolved questions in this field.

In conclusion, the management of NSCLC with rare EGFR mutations such as E709X and E709_T710delinsX remains challenging due to their heterogeneity and limited clinical data. This case highlights the clinical value of individualized treatment strategies combining sequential EGFR TKIs, including afatinib and osimertinib, and adjunct therapies such as bevacizumab and radiotherapy. Second-generation TKIs, particularly afatinib, appear to offer improved efficacy for exon 18 mutations compared to first-generation TKIs, while third-generation TKIs may serve as effective alternatives upon resistance. The integration of genomic monitoring and multidisciplinary approaches is essential for optimizing treatment in these complex cases. Further prospective studies and real-world evidence are needed to establish standardized protocols and improve outcomes for patients harboring uncommon EGFR mutations.

Acknowledgements

The authors would like to thank the doctors who gave their advice during the treatment of the patient: Professor Qin Wu (Oncology Department), Professor Linfeng Wang (Neurosurgery Department), Professor Zhibin Hu (Imaging Department) and Professor Yongqiao Liu (Pathology Department) (The People's Hospital of Yingcheng City, Xiaogan, China), Professor Junhong Zhang (Oncology Department, Zhongnan Hospital, Wuhan University, Wuhan, China), Professor Peng Zhang (Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China), Professor Rui Meng (Department of Oncology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China), Professor Wuling Ou (Department of Oncology, Hubei Provincial Cancer Hospital, Wuhan, China) and Professor Wei Li, Professor Lilin He, Professor Lian Dong, Professor Rui Song and Professor Cong Chen (Department of Oncology, The First People's Hospital of Tianmen City, Tianmen, Hubei, China) provided consultation services such as diagnosis and treatment. Dr Kaiyuan Diao (Guangzhou KingMed Center for Clinical Laboratory Co., Ltd., Guangzhou, China) provided solid tumor gene sequencing and report interpretation.

Funding

The present study was supported by the Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Science and Technology (grant no. JF2024-Y19); the Hubei Provincial Natural Science Foundation (grant no. 2022CFB514) and its Key-Area R&D Program (grant no. 2022BCE067).

Availability of data and materials

The whole-genome sequencing data generated and analyzed in the present study have been deposited in the NCBI Sequence Read Archive (SRA) under the accession no. PRJNA1276985, which are publicly accessible at: <https://www.ncbi.nlm.nih.gov/sra/PRJNA1276985>. The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JS devised the methodology, organized laboratory data, wrote the original draft, and edited and reviewed the manuscript. QW, LH and LD devised the methodology, organized medical record data, and edited and reviewed the manuscript. LC performed imaging diagnosis, obtained the imaging data and edited and reviewed the manuscript. HL provided organopathology and immunohistochemical diagnosis, obtained the pathology data and edited and reviewed the manuscript. KD obtained the molecular pathology data, conducted the formal analysis and edited and reviewed the manuscript. HY devised the methodology, obtained funding for the present study and edited and reviewed the manuscript. JS and QW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethical Committee of The First People's Hospital of Tianmen City (approval no. 20240286). The patient provided written informed consent to the treatment plan and genetic testing given by the attending physician.

Patient consent for publication

The patient provided written informed consent for the publication of data and images in the present study.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools [OpenAI.(2023). and ChatGPT-4o] were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
2. Midha A, Dearden S and McCormack R: EGFR mutation incidence in non small cell lung cancer of adenocarcinoma histology: A systematic review and global map by ethnicity (MutMapII). *Am J Cancer Res* 5: 2892-2911, 2015.
3. Robichaux JP, Le X, Vijayan RSK, Hicks JK, Heeke S, Elamin YY, Lin HY, Udagawa H, Skoulidis F, Tran H, *et al*: Structure-based classification predicts drug response in EGFR-mutant NSCLC. *Nature* 597: 732-737, 2021.
4. Hama T, Yuza Y, Suda T, Saito Y, Norizoe C, Kato T, Moriyama H and Urashima M: Functional mutation analysis of EGFR family genes and corresponding lymph node metastases in head and neck squamous cell carcinoma. *Clin Exp Metastasis* 29: 19-25, 2011.
5. Kobayashi Y, Togashi Y, Yatabe Y, Mizuuchi H, Jangchul P, Kondo C, Shimoji M, Sato K, Suda K, Tomizawa K, *et al*: EGFR exon 18 mutations in lung cancer: Molecular predictors of augmented sensitivity to afatinib or neratinib as compared with first- or third-generation TKIs. *Clin Cancer Res* 21: 5305-5313, 2015.

6. Yang JC, Schuler M, Popat S, Miura S, Park K, Passaro A, De Marinis F, Solca F, Märten A and Kim ES: Afatinib for the treatment of non-small cell lung cancer harboring uncommon EGFR mutations: An updated database of 1023 cases brief report. *Front Oncol* 12: 834704, 2022.
7. Xu H, Yang G, Li W, Li J, Hao X, Xing P, Yang Y and Wang Y: EGFR exon 18 mutations in advanced non-small cell lung cancer: A real-world study on diverse treatment patterns and clinical outcomes. *Front Oncol* 11: 713483, 2021.
8. Borgeaud M, Parikh K, Banna GL, Kim F, Olivier T, Le X and Addeo A: Unveiling the landscape of uncommon EGFR mutations in NSCLC-A systematic review. *J Thorac Oncol* 19: 973-983, 2024.
9. Rolfo C, Mack P, Scagliotti GV, Aggarwal C, Arcila ME, Barlesi F, Bivona T, Diehn M, Dive C, Dziadziuszko R, *et al*: Liquid biopsy for advanced NSCLC: A consensus statement from the international association for the study of lung cancer. *J Thorac Oncol* 16: 1647-1662, 2021.
10. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V, *et al*: The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 11: 39-51, 2016.
11. National Comprehensive Cancer, N., NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 2.2024. 2024, National Comprehensive Cancer Network.
12. Wei Y, Cui Y, Guo Y, Li L and Zeng L: A lung adenocarcinoma patient with a rare EGFR E709_T710delinsD mutation showed a good response to afatinib treatment: A case report and literature review. *Front Oncol* 11: 700345, 2021.
13. Du Z, Sun J, Zhang Y, Hesilaiti N, Xia Q, Cui H, Fan N and Xu X: Structure-guided strategies of targeted therapies for patients with EGFR-mutant non-small cell lung cancer. *Biomolecules* 13: 210, 2023.
14. Heigener DF, Schumann C, Sebastian M, Sadjadian P, Stehle I, Märten A, Lüers A, Griesinger F and Scheffler M: Afatinib Compassionate Use Consortium (ACUC): Afatinib in non-small cell lung cancer harboring uncommon EGFR mutations pretreated with reversible EGFR inhibitors. *Oncologist* 20: 1167-1174, 2015.
15. Kobayashi Y and Mitsudomi T: Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. *Cancer Sci* 107: 1179-1186, 2016.
16. Janne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, Ahn MJ, Kim SW, Su WC, Horn L, *et al*: AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 372: 1689-1699, 2015.
17. Kuiper JL, Hashemi SM, Thunnissen E, Snijders PJ, Grünberg K, Bloemena E, Sie D, Postmus PE, Heideman DA and Smit EF: Non-classic EGFR mutations in a cohort of Dutch EGFR-mutated NSCLC patients and outcomes following EGFR-TKI treatment. *Br J Cancer* 115: 1504-1512, 2016.
18. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, *et al*: Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 3: 75ra26, 2011.
19. Park S, Park S, Kim TM, Kim S, Koh J, Lim J, Yi K, Yi B, Ju YS, Kim M, *et al*: Resistance mechanisms of EGFR tyrosine kinase inhibitors, in EGFR exon 20 insertion-mutant lung cancer. *Eur J Cancer* 208: 114206, 2024.
20. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, Singh B, Heelan R, Rusch V, Fulton L, *et al*: EGF receptor gene mutations are common in lung cancers from 'never smokers' and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA* 101: 13306-13311, 2004.
21. Wu JY and Shih JY: Effectiveness of tyrosine kinase inhibitors on uncommon E709X epidermal growth factor receptor mutations in non-small-cell lung cancer. *Onco Targets Ther* 9: 6137-6145, 2016.
22. Huang Y, Xu C, Sun Y, Wang W, Li X, Liao J, Pang L, Zeng L, Li J, Wang X, *et al*: Rare EGFR E709-T710delinsX: Molecular characteristics and superior response to afatinib treatment in NSCLC patients. *Lung Cancer* 172: 117-123, 2022.
23. Ackerman AGM, Goldstein MA, Kobayashi S and Costa DB: EGFR delE709_T710insD: A rare but potentially EGFR inhibitor responsive mutation in non-small-cell lung cancer. *J Thorac Oncol* 7: e19-e20, 2012.
24. Wu JY, Yu CJ, Chang YC, Yang CH, Shih JY and Yang PC: Effectiveness of tyrosine kinase inhibitors on 'uncommon' epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer. *Clin Cancer Res* 17: 3812-3821, 2011.
25. Goldman JW, Bueno AM, Dooks C, Jhaveri K, de Miguel M, Piha-Paul SA, Unni N, Zick A, Mahipal A, Suga JM, *et al*: Neratinib efficacy in patients with EGFR exon 18-mutant non-small-cell lung cancer: Findings from the SUMMIT basket trial. *Clin Lung Cancer* 26: 191-200 e191, 2025.
26. Wang P, Fabre E, Martin A, Chouahnia K, Benabadji A, Matton L and Duchemann B: Successful sequential tyrosine kinase inhibitors to overcome a rare compound of EGFR exon 18-18 and EGFR amplification: A case report. *Front Oncol* 12: 918855, 2022.
27. Xu Z, Teng F, Hao X, Li J and Xing P: Bevacizumab combined with continuation of EGFR-TKIs in NSCLC beyond gradual progression. *Cancer Manag Res* 14: 1891-1902, 2022.
28. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilienbaum R and Johnson DH: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355: 2542-2550, 2006.
29. Isaksson S, Hazem B, Jönsson M, Reuterswärd C, Karlsson A, Griph H, Engleson J, Oskarsdóttir G, Öhman R, Holm K, *et al*: Clinical utility of targeted sequencing in lung cancer: Experience from an autonomous Swedish health care center. *JTO Clin Res Rep* 1: 100013, 2020.
30. Sousa AC, Silveira C, Janeiro A, Malveiro S, Oliveira AR, Felizardo M, Nogueira F, Teixeira E, Martins J and Carmo-Fonseca M: Detection of rare and novel EGFR mutations in NSCLC patients: Implications for treatment-decision. *Lung Cancer* 139: 35-40, 2020.
31. Klughammer B, Brugger W, Cappuzzo F, Ciuleanu T, Mok T, Reck M, Tan EH, Delmar P, Klingelschmitt G, Yin AY, *et al*: Examining treatment outcomes with erlotinib in patients with advanced non-small cell lung cancer whose tumors harbor uncommon EGFR mutations. *J Thorac Oncol* 11: 545-555, 2016.
32. Ibrahim U, Saqib A and Atallah JP: EGFR exon 18 delE709_T710insD mutated stage IV lung adenocarcinoma with response to afatinib. *Lung Cancer* 108: 45-47, 2017.
33. D'Haene N, Le Mercier M, Salmon I, Mekinda Z, Rummelink M and Berghmans T: SMAD4 mutation in small cell transformation of epidermal growth factor receptor mutated lung adenocarcinoma. *Oncologist* 24: 9-13, 2019.
34. Martin J, Lehmann A, Klauschen F, Hummel M, Lenze D, Grohé C, Tessmer A, Gottschalk J, Schmidt B, Pau HW, *et al*: Clinical impact of rare and compound mutations of epidermal growth factor receptor in patients with non-small-cell lung cancer. *Clin Lung Cancer* 20: 350-362, 2019.
35. Liu Y, Wu Y, Wu F and Hu C: Lung adenocarcinoma harboring triple rare EGFR exon 18 mutations rapidly developed resistance to multiple therapies. *Chemotherapy* 67: 248-252, 2022.
36. Frega S, Conte P, Fassan M, Polo V and Pasello G: A triple rare E709K and L833V/H835L EGFR mutation responsive to an irreversible Pan-HER inhibitor: A case report of lung adenocarcinoma treated with afatinib. *J Thorac Oncol* 11: e63-e64, 2016.



Copyright © 2025 Song et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.