Lung Cancer: Targets and Therapy

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CASE REPORT

Epidermal Growth Factor Receptor Kinase Domain Duplication in Lung Adenocarcinoma with Sensitive Response to Afatinib: A Case Report and Literature Review

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Abstract: Epidermal growth factor receptor kinase domain duplication (EGFR-KDD) is a rare form of EGFR mutation. Unlike the classical mutations such as exon 19 deletion and exon 21 p.L858R point mutation, EGFR-KDD is a special type of large genomic rearrangement (LGR) that results in the duplication of the tyrosine kinase domain at the protein level, leading to the formation of an intramolecular dimer and activation of the EGFR signaling pathway. Case reports and in vitro experiments have shown that EGFR-KDD patients can benefit from EGFR TKI treatment. Similar to classical EGFR mutations, EGFR-KDD inevitably develops resistance during EGFR TKI treatment, leading to disease progression. Due to the rarity of EGFR-KDD, the acquired resistance mechanisms are not yet fully understood, but known mechanisms include EGFR amplification and T790M mutation. In this study, we report a 71-year-old female EGFR-KDD patient who showed a positive response to afatinib treatment initially, but developed resistance upon tumor progression. Subsequent next-generation sequencing (NGS) on the re-biopsy revealed TP53 exon c.688_764 deletion and MET exon 15–20 duplication, suggesting that MET bypass activation might be the acquired resistance mechanisms. Additionally, we conducted a literature review on EGFR-KDD and examined case reports of EGFR-KDD patients treated with EGFR TKIs to summarize the treatment outcomes and resistance mechanisms. We hope to provide more treatment information for patients with rare gene mutations in lung cancer.

Plain Language Summary: Lung cancer is one of the most common and deadliest malignant tumors worldwide. In recent years, the development of genetic testing technology and the widespread use of targeted therapy have greatly improved the prognosis for lung cancer patients with targetable mutations. EGFR is the most common target for lung cancer and it exhibits various mutation forms. For classical EGFR mutations, the efficacy of targeted therapy is well-established. However, for rare mutation forms such as EGFR-KDD, there is a lack of randomized controlled trials to confirm the effectiveness of targeted therapy. In this study, we report a case of an EGFR-KDD patient who showed promising response to targeted therapy, and we also conduct a literature review on EGFR-KDD to provide treatment information for patients with rare mutations.

Keywords: EGFR kinase domain duplication, targeted therapy, adenocarcinoma of lung, acquired resistance, tyrosine kinase inhibitors, afatinib

Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and mortality around the world.[1] Adenocarcinoma is the most common cell type, accounting for approximately 45% of all lung cancer cases.[2] Significant advancements in targeted therapy have led to a marked improvement in the prognosis of patients with locally advanced and advanced adenocarcinoma in the past two decades.[3–6] The most common therapeutic target is the EGFR, with classical mutation

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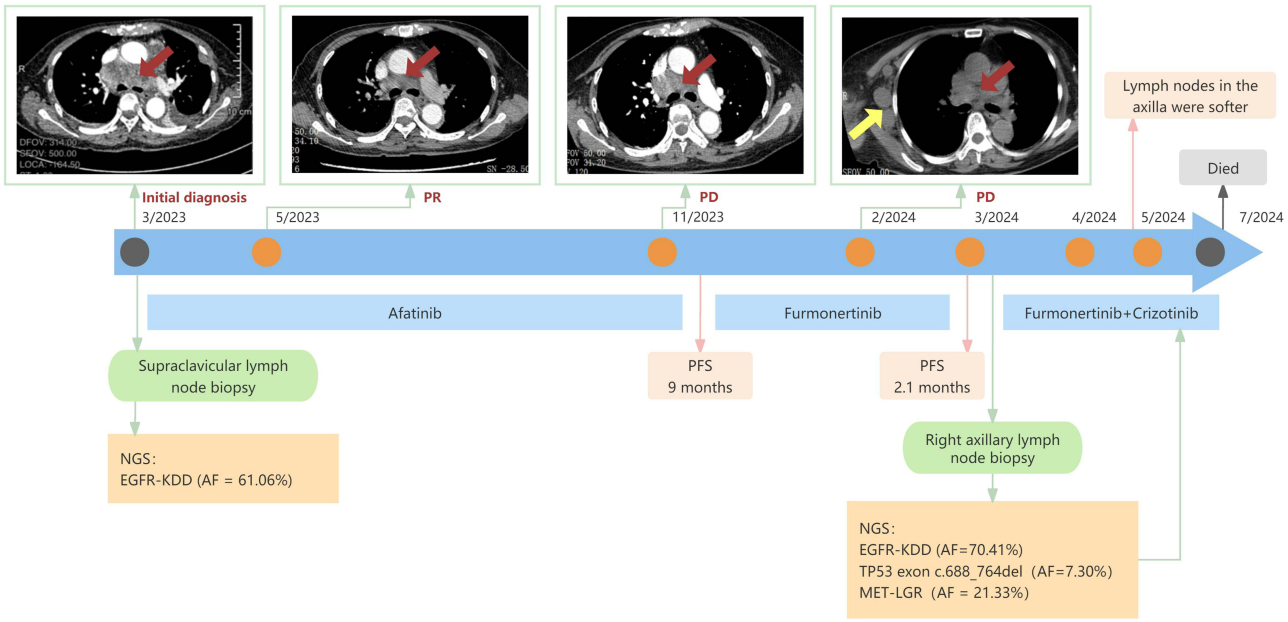
Graphical Abstract



types including exon 19 del and exon 21 p.L858R point mutation.[7] In patients harboring EGFR classical mutations, the objective response rate (ORR) to EGFR tyrosine kinase inhibitor (EGFR TKI) ranges from 56% to 83%, with a corresponding progression-free survival (PFS) of 9.2 to 18.9 months.[8] For EGFR non-classical mutations, such as G719X, L861Q, S768I, etc, EGFR TKI also show certain efficacy.[9] In addition to the EGFR gene small fragment deletions and point mutations mentioned above, there are also rare large fragment rearrangements in the EGFR gene, such as KDD. EGFR-KDD refers to a gene rearrangement involving the exon 18–25 region of the EGFR gene, functioning through the formation of asymmetric EGF-independent intramolecular and EGF-dependent intermolecular dimers and was first identified in 2015 as an oncogenic and therapeutically actionable alteration in lung cancer.[10,11] Some studies and clinical case reports suggest that EGFR TKI have certain effectiveness against EGFR-KDD, but drug resistance ultimately inevitably develops.[10–12] Due to the low mutation rate of EGFR-KDD, which is only 0.2–0.24%, the acquired resistance mechanisms to EGFR TKI in EGFR-KDD patients remain unclear.[13,14] This article reports a case of EGFR-KDD patient who showed profound response to afatinib treatment. Upon disease progression, a re-biopsy with NGS revealed TP53 exon c688_764 deletion and MET exon15-20 duplication, suggesting that these alterations may be potential acquired resistance mechanisms. Furthermore, we have reviewed all the reported case reports on EGFR-KDD and summarized the treatment efficacy and acquired resistance mechanisms of EGFR TKIs in non-small cell lung cancer (NSCLC) patients with EGFR-KDD mutations. Through our case and literature review, we believe that EGFR TKIs are an effective treatment for EGFR-KDD. Notably, we report for the first time that MET amplification may emerge as an EGFR TKI resistance mechanism in EGFR-KDD.

Case Report

A 71-year-old woman presenting with a six-month history of chest tightness, shortness of breath, and left-sided chest pain was admitted to our hospital in March 2023. Chest computed tomography (CT) scan revealed irregular masses in the left hilum, left lower lobe, and mediastinum, invading the pulmonary vessels and left main bronchus, and enlarged lymph nodes in the mediastinum and root of the neck. There were also cancer thrombi in the left atrium and superior vena cava, bone metastasis with a fracture of the right 10th rib and bilateral pleural effusion (Figure 1A and B). The neck lymph node ultrasound showed multiple enlarged lymph nodes above the clavicles on both sides. A supraclavicular lymph node

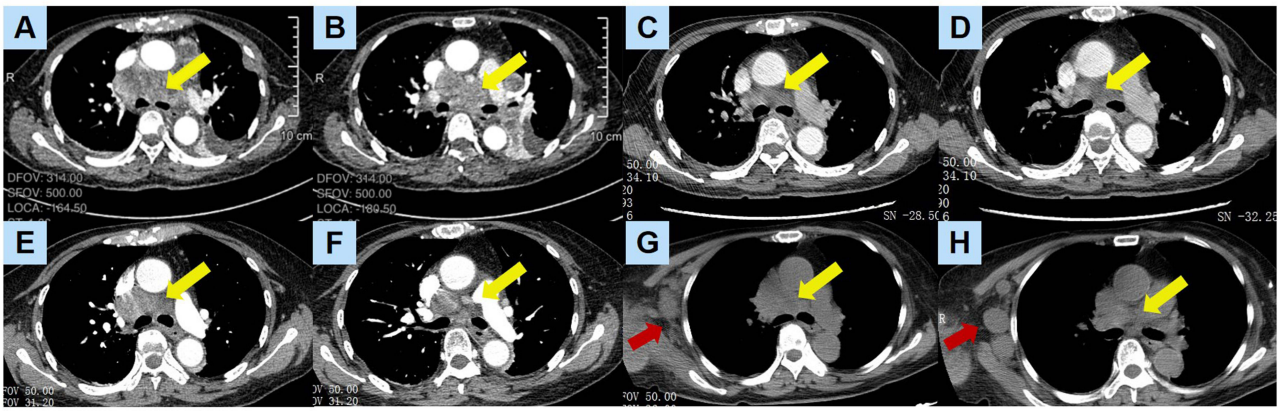


Figure 1 Chest CT scans at different time points. (**A** and **B**) baseline (3/2023), multiple enlarged mediastinal lymph nodes, with the largest measuring of 44.2*30.8mm; (**C** and **D**) after Afatinib treatment (5/2023), multiple enlarged mediastinal lymph nodes, with the largest measuring of 19.8*16.0mm; (**E** and **F**) the first time with disease progression (11/2023), multiple enlarged mediastinal lymph nodes, with the largest measuring of 37.4*25.7mm; (**G** and **H**) the second time with disease progression (2/2024), fusion of enlarged lymph nodes with maximum diameter of 48.0*27.2mm; a right axillary lymph node with maximum diameter of 25.5*19.4mm; Yellow arrows denote mediastinal lymph node lesions; red arrows indicate the axillary lymph node lesion.

biopsy was performed on March 16, and the pathology report confirmed a diagnosis of poorly differentiated adenocarcinoma. The immunohistochemical (IHC) results: TTF-1(+); CK5/6(−); P40(−); CgA(−); Syn(−); CD56 (focal weak+); Ki-67(~30%); INSM1/control(−); CK-pan (AE1/AE3)(+). PD-L1 (22C3) (positive, TPS = 90%). The stage was classified as cT4N3M1c IVB (the 8th edition of AJCC TNM classification). NGS revealed EGFR exon 18–25 duplication (allele frequency, AF = 61.06%). The patient could not tolerate chemotherapy and immunotherapy with an ECOG performance status of 4. Therefore, she was treated with afatinib (30 mg once daily), and zoledronic acid (4 mg per 4 weeks) to prevent skeletal-related events. The patient's condition gradually improved. And follow-up chest CT scan showed a significant reduction in the size of the mass compared to before (Figure 1C and D). Treatment response evaluation: Partial Response (PR).

A follow-up chest CT in November 2023 revealed the mediastinal lymph nodes had significantly increased in size compared to before (Figure 1E and F). Bronchoscopy with re-biopsy was recommended, but the patient refused. Chemotherapy combined with immunotherapy was also suggested, but the patient refused due to the adverse reactions. The patient subsequently received second-line treatment with furmonertinib 80 mg once daily (a third generation EGFR TKI developed by Shanghai Allist Pharmaceuticals, China) from December 2023.

On February 26, 2024 (after more than two months of treatment with furmonertinib), a follow-up chest CT revealed a further increase in the size of the mediastinal lymph nodes, accompanied by significant enlargement of the right axillary lymph node. (Figure 1G and H). A right axillary lymph node biopsy was performed in March 2024, and the pathology report indicated metastatic poorly differentiated carcinoma with necrosis. IHC: TTF-1(+), Napsin-A (+), CK7(+), P53(-), CK5/6(focal +), CD56(−), HER2(0, external control 3+), Ki-67(40%+). NGS: EGFR-KDD)(AF=70.41%), TP53 exon c.688_764del(AF=7.30%), MET exon15–20 duplication (AF = 21.33%). The IHC result indicated the right axillary lymph node consistent with lung metastasis. Considering the MET exon15–20 duplication, the treatment was switched to a combination therapy of 80mg of furmonertinib once daily and 250mg of crizotinib twice daily as a dual-target treatment. After one month, the patient reported an improved physical condition and a softening of the texture of the axillary lymph nodes. However, two months later, the patient succumbed to the worser condition.

Discussion

KDD, a special type of LGR, is an intragenic partial duplication that confers cancer cells with the ability to acquire new protein isoforms, resulting in tyrosine kinase activation. KDD can be observed in various driver genes, such as EGFR-KDD, MET-KDD, RET-KDD, etc, and is associated with a poor prognosis.[15] Approximately 0.097% of patients with malignant tumors in China harboring with KDD.[15] EGFR-KDD refers to a gene rearrangement that involves the exon 18–25 region of the EGFR gene, leading to a duplication of the tyrosine kinase domain encoded by exons 18–25 at the

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protein level. This duplication results in the formation of an intramolecular dimer and activates the EGFR signaling pathway.[10] EGFR-KDD is mostly observed in glioma and NSCLC.[11] In NSCLC patients, EGFR-KDD accounts for 0.2%–0.24% of all EGFR gene-related mutations.[13,14] Due to the limitations of conventional methods such as Sanger sequencing, polymerase chain reaction (PCR), and amplification refractory mutation system (ARMS) in detecting EGFR-KDD, there is a possibility of underestimating the frequency of EGFR-KDD. Since the widespread clinical application of NGS, there have been continuous detections of EGFR-KDD. Notably, NGS analysis confirmed an EGFR KDD patient who had been diagnosed in 1995. There was no EGFR mutation detected by PCR, but the patient greatly benefited from EGFR TKI treatment, achieving a PFS of over 10 years.[16]

Due to the lack of current evidence to support the efficacy of EGFR TKI in EGFR-KDD patients, and NCCN guidelines recommend against the use of EGFR TKI in patients who do not have classical mutations such as EGFR 19del, 21L858R, or other non-classical mutations like S768I, G719X, L861Q.[17] Therefore, currently, for advanced lung cancer patients with EGFR-KDD, treatment should follow the principles of treating advanced NSCLC without targetable mutations. The first consideration should be the use of immune checkpoint inhibitors (ICIs) or combination therapy with chemotherapy.[17] However, several reported cases of EGFR-KDD have shown poor response to chemotherapy and ICIs, while EGFR TKI treatment has demonstrated better efficacy.[10,18] In in vitro studies, afatinib has been proven to have the ability to inhibit EGFR-KDD activity by blocking intramolecular dimerization.[11] To explore whether EGFR TKIs could be an effective treatment method for EGFR-KDD, Gallant et al conducted an in vitro experiment where erlotinib, afatinib, and osimertinib were separately used to treat EGFR-KDD cells.[10] All three EGFR TKIs were able to inhibit EGFR-KDD tyrosine phosphorylation in a dose-dependent manner, albeit to different levels. Among them, afatinib exhibited the best inhibitory effect on the proliferation of EGFR-KDD cells. Subsequently, another vitro study conducted by Lee once again confirmed that afatinib and dacomitinib exhibited the best inhibitory effect on the activity of EGFR-KDD cells.[12]

Additionally, the efficacy of afatinib in treating EGFR-KDD has been validated in some case reports.[10,19–21] There are also individual case reports suggesting that other EGFR TKIs, such as gefitinib, erlotinib, and osimertinib, have shown certain therapeutic effects in patients with EGFR-KDD (Table 1).[14,16,18,22,23] The patient in this study had a poor general condition at the time of being diagnosed with lung adenocarcinoma, with an ECOG performance status score of 4, indicating an inability to tolerate immunotherapy and chemotherapy. Based on the aforementioned in vitro experiments and successful case reports of treatment with EGFR TKIs, afatinib was administered as the first-line treatment for this patient. After the treatment with afatinib, the tumor significantly shrank, and the PFS was 9 months.

Similar to EGFR classical mutations, EGFR-KDD patients also develop disease progression after a median of 2 to 72 months on EGFR TKI.[10,18,22] In-depth research about acquired resistance mechanisms of EGFR classical mutations is currently underway. In addition to the most common T790M mutation, MET amplification is considered the most frequent bypass activation mechanism leading to TKI resistance.[32] Amplification of MET, which is a transmembrane receptor tyrosine kinase that activates several pathway including the PI3K/AKT, RAS/RAF/MEK/ERK, and STAT3.[33] The potential mechanism by which MET amplification leads to resistance to EGFR TKI inhibition may be related to the phosphorylation of ErbB3 (HER3).[32,34] HER3, a key activator of the PI3K/AKT and MEK/MAPK pathways, provides bypass signaling activation in the presence of EGFR TKI.[32,34] Several clinical studies have demonstrated that the combination of MET inhibitor with EGFR TKI can overcome resistance mediated by MET amplification.[35,36] Due to the rarity of EGFR-KDD, which has only been observed in a limited number of published cases, the acquired resistance mechanisms remain unclear.

We reviewed the relevant literature and summarized that among the 23 EGFR-KDD patients mentioned above, there were 12 patients underwent re-biopsy and gene testing after disease progression on EGFR TKI treatment. Among them, 6 cases showed EGFR amplification, 3 cases showed T790M mutation, and each of the following mutations was observed in 1 case: CTNNB1 p.S37C, PIK3R1 Y463F, MAP2K4 S12 fs, RELN p.G1774E, TP53 R65fs*58, FGFR4 R248Q, ATRX R498G, VEGFA S186F, FANCD truncation, ERBIN p.P814S, MAP3K4 p.A207G, and CYP2A6 p.P468L (Table 1). In this case report, the patient underwent a re-biopsy after disease progression on EGFR TKI treatment, and NGS test revealed the presence of TP53 exon c688_764del and MET exon15-20 duplication. By combining the common signaling pathways that the EGFR and the MET receptor both activate, which were mentioned above, it is speculated that MET bypass activation may be an acquired resistance mechanism.

Table 1 Clinical Characteristics and Outcomes of Patients with NSCLC EGFR-KDD Mutation Treating with EGFR TKI in Previous Studies

No.	Publication	Year of Publication	Age (Year)	Gender/ Ethnicity	Stage	Concurrent Mutation	EGFR TKI Treatment	Response to TKI	PFS	NGS Results After TKI Resistance
1	Gallant et al[10]	2015	33	Male/ American	IV	None	Afatinib	PR	10 mo.	EGFR amp.
2	Baik et al[16]	2015	45	Female/ American	NA	None	Gefitinib→ Erlotinib	PR PR	6 yr. 5 yr.	EGFR p.T790M CTNNB1 p.S37C
3	Wiest et al[24]	2016	72	NA/ Germany	NA	None	Afatinib	PR	NA	NA
4	Zhu et al[25]	2018	63	Female/ Chinese	IV	NA	Icotinib	SD	11 mo. NR	NA
5	Wang et al[14]	2019	1# 61 2# 63 3# 60 4# 67 5# 43	1# male/ Chinese 2# male/ Chinese 3# female/ Chinese 4# male/ Chinese 5# female/ Chinese	1# IV 2# IV 3# IV 4# IV 5# IV	1# TP53 R280G 2# ERBB2 amp. 3# NA 4# TP53 Y220C, PIK3CA E81G 5# NA	1# Erlotinib→ Osimertinib 2# Gefitinib→ Afatinib→ Osimertinib 3# Gefitinib 4# Icotinib+patinib 5# Gefitinib→ Erlotinib	1#PD PD 2#PR PD PR 3#SD 4#PR 5#PD PD	1# 2 mo. 2 mo. 2# 5 mo. 2 mo. 4 mo. NR 3# 11 mo. 4# 4 mo. NR 5# 3 mo. 5 mo.	1#EGFR amp., PIK3R1 Y463F 2# NA 3#EGFR T790M, EGFR amp. 4# NA 5#EGFR amp., MAP2K4 S12 fs
6	Wang et al[19]	2019	74	Female/ Chinese	IIB	None	Afatinib	PR	6 mo.NR	NA
7	Chen et al[20]	2020	59	Male/ Chinese	IV	TP53 p.R282W, CTNNB1 p.S37Y	Afatinib	SD	10 mo. NR	NA
8	Li et al[18]	2020	45	Male/ NA	IIIA	EGFR amp., TP53 p.Y220C, RB1 single copy loss	Icotinib→ Osimertinib	PR PR	4 mo. 21 mo.	EGFR amp., TP53 p.Y220C, RELN p.G1774E
9	Yang et al[26]	2020	39	Female/ NA	IV	TP53 E285K	No TKI treatment	N/A	N/A	NA

(*Continued*)

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Table 1 (Continued).

No.	Publication	Year of Publication	Age (Year)	Gender/ Ethnicity	Stage	Concurrent Mutation	EGFR TKI Treatment	Response to TKI	PFS	NGS Results After TKI Resistance
10	Kim et al[27]	2020	40+	Male/ NA	IV	None	Osimertinib	PR	5 mo. NR	NA
11	Zhao et al[21]	2021	61	Male/ Chinese	IIIB	None	Afatinib	PR	12 mo. NR	NA
12	Hirokawa et al[22]	2021	45	Female/ Japanese	NA	EGFR amp.	Erlotinib→ Osimertinib→ Afatinib	PR PR PD	133 day 14.5 mo. 1 mo.	EGFR amp., TP53 R65fs*58, FGFR4 R248Q, ATRX R498G, VEGFA S186F
13	Zhang et al[23]	2021	1#44 2#61	1# male/ Chinese 2# female/ Chinese	1# IVA 2# IVB	1# CDK6 amp., TP53 2# PTEN exon 8 point mutations	1# Afatinib→ Osimertinib 2# Icotinib	1# PR SD 2# PR	1# 7 mo. 20.5 mo. 2# 8 mo.	1# EGFR amp., CDK6 amp., TP53 2# NA
14	Qian et al[28]	2021	66	NA/ Chinese	NA	None	Afatinib	SD	9 mo. NR	NA
15	Kim et al[29]	2022	50	Male/ African-American	IV	None	Osimertinib→ Afatinib	PR NR	2 mo. NR	FANCD truncation EGFR amp.
16	Lee et al[12]	2022	56	Male/ NA	IV	None	Erlotinib→ Osimertinib	PR PR	8 mo. 7 mo.	EGFR T790 M
17	Shi et al[30]	2022	63	Female/ Chinese	IVA	EGFR amp.	Bevacizumab +Icotinib→ Almonertinib	PR PR	11 mo. 3 mo.	ERBIN p.P814S MAP3K4 p.A207G CYP2A6 p.P468L
18	Lin et al[31]	2024	66	Male/ Chinese	IVB	TP53 D281F indel	Furmonertinib	PR	16 mo.	NA
19	Our Case	2025	71	Female/ Chinese	IVB	None	Afatinib→ furmonertinib→ furmonertinib +Crizotinib	PR PD PD	9 mo. 2 mo. 2 mo.	TP53 exon c688_764del MET-LGR

Note: #A report with multiple patients.
Abbreviations: No., number; NA, not available; SD, stable disease; PR, partial response; NR, not reach; PD, progressive disease; mo., month; yr., year; amp., amplification.

According to a retrospective study on different types of tumors patients with KDD mutation in China, enrichment of immune-related pathways, especially the cytokine receptors pathway, was found in more than 90% of the KDD carriers.[15] The tumor cells are known to secrete cytokines that can both in autocrine fashion generate a forward-feedback loop to stimulate self-proliferation, expansion, and drug resistance, and in paracrine fashion induce recruitment, activation, and differentiation of other cells in the TME, such as IL-6, IL-8 and even VEGF.[15,37,38] Moreover, a study has shown that after EGFR TKI treatment, the tumor immune microenvironment in NSCLC patients undergoes remodeling, with upregulation of PDCD1 (the gene encoding PD-1 protein) and other inhibitory-checkpoint genes.[39] The above studies all suggest that immunotherapy may be effective for patients who develop TKI resistance. However, there is only one reported case where a KDD patient achieved PR with PFS of 7 months when treated with Nivolumab after osimertinib resistance.[18]

Through our case and literature review, we believe that EGFR TKIs are an effective treatment for EGFR-KDD, although this finding needs to be confirmed by randomized clinical trials. Taking into account in vitro research results, it appears that second-generation EGFR TKIs, such as afatinib, may have the most favorable treatment outcomes. The reported mechanisms of acquired resistance to EGFR TKIs in EGFR-KDD patients include EGFR amplification, T790M mutation, etc. In this study, the patient developed TP53 exon c688_764del and MET exon15-20 duplication after EGFR TKI treatment, suggesting that MET gene mutations may be one of the resistance mechanisms in EGFR-KDD after developing resistance to EGFR TKIs.

However, the occurrence time of these mutations remained unclear. After first-line treatment with afatinib, the patient's physical condition improved (ECOG grade: 1). Due to the fear of disease progression and discomfort associated with re-biopsy, re-biopsy via bronchoscopy was declined. Considering the adverse affects of chemotherapy, the patient also declined this option. Combining with the rapid progression of the disease under the second-line treatment (furmonertinib), it is highly plausible that these resistance mutations had already emerged during the first progression event. Because of the rejection of re-biopsy, we obtained the resistance mutations only after the second disease progression. This delay potentially affected subsequent treatment and altered the clinical outcomes. Consequently, early re-biopsy or non-invasive molecular profiling (eg, cfDNA-based NGS) at initial progression is recommended for patients with disease progression, especially in rare mutations like EGFR-KDD where resistance patterns remain poorly understood and therapeutic windows narrow quickly. This approach might have revealed these actionable mutations earlier and allowed for timely initiation of combination therapy (eg, MET inhibitior).

We aim to provide more treatment information for EGFR-KDD patients through our case study and literature review. Additionally, for lung cancer patients, we recommend utilizing NGS method for gene mutation testing to maximize the positive detection rate of therapeutic mutations, thereby increasing the opportunities for targeted therapy and improving patient prognosis.

Some limitations are associated with our research. Due to the nature of our study, only single cases were included, resulting in a lack of functional verification at the molecular level. In-depth research should be conducted to verify the role of MET, through approaches such as in vitro studies or multicenter cohort studies.

Conclusion

In this study, the EGFR-KDD patient treated with afatinib showed tumor shrinkage and achieved a 9-month PFS. Combined with previous case reports and in vitro experiments, EGFR TKIs can be considered as one of the treatment options for EGFR-KDD patients, with afatinib potentially offering the best therapeutic efficacy. Similar to classical EGFR mutations, EGFR-KDD patients inevitably develop resistance during EGFR TKI treatment, with the most common acquired resistance mechanisms being EGFR amplification and T790M mutation. The resistance mechanisms of the patients in this study may involve MET bypass activation.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient's son for publication of this case report and any accompanying images. Institutional approval was not required by the Ethics Committee of The Second Affiliated Hospital of Zhejiang Chinese Medical University to publish the case details.

Consent for Publication

Written consent was obtained for publication of de-identified medical information.

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We sincerely appreciate the patient's son for granting consent to publish the patient's information.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflict of interest.

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