Individualized management strategies for advanced non-small cell lung cancer with *EGFR* exon 19 deletion and L861Q compound mutations based on circulating tumor DNA monitoring: A case report

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Abstract. Epidermal growth factor receptor (EGFR) mutations are major oncogenic drivers in non-small cell lung cancer (NSCLC). These alterations, particularly prevalent in lung adenocarcinoma among the Chinese population, include the exon 19 deletion (19del), L858R point mutation and the less frequent L861Q variant. However, to the best of our knowledge, no standardized treatment regimen exists for patients harboring both common and rare EGFR mutations. The current study presents a case of advanced metastatic lung adenocarcinoma with concurrent EGFR 19del and L861Q mutations, managed with tyrosine kinase inhibitors targeting EGFR and dynamic plasma circulating tumor DNA (ctDNA) monitoring. The patient achieved a progression-free survival time of 11 months. Serial plasma ctDNA monitoring detected molecular progression, characterized by an increase in total ctDNA and a rising *EGFR* C797S allele fraction, prior to radiographic changes. The present case emphasized the importance of individualized management and the key role of ctDNA in real-time treatment monitoring, offering a potentially novel approach for precise disease evaluation in the future. Further research and the development of novel therapies are warranted to potentially improve outcomes in patients with advanced *EGFR*-mutated NSCLC.

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Abbreviations: ADC, antibody-drug conjugate; CSCO, Chinese Society of Clinical Oncology; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; MRD, minimal residual disease; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TROP2, tumor-associated calcium signal transducer 2; TTF-1, thyroid transcription factor-1; VUS, variant of unknown significance; 19del, exon 19 deletion

Key words: EGFR mutation, NSCLC, ctDNA, almonertinib, ADC

Introduction

Epidermal growth factor receptor (*EGFR*) mutations are major oncogenic drivers in non-small cell lung cancer (NSCLC). In the Chinese NSCLC population, ~28.2% of patients harbor *EGFR* mutations, with their prevalence in lung adenocarcinoma exceeding 50% (1). The most common *EGFR* mutations, exon 19 deletion (19del) and the L858R point mutation, account for ~85% of cases, while the remaining 15% are rare, highly heterogeneous mutations occurring at low frequencies (2). Rare mutations frequently respond poorly to standard targeted therapies, and evidence guiding treatment for patients with concurrent common and rare *EGFR* mutations remains limited, posing notable clinical challenges.

Among the rare *EGFR* mutations, the L861Q mutation accounts for 1-2% of cases (2). The L861Q mutation is typically resistant to first-generation EGFR tyrosine kinase inhibitors (TKIs) but demonstrates sensitivity to second- and third-generation TKIs (3,4). Epidemiologically, *EGFR* mutations are detected in 30-50% of Asian patients with NSCLC, compared with 10-20% in Western populations (5,6). While most *EGFR* alterations are classical sensitizing mutations

(19del and L858R, 80-90% of cases), uncommon mutations such as L861Q, G719X and S768I comprise 10-15%, presenting unique therapeutic challenges due to variable drug sensitivity (7,8). Compound *EGFR* mutations, defined as the coexistence of two or more alterations within the same tumor, are rare. Among these, the coexistence of 19del with L861Q is notably uncommon, and its clinical significance and optimal management strategies remain poorly defined, to the best of our knowledge (9).

Almonertinib, a third-generation EGFR TKI, has demonstrated promising efficacy, achieving a progression-free survival (PFS) time of up to 19.3 months as first-line therapy in advanced *EGFR*-mutant NSCLC (10). Several novel agents have emerged for subsequent-line treatment, including antibody-drug conjugates (ADCs), which combine monoclonal antibodies with cytotoxic agents and have garnered considerable attention. In the OptiTROP-Lung03 study, the tumor-associated calcium signal transducer 2 (TROP2)-targeted ADC, sacituzumab tirumotecan, demonstrated notable efficacy in patients resistant to EGFR TKIs, achieving a median PFS time of 11.5 months (11). Despite these advances, no standardized treatment exists for advanced NSCLC harboring both common and rare *EGFR* mutations, leaving clinicians without clear guidance.

According to the latest National Comprehensive Cancer Network (NCCN) and Chinese Society of Clinical Oncology (CSCO) guidelines (12,13), targeted therapy remains the recommended first-line approach for *EGFR*-mutant NSCLC. However, to the best of our knowledge, evidence for rare compound mutations, such as 19del + L861Q, is limited. Furthermore, tissue samples for mutation analysis are often insufficient in advanced or metastatic disease (14). Plasma circulating tumor DNA (ctDNA) has emerged as a non-invasive alternative for molecular profiling, providing real-time insights into tumor mutation status (15). Dynamic ctDNA monitoring is increasingly recognized as a valuable tool in evaluating treatment efficacy and guiding therapy adjustments.

The present case report presents the treatment and ctDNA-guided management of a patient with advanced metastatic lung adenocarcinoma harboring both *EGFR* 19del and L861Q mutations. It highlights the integration of ctDNA monitoring with conventional diagnostic tools, including imaging to inform individualized therapeutic strategies for complex *EGFR*-mutant NSCLC.

Case report

A 63-year-old Chinese man, with no smoking history, was admitted to Ruijin Hospital, Shanghai Jiao Tong University School of Medicinel (Shanghai, China), in June 2023 after a routine health examination detected a pulmonary lesion in the right lung. PET-CT revealed suspected metastases in the mediastinal and bilateral supraclavicular lymph nodes, right cardiophrenic angle lymph nodes, pleura, bones and pancreatic head. Lung biopsy confirmed adenocarcinoma (Fig. 1A). Immunohistochemical analysis demonstrated positive thyroid transcription factor-1 (TTF-1) expression (Fig. 1B), using a standard HRP/DAB method as described in Appendix S1. The patient was staged as cT4N3M1c (stage IVb) according to the 8th edition of the TNM classification for lung cancer (16). As recorded in the medical records, initial tissue analysis identified an *EGFR* exon 21 L861Q mutation using an amplification refractory mutation system PCR assay (AmoyDX) and programmed death-ligand 1 tumor proportion score <1% assessed by immunohistochemistry (IHC) using the 22C3 pharmDx kit (Agilent Technologies, Inc.), performed according to the manufacturers' instructions. Repeat tissue-based next-generation sequencing (NGS) was not performed due to the invasive nature of re-biopsy. In line with the NCCN and CSCO NSCLC guidelines (12,13), plasma-based NGS using ultra-deep sequencing of a 2,365-gene panel was performed at Nanjing Geneseeq Technology Inc. for ctDNA testing. Detailed procedures for cell-free DNA extraction, library preparation, sequencing and bioinformatics analysis are provided in Appendix S1. The analysis identified *EGFR* 19del and L861Q as driver mutations (Table I). Variant allele frequency (VAF) analysis indicated L861Q (30.53%) as the dominant clone compared with exon 19del (0.45%).

Following multidisciplinary team (MDT) consultation, the patient initiated first-line almonertinib (165 mg, orally administered once daily) in July 2023 (Fig. 2A). Bone metastases were managed concurrently with denosumab (120 mg subcutaneously monthly). This approach aligned with guideline recommendations from the NCCN and CSCO (12,13), supporting the use of third-generation EGFR TKIs, even for rare compound mutations. Serial plasma ctDNA monitoring facilitated dynamic assessment of clonal evolution and guided subsequent therapy adjustments, highlighting the complementary role of liquid biopsy alongside conventional imaging and tumor markers (17).

Subsequently, 1 month later, follow-up lung CT revealed notable right pleural effusion (Fig. 2B). Pleural fluid drainage alleviated symptoms and cytology confirmed malignancy (H&E staining and TTF-1 IHC; Fig. 1C and D). Detailed staining procedures are described in Appendix S1. The ctDNA equivalent, expressed as haploid genome equivalents (hGE)/ml, quantitatively reflects ctDNA levels and serves as a surrogate marker of tumor burden (18). Reassessment of plasma ctDNA indicated a notable decline from 269.5 to 38.7 hGE/ml (Fig. 3). Based on clinical improvement and early molecular response, consistent with evidence that rapid ctDNA decline is associated with treatment efficacy (19,20), the MDT recommended continuation of almonertinib.

In November 2023, imaging demonstrated a partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (21) (Fig. 2B). In March 2024, ctDNA remained low (28.9 hGE/ml; Fig. 3); however, a low-abundance *EGFR* C797S mutation was detected by ctDNA testing, with a VAF of 0.09% (Table I). An *EGFR* C797S mutation is a known resistance mechanism to third-generation TKIs (22,23); therefore, serial ctDNA surveillance was implemented to monitor early progression.

In June 2024, ctDNA increased markedly to 70.4 hGE/ml (Fig. 3), with the *EGFR* C797S allele fraction increasing to 0.30% (Table I), suggesting molecular progression despite stable imaging. The patient achieved a PFS of 11 months on almonertinib (Fig. 2A). Subsequently, therapy was switched to osimertinib (80 mg, administered orally once daily) as an individualized bridging strategy, despite lateral third-generation TKI switching not being the standard guideline

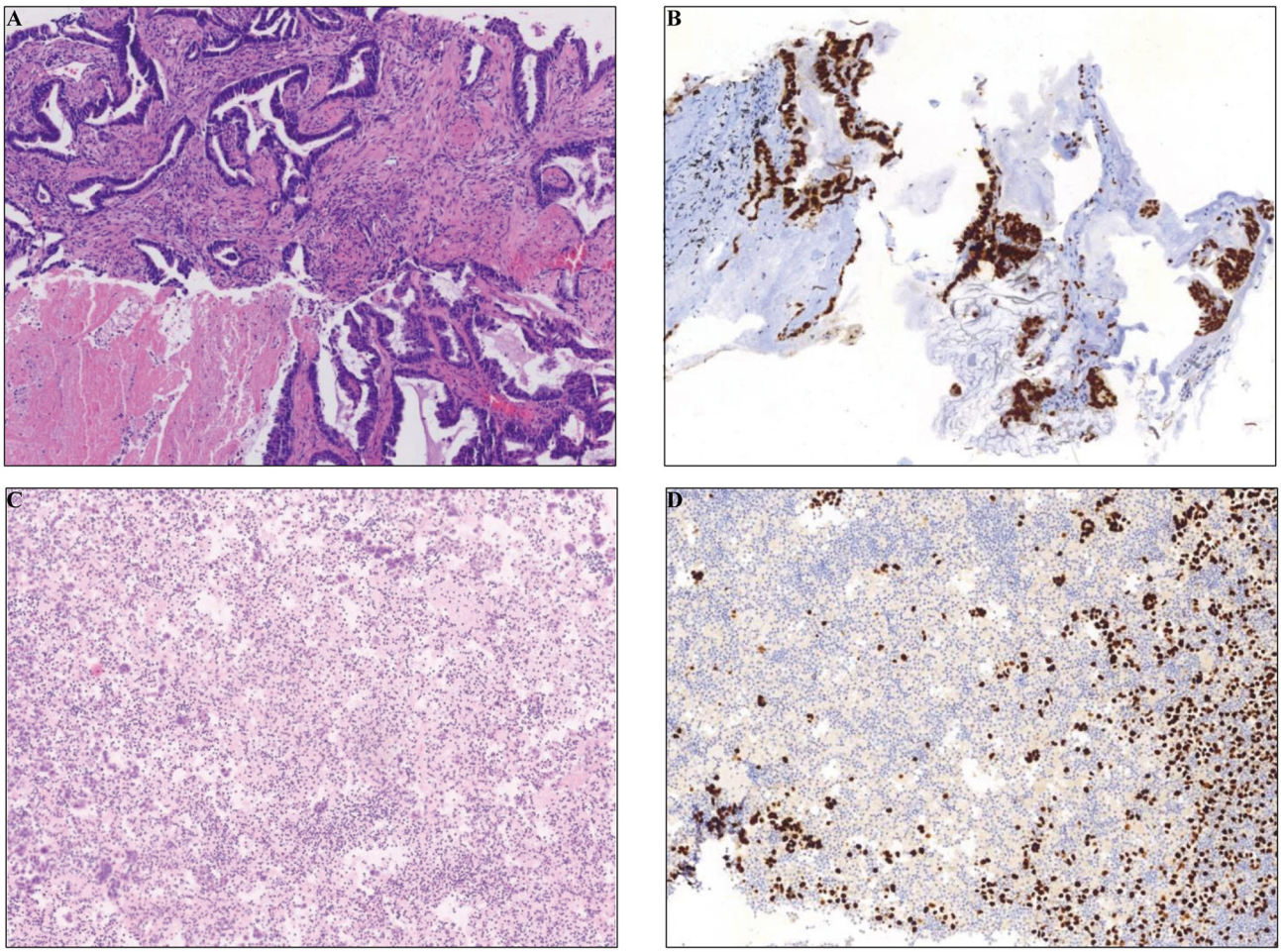

Figure 1. Histopathological and immunohistochemical evaluation of tumor tissue and pleural effusion cells. (A) H&E staining of tumor tissue from the left lung (x40 magnification). (B) TTF-1 staining of tumor tissue from the left lung (x40 magnification). (C) H&E staining of pleural effusion sediment cells (x40 magnification). (D) TTF-1 staining of pleural effusion sediment cells (x40 magnification). TTF-1, thyroid transcription factor-1.

practice (12,13). In addition, in August 2024, ctDNA decreased from 1,874.5 hGE/ml to 192.3 hGE/ml (Fig. 3), but levels did not continue to decline.

By September 2024, imaging revealed stable pulmonary lesions (Fig. 2B) but progression in bone lesions (pelvis, spine and femur) (Fig. S1A). Therefore, in September 2024, the treatment regimen was modified to furmonertinib (80 mg, administered orally once daily) combined with pemetrexed (800 mg) and carboplatin (450 mg), both administered intravenously every 3 weeks (PC regimen), the standard of care following EGFR-TKI resistance (13). ctDNA declined from 380.7 to 120.2 hGE/ml; however, the patient discontinued chemotherapy after 1 month due to intolerance. Following a third MDT consultation, due to the chemotherapy intolerance of the patient, disease progression, and the strong preference of the patient and their family to avoid further cytotoxic therapy, treatment with the TROP2-targeted ADC sacituzumab tirumotecan (300 mg, administered intravenously every 2 weeks) was initiated in November 2024. Although the drug was not yet approved at the time of administration, it subsequently received approval on March 10, 2025, by the National Medical Products Administration for adults with locally advanced or metastatic *EGFR*-mutated NSCLC who had progressed after EGFR-TKI and platinum-based chemotherapy (24), which further supports its use as an individualized option in the present case. Subsequently, in December 2024, ctDNA decreased to 33.6 hGE/ml, indicating an early molecular response.

In February 2025, plasma ctDNA monitoring detected a slight ctDNA increase, and imaging indicated pulmonary lesion shrinkage (Fig. 2B), whereas earlier imaging in January 2025 revealed notable intracranial progression (Fig. S1B). Central nervous system-directed therapy was considered, in line with European Association of Neuro-Oncology-European Society for Medical Oncology and NCCN recommendations (12,25). During plasma ctDNA monitoring, *TP53* and *RB1* mutations were identified, both of which have been reported to be associated with unfavorable prognosis in lung cancer (26). Follow-up was conducted approximately monthly during hospital visits for blood sampling, with the last follow-up in February 2025. All mutations detected using plasma ctDNA monitoring are summarized in Table SI.

Discussion

The present case highlighted the clinical complexity of managing advanced NSCLC with a compound *EGFR* mutation (19del + L861Q), a rare scenario with limited treatment

Table I. Longitudinal monitoring of variant allele frequencies of key genes in serial plasma ctDNA samples.

		Serial monitoring timepoints											
Gene	Variant	2023.07	2023.08	2024.03	2024.04	2024.05	2024.06	2024.07	2024.08	2024.09	2024.10	2024.11	2024.12	2025.02
EGFR	p.L861Q	30.53	0.39	1.11	2.85	6.93	1.11	0.69	15.62	1.69	3.96	4.59	0.29	0.00	0.00
EGFR	p.E746_A750 del (19del)	0.45	0.00	0.34	1.37	0.93	2.30	29.81	1.33	9.53	15.32	6.34	1.97	1.66	1.83
EGFR	p.C797S[a]	0.00	0.00	0.09	0.08	0.07	0.30	0.34	0.25	0.68	1.01	0.80	0.28	0.83	0.12
PIK3CA	p.R88Q	0.00	0.00	0.00	0.00	0.00	1.27	17.08	0.71	4.74	11.89	2.95	0.99	0.09	1.07
TP53	p.R337L	0.39	0.00	0.11	0.42	0.37	1.13	23.39	0.93	5.97	13.88	3.79	1.00	0.78	1.05
TP53	p.S241C	2.31	0.05	0.00	0.07	0.25	0.09	0.00	0.21	0.13	0.32	0.30	0.00	0.00	0.00
RB1	c.1498+2T>C	2.19	0.00	0.00	0.00	0.42	0.00	0.00	0.00	0.00	0.16	0.35	0.00	0.00	0.00

[a]Resistance mutation. ctDNA, circulating tumor DNA; *EGFR*, epidermal growth factor receptor; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α.

evidence. Co-occurring *RB1* and *TP53* mutations may partly explain the shorter PFS of 11 months observed in this case, compared with the median PFS of 19.3 months reported for almonertinib in the AENEAS trial (10). This observation is consistent with prior reports showing that baseline concurrent *TP53*/*RB1* alterations are associated with inferior PFS and an increased risk of histologic transformation on first-line third-generation EGFR TKIs (26,27). In terms of prevalence, *EGFR* L861Q occurs in 1-2% of patients with *EGFR*$^+$ NSCLC, while compound *EGFR* mutations account for 3-14% of *EGFR*$^+$ cases (28). To the best of our knowledge, Zhao *et al* (9) reported the largest cohort of *EGFR* compound mutations to date, including 1,025 patients, in which compound variants comprised 12.7% of *EGFR*-mutated NSCLC. Within this cohort, the 19del + L861Q combination was categorized as a 'common + rare' subtype and occurred less frequently compared with L858R combined with uncommon variants. By contrast, common mutations such as 19del or L858R alone represent 85-90% of *EGFR*-mutated NSCLC (28). Clinically, patients with rare or compound *EGFR* mutations typically exhibit reduced sensitivity to first-generation TKIs and a shorter PFS compared with patients with common mutations (9). Second- and third-generation TKIs may still offer benefit in certain patients (28), as illustrated in the present case in which almonertinib achieved an 11-month PFS with manageable toxicity and sustained disease control. However, to the best of our knowledge, clinical data on metastatic patterns and other features of 19del + L861Q subtype remain limited due to its rarity. The present case report adds to current evidence by documenting longitudinal clinical outcomes and molecular monitoring in a patient with this uncommon compound mutation. Although clinical evidence for ctDNA-guided therapy in compound *EGFR* mutations is limited, emerging evidence supports the utility of serial plasma ctDNA monitoring to inform dynamic treatment decisions in such rare cases (29).

In NSCLC tumors harboring compound *EGFR* mutations, variants of unknown significance (VUSs) within the kinase domain of EGFR may occur more frequently (9). The kinase domain, which mediates the tyrosine kinase activity of EGFR, is the primary binding site for TKIs. VUSs are genetic alterations whose functional or clinical relevance has not yet been clearly established. When multiple mutations coexist, certain VUSs may alter the three-dimensional structure of the kinase domain, particularly the regions targeted by TKIs. Such structural changes can reduce TKI binding efficiency, potentially decreasing drug efficacy or promoting resistance (9). Therefore, compound mutations are not simply the sum of two or more known driver mutations; they may also involve additional, previously uncharacterized variants that influence drug binding and treatment response. This complexity underscores the need for individualized monitoring and adaptive treatment strategies, such as serial ctDNA analysis.

In the present case, early ctDNA dynamics provided actionable insights. The detection of low-abundance *EGFR* C797S mutation in March 2024 prompted increased surveillance and therapy adjustments. Subsequent ADC therapy with sacituzumab tirumotecan induced a rapid molecular response despite prior TKI and chemotherapy exposure. The rationale for using an ADC in this context lies in its ability to circumvent conventional TKI resistance by delivering cytotoxic agents

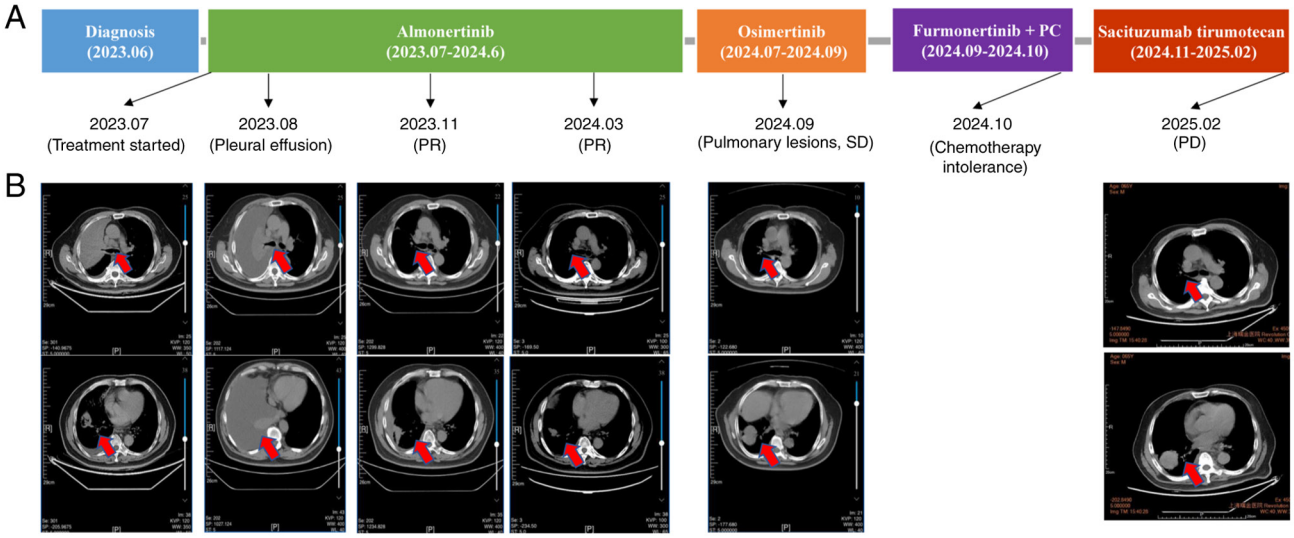

Figure 2. Treatment timeline and corresponding radiographic assessments at key monitoring points. (A) Timeline of systemic treatments, including almonertinib, osimertinib, furmonertinib combined with PC and sacituzumab tirumotecan. (B) Representative axial CT images captured at each monitoring point. The top row displays lesions located in the upper lobe of the right lung and the bottom row displays lesions in the lower lobe of the right lung. Red arrows indicate tumor sites. PC, pemetrexed plus carboplatin; PR, partial response; PD, progressive disease; SD, stable disease.

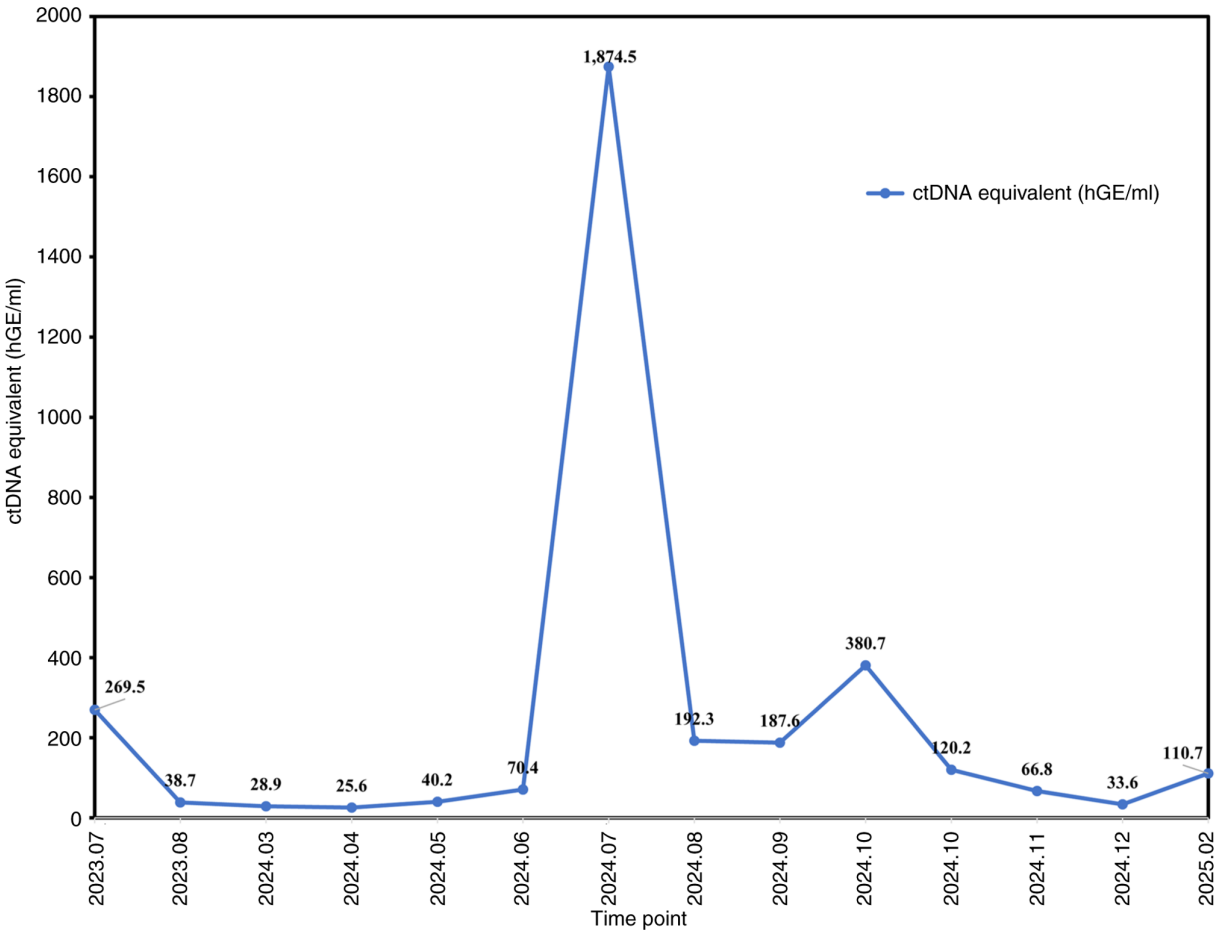

Figure 3. Dynamic monitoring of ctDNA and tumor markers. ctDNA equivalent is expressed as hGE/ml, representing the quantitative amount of tumor-derived ctDNA in plasma and serving as a surrogate for tumor burden. ctDNA, circulating tumor DNA; hGE, haploid genome equivalents.

directly to tumor cells, independent of *EGFR* mutation status. Beyond sacituzumab tirumotecan, other ADCs, such as patritumab deruxtecan (HER3-DXd) and datopotamab deruxtecan (Dato-DXd, a TROP2-directed ADC), are under investigation for *EGFR*-mutant NSCLC post-TKI resistance. Ongoing trials, including TROPION-Lung14 (ClinicalTrials.gov identifier:

NCT06350097), TROPION-Lung15 (ClinicalTrials.gov identifier: NCT06417814) and HERTHENA-Lung02 (30) aim to further evaluate their safety and efficacy.

Several previous studies have demonstrated the clinical utility of ctDNA in advanced NSCLC. In the AURA trial, plasma detection of T790M predicted outcomes with osimertinib similar to tissue-based analysis (31). Similarly, the SWOG S1403 study reported that early clearance of mutant EGFR ctDNA in plasma markedly predicted PFS and overall survival, outperforming RECIST in anticipating long-term benefit (32). Another previous study confirmed that decreasing ctDNA levels during EGFR TKI therapy are associated with longer survival (33). In addition to its applications in advanced disease, ctDNA has also demonstrated value in assessing minimal residual disease (MRD) in early-stage NSCLC. The TRACERx study demonstrated that ctDNA detected relapse earlier compared with imaging (34) and subsequent trials validated that MRD positivity predicts recurrence risk (35,36). Collectively, these findings highlighted the broad clinical utility of ctDNA, from monitoring treatment response in advanced NSCLC to guiding risk stratification in curative settings. The present case further illustrated the potential of serial ctDNA surveillance to inform clinical decisions, emphasizing its value as a non-invasive biomarker to guide individualized therapy for rare compound *EGFR* mutations. Combining ctDNA with imaging and tumor markers may improve assessment in complex scenarios such as pseudo-progression or discordant radiographic findings (37). As a single-patient report, the present case findings require validation in larger cohorts to establish the potential effectiveness of ctDNA-guided therapy in compound *EGFR*-mutated NSCLC in the future.

In conclusion, the present case highlighted the challenges of managing advanced NSCLC with rare *EGFR* compound mutations. Dynamic plasma ctDNA monitoring complemented conventional diagnostics, enabling real-time assessment of tumor evolution and therapy response. Personalized therapy guided by ctDNA, imaging and tumor markers facilitated timely therapy adjustments, including ADC introduction after TKI and chemotherapy resistance. With ongoing research and emerging treatments, integrating ctDNA into routine clinical practice may potentially improve outcomes for patients with complex *EGFR*-mutant NSCLC in the future.

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Availability of data and materials

The sequencing data generated in the present study are deposited in the Genome Sequence Archive for Human (GSA-Human) under accession number HRA013443 or at the following URL: https://ngdc.cncb.ac.cn/gsa-human/s/0ee9t310. The other data generated in the present study may be requested from the corresponding author.

Authors' contributions

JZ conceived and designed the present case report, and supervised the study. XBZ, YS and XC collected clinical data and performed patient follow-ups. CL contributed to data interpretation and critically revised the manuscript. RC, XWZ and WZ contributed to data analysis and interpretation, and assisted with manuscript revision. AS contributed to study design, data interpretation and manuscript editing. XBZ, YS, CL, RC, WZ, XWZ, AS, and JZ drafted and critically revised the manuscript. XBZ and JZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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