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CASE REPORT

# Cerebrospinal Fluid based liquid biopsy to inform diagnosis and management of Leptomeningeal Metastases in *EGFR*-Mutant Lung Cancer – A Case Report

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## ABSTRACT

Leptomeningeal disease (LMD) in advanced non-small cell lung cancer (NSCLC) carries a poor prognosis and is challenging to diagnose without invasive biopsy. Traditional cerebrospinal fluid (CSF) cytology considered the gold standard in diagnosis is only 33% sensitive and often requires patients to undergo multiple lumbar punctures to receive an accurate diagnosis. Innovative technologies that utilize cerebrospinal fluid (CSF) based liquid biopsy have facilitated the detection of tumor derived DNA as a surrogate for cytology, at a much earlier time period than imaging would indicate a definitive diagnosis. This study presents a 47-year-old male diagnosed with non-small cell lung cancer who presented with an increase in intraocular pressure. Subsequent testing using the Belay Summit™ test revealed an EGFR T790M mutation in the CSF. Following the detection of this variant, the patient received treatment with osimertinib (Tagrisso®), which proved beneficial for his condition.

**Keyword: Lung cancer, Leptomeningeal disease, CNS metastasis, genomic testing, CSF**

## Introduction

Non-small cell lung cancer (NSCLC) makes up about 85% of lung cancer cases and is a major cause of cancer-related deaths worldwide. NSCLC includes subtypes like adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, with adenocarcinoma being the most common, particularly in non-smokers and patients with identifiable molecular drivers.[1] Metastatic dissemination is a hallmark of advanced NSCLC, particularly affecting critical organs like the brain, liver, bones, and adrenal glands[2]. Among these, central nervous system (CNS) is a common site for metastasis in advanced NSCLC affecting 23–36% of patients[2,3]. Brain and leptomeningeal metastases significantly affect patient health, causing headaches, seizures, cognitive decline, cranial nerve deficits, and neurological impairment[4]. The management of CNS metastases in NSCLC requires prompt diagnosis and a collaborative treatment approach.

Recent advances in molecular oncology have uncovered various genomic alterations in NSCLC, including *EGFR* mutations, *ALK* rearrangements, and *ROS1* fusions. These findings have enabled the creation of targeted therapies, leading to better clinical outcomes for certain patient groups and reduced toxicity compared to traditional chemotherapy[5,6]. Patients with NSCLC harboring an *EGFR* mutation face a higher risk of developing leptomeningeal disease (LMD) than those with wild-type *EGFR* (9% vs. 2% incidence)[7]. This elevated risk is thought to result from both biological factors intrinsic to *EGFR*-mutant tumors as well as the prolonged survival of these patients due to effective systemic therapies, which may allow for eventual CNS progression[8]. LMD is associated with poor outcomes, median overall survival of around three months and a high symptom burden that affects clinical functioning[9]. The approval of third-generation tyrosine kinase inhibitors (TKIs), like osimertinib, represents a significant advancement in targeted therapy. These agents target *EGFR*-activating mutations as well as resistance mutations with improved ability to penetrate the blood-brain barrier (BBB), enhancing their effectiveness against CNS cancer involvement[10]. This improved CNS penetration is especially critical, as the central nervous system often serves as a sanctuary site for cancer cells, limiting the efficacy of many systemic treatments[2]. Osimertinib demonstrated higher intracranial response rates and longer progression-free survival in patients with *EGFR*-mutant NSCLC including those with leptomeningeal metastases, compared to earlier-generation tyrosine kinase inhibitors[11,12].

Diagnosing LMD is challenging due to its diverse clinical presentations and requires neurological examination, magnetic resonance imaging (MRI) of the brain and spine, and CSF analysis[12]. Clinical manifestations can vary and may include headaches, cranial nerve deficits, altered mental status, and gait disturbances, which can mimic other neurologic or paraneoplastic conditions. MRI findings may reveal contrast enhancement of the leptomeninges or hydrocephalus[13,14]. While CSF analysis remains the diagnostic gold standard but may require multiple lumbar punctures due to limited sensitivity[15]. Given these limitations, CSF liquid biopsy offers a minimally invasive and increasingly reliable option for detecting and monitoring CNS malignancies[16,17]. Summit™ utilizes targeted next-generation sequencing (NGS) to evaluate variants in 32 genes along with chromosome arm level aneuploidy[18]. This case underscores the importance of genomic profiling of tumor-derived DNA from CSF in informing the diagnosis and management of metastatic lung cancer with concerns for LMD and reviews the molecular features of leptomeningeal disease in NSCLC along with potential treatment options.

## Case Report

A 47-year-old man was diagnosed with NSCLC in June 2024 (Figure 1). At the time of his diagnosis, brain MRI was performed, which showed no signs of metastasis. Molecular profiling of the primary tumor performed in July 2024 identified clinically relevant genomic alterations, including EGFR T790M, EGFR L858R, TP53 L130V, and *CCNE1* amplification.

Treatment with osimertinib at a daily dose of 80 mg was initiated and the patient exhibited an excellent clinical response, especially in his respiratory function. However, in November 2024, he started experiencing pain and pressure in his right eye. Evaluation revealed elevated intraocular pressure, but cytological analysis of the intraocular fluid was negative for malignant cells. In February 2025, he was admitted to the hospital again with recurrent symptoms, including uveitis and increased intraocular pressure. A lumbar puncture (LP) performed during this admission was negative for CSF cytology. However, a follow-up brain MRI showed multiple new areas of enhancement, raising concerns for LMD, while the spine MRI remained unremarkable. A second LP was done and CSF analysis by Belay Summit™[18] detected an EGFR T790M mutation with a variant allele frequency (VAF) of 52.2%. Based on these findings, the patient was started on a high dose of osimertinib (160 mg daily). Subsequently, he reported significant improvement in visual symptoms and normalization of intraocular pressure after 28 days of therapy. A follow-up brain MRI performed after 8 weeks of therapy demonstrated resolution of the majority of the leptomeningeal enhancement. He is planned for serial monitoring via Belay Summit™ testing periodically throughout his treatment in order to track his response to his therapy.

## Technique

The Belay Summit™ test[18] was ordered for molecular profiling in CSF. Summit is a CLIA/CAP validated NGS-based test that can detect single nucleotide variants (SNV), multi-nucleotide variants (MNV), and insertions/deletions in a targeted, 32-gene panel in CSF using duplex sequencing technology as well as aneuploidy in the form of chromosomal arm level alterations using low pass whole genome sequencing[18]. Summit™ reported the pathogenic variant EGFR T790M, a missense substitution located within the EGFR tyrosine kinase domain[19]. This variant confers a well-established mechanism of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) in NSCLC[20]. This mutation occurs when threonine is replaced by methionine at position 790 in the ATP-binding pocket of the EGFR kinase domain, resulting in a decreased ability of TKIs to bind ATP and thus reducing their therapeutic effectiveness[6].

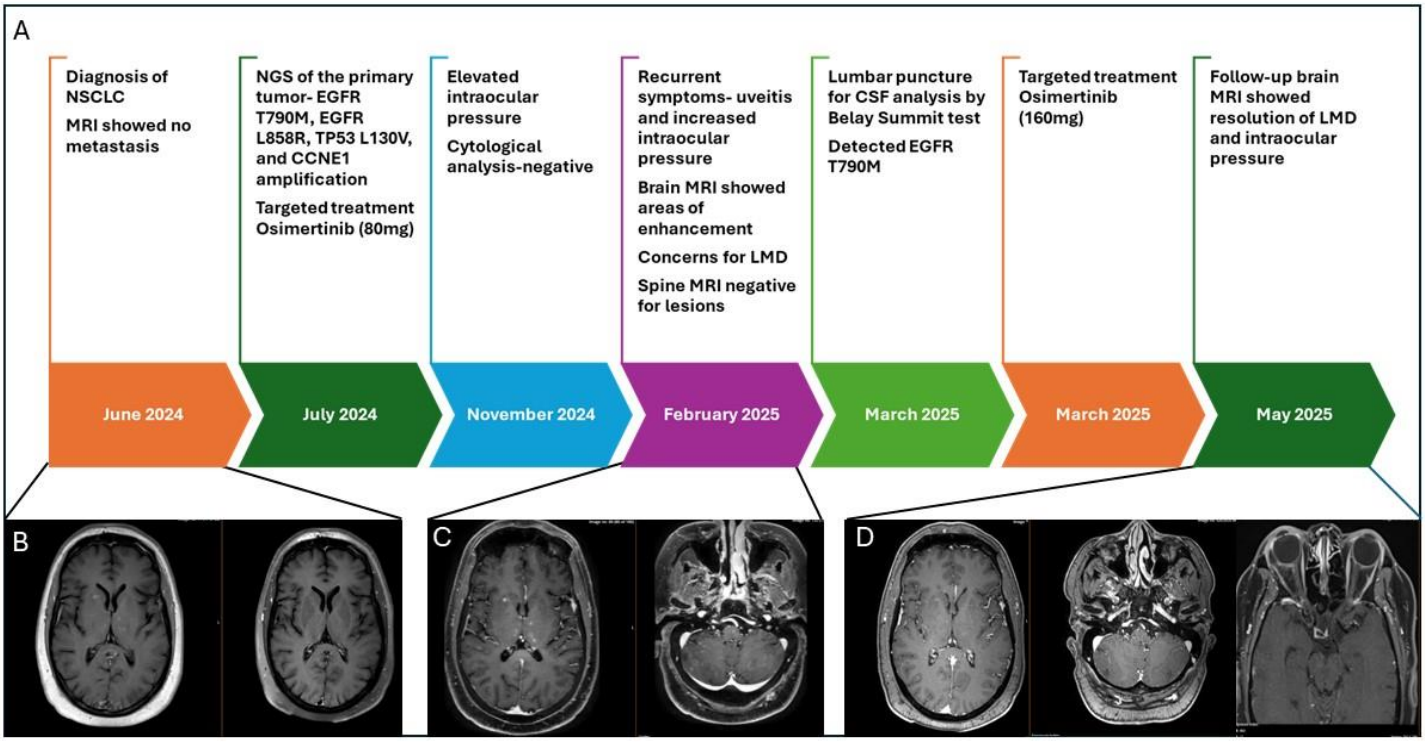


**Figure 1** – (A) Timeline of patient clinical presentation; (B) MRI at the time of initial NSCLC diagnosis; (C) Shows two images of the new abnormal leptomeningeal enhancement; (D) shows resolution of a significant portion of the abnormal enhancement surrounding the optic nerves in 3 different images.

## Discussion

This case emphasizes the vital importance of CSF analysis in the diagnosis and management of CNS metastases in lung cancer, particularly in patients with identified *EGFR* mutations. The presented case highlights an NSCLC patient marked by worsening symptoms, raising concerns for progression of LMD. Testing of the tumor-derived DNA from CSF by Belay Diagnostics assisted in identifying EGFR T790M, consistent with previous primary tumor profiling on this individual. Detection of the EGFR T790M mutation is critical for treatment options due to the variant conferring resistance to both first- and second-generation EGFR TKIs. Multiple studies and clinical reports consistently showed that this mutation occurs in approximately 50-60% of patients undergoing TKI treatment[21] and reduces the efficacy of first- and second-generation EGFR TKIs limiting their ability to control disease progression[22].

*EGFR* mutations, particularly deletions in exon 19 and L858R substitutions, are associated with enhanced responsiveness to first-generation TKIs such as gefitinib and erlotinib. These treatments demonstrate response rates of approximately 60-70%, with median progression-free survival (PFS) ranging from 9 to 13 months[23]. However, despite the initial success, many patients develop acquired resistance within 9 to 14 months, with T790M identified as a main mechanism behind this resistance. This gatekeeper mutation alters the ATP-binding site, resulting in decreased binding affinity of the drug and thereby limiting the effectiveness of TKIs. Although second-generation TKIs, including afatinib and dacomitinib, possess improved binding profiles, they still face challenges in effectively targeting T790M[22,24-26]. Detecting EGFR T790M is crucial for transitioning to third-generation TKIs like osimertinib, known for its significant CNS penetration and efficacy[6]. Results presented here enabled a tailored therapeutic approach with high-dose osimertinib (160 mg daily), which led to significant clinical improvement and substantial regression of LMD. These findings are consistent with the BLOOM study which established high dose of osimertinib (160 mg) once daily as an effective and tolerable option for *EGFR*-mutant NSCLC patients with LMD following progression on prior EGFR-TKIs[12]. In the BLOOM study, patients with radiographically and cytologically confirmed LMD had a median overall survival of 11 months, significantly surpassing historical expectations for this group[12]. Furthermore, clinical trials such as AURA3 and FLAURA have shown osimertinib's superiority in managing CNS metastases compared to standard EGFR-TKIs. In the AURA3 trial, osimertinib achieved a CNS objective response rate of 70% and prolonged intracranial progression-free survival compared to chemotherapy in patients with T790M-positive NSCLC. The FLAURA trial demonstrated that osimertinib significantly delayed CNS progression in treatment-naïve patients, achieving a CNS disease control rate of 91%[27,28]. The patient's clinical and radiologic response to osimertinib further supports its effectiveness in cases of CNS-dominant progression, especially when molecular profiling is guided by CSF analysis.

Standard testing of plasma or tumor tissue may not reliably detect mutations in the CNS due to the blood-brain barrier and compartmentalization of metastatic disease[29]. In such scenarios, CSF has a higher tumor fraction and a better detection rate for CNS-specific mutations making it a potentially more effective tool for patients with CNS metastases or leptomeningeal disease[30]. A study involving 22 patients with NSCLC and suspected LMD demonstrated that 7 patients who had adequate circulating tumor cells (CTCs) in their CSF for molecular analysis showed 100% concordance with tissue NGS results for known driver mutations[31]. Likewise, Summit™ demonstrated a clinical sensitivity of 90% across a cohort of 124 primary and metastatic CNS tumors, including 7 cases of metastatic lung cancer in which the assay achieved 100% sensitivity[18].

Overall, this case reinforces the increasing evidence supporting the use of CSF-based molecular testing in NSCLC patients who have suspected or confirmed leptomeningeal disease or brain metastases. It also

highlights the critical importance of CSF testing as a powerful diagnostic tool in detecting targetable driver events and personalized treatment strategies based on the spatial heterogeneity of tumor evolution.

## Conclusion

In summary, this case emphasizes the crucial role of advanced molecular diagnostics techniques in the detection and management of leptomeningeal disease. Cutting-edge techniques, such as the Belay Summit™ CSF-based liquid biopsy, enables the rapid and non-invasive identification of mutations such as the EGFR T790M resistance variant, facilitating the timely initiation of targeted therapy with osimertinib. Hence, integrating CSF molecular profiling into clinical practice improves diagnosis and aids in guiding personalized treatment plans for patients suspected of having LMD.

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### *Conflict of Interest*:

MY has no conflicts to disclose. AL, VU, KFS, QN and HVR are employees of Belay Diagnostics and receive a salary and stock options.

### *Patient Consent:*

The patient has consented to the submission of the case report for publication.

### *Authorship*:

Writing – Original draft – VU, HVR; Writing review and editing - All authors. All authors approved the final version of the manuscript.

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