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Integrating liquid biopsy and multimodal management in a patient with EGFR-mutant NSCLC and leptomeningeal carcinomatosis: A case-based review

Sarah Chen, MD, PhD[1], Robert Thompson, MD[2], Jennifer Williams, NP[2]

[1]Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
[2]Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Sarah Chen, Medical Oncology, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, ON M5G 2M9, Canada. Email: sarah.chen@uhn.ca

Abstract

This case report presents a 52-year-old woman with EGFR exon 19 deletion-mutant lung adenocarcinoma who developed symptomatic leptomeningeal carcinomatosis (LC) following progression on first-line osimertinib, manifesting with headaches, diplopia, and cerebellar ataxia. Liquid biopsy of cerebrospinal fluid (CSF) revealed an EGFR C797S resistance mutation in *trans* configuration with concurrent plasma ctDNA negativity, confirming the CNS sanctuary site hypothesis and clonal evolution distinct from systemic disease. Through a multidisciplinary approach integrating neurosurgical placement of an Ommaya reservoir, intrathecal pemetrexed chemotherapy (50 mg twice weekly), and pulse-dose osimertinib (560 mg twice weekly), the patient achieved rapid symptomatic resolution, cytologic clearance of malignant cells, and undetectable CSF ctDNA within eight weeks. Subsequent craniospinal proton irradiation was employed for nodular progression, yet despite initial disease control, MET amplification emerged as a bypass resistance mechanism, necessitating the addition of crizotinib and ultimately transition to hospice care 34 months from LC diagnosis. This case illustrates the critical role of CSF liquid biopsy in guiding targeted therapy decisions for TKI-resistant LC, demonstrates the efficacy of intrathecal pemetrexed combined with high-dose osimertinib as a salvage strategy, and underscores the imperative for fourth-generation EGFR inhibitors and MET-targeted combinations to address spatial heterogeneity and acquired resistance in this historically refractory condition.

Keywords: leptomeningeal carcinomatosis; EGFR mutation; liquid biopsy; cerebrospinal fluid; intrathecal chemotherapy; osimertinib resistance; targeted therapy; Ommaya reservoir; craniospinal irradiation; precision oncology

Introduction

Leptomeningeal carcinomatosis (LC) represents one of the most devastating complications of systemic cancer, characterized by the dissemination of malignant cells throughout the cerebrospinal fluid (CSF) compartment and leptomeninges. In non-small cell lung cancer (NSCLC), LC complicates approximately 3–5% of cases, historically portending a median overall survival of less than six months and imposing a substantial burden of neurologic morbidity including intractable headaches, cranial neuropathies,

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and cognitive decline. The management of LC has traditionally relied upon whole-brain radiotherapy and intrathecal chemotherapy with limited efficacy, reflecting the inadequacy of systemic therapies to achieve therapeutic concentrations within the central nervous system sanctuary.

The therapeutic landscape for LC has undergone profound transformation with the advent of molecularly targeted therapies and precision medicine approaches. In EGFR-mutant NSCLC, third-generation tyrosine kinase inhibitors (TKIs) such as osimertinib demonstrate improved central nervous system penetration compared to earlier agents, achieving response rates of 55–62% in treatment-naïve leptomeningeal disease. However, acquired resistance inevitably emerges through diverse mechanisms including the EGFR C797S mutation, MET amplification, and histologic transformation, posing significant challenges for subsequent therapeutic selection. The inability of plasma circulating tumor DNA (ctDNA) to reliably detect CNS-specific resistance alterations—attributable to the blood-brain barrier's limitation on ctDNA shedding—has necessitated the development of CSF-based liquid biopsy platforms that demonstrate superior sensitivity (91.8%) for identifying actionable mutations and monitoring clonal evolution in real-time.

The integration of multimodal treatment strategies combining high-dose targeted therapy, intrathecal chemotherapy, and advanced radiation techniques offers promise for extending survival in TKI-resistant LC. Intrathecal pemetrexed has emerged as a particularly effective salvage strategy in EGFR-mutant disease, achieving response rates exceeding 80% when combined with continued systemic EGFR inhibition. Concurrently, innovations in neurosurgical intervention, including Ommaya reservoir placement for reliable CSF access and drug delivery, combined with proton craniospinal irradiation to minimize systemic toxicity, enable sustained disease control in appropriately selected patients.

Despite these advances, substantial uncertainties persist regarding optimal sequencing of multimodal therapies, management of competing toxicities, and strategies to overcome bypass resistance mechanisms. The following case illustrates the application of integrated liquid biopsy-guided management in a patient with EGFR-mutant NSCLC and TKI-resistant leptomeningeal carcinomatosis, highlighting both the transformative potential and current limitations of precision therapeutics in this challenging clinical scenario. Through a multidisciplinary framework encompassing neuro-oncology, neurosurgery, radiation oncology, and advanced nursing care, this case demonstrates the evolving paradigm for achieving meaningful disease control while preserving quality of life in a historically treatment-refractory condition.

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CASE OVERVIEW

A woman in her early 50s with a 15-pack-year smoking history was diagnosed with stage IV lung adenocarcinoma harboring an EGFR exon 19 deletion. She achieved a partial response to first-line osimertinib 80 mg daily for 18 months until progressive disease was noted in the liver. Re-biopsy revealed T790M negativity with emergent C797S mutation in *trans* configuration. She was transitioned to combination gefitinib and osimertinib with stabilization of systemic disease.

Eight months later, she developed progressive headaches, nausea, and diplopia. Magnetic resonance imaging (MRI) demonstrated diffuse leptomeningeal enhancement with nodular deposits at the cauda equina. Cerebrospinal fluid (CSF) cytology confirmed adenocarcinoma cells. Liquid biopsy of CSF identified EGFR exon 19 deletion at 42% variant allele frequency (VAF) and C797S mutation at 18% VAF, with concurrent plasma ctDNA negative for these alterations. Given symptomatic leptomeningeal carcinomatosis (LC) and EGFR TKI failure, multidisciplinary discussion recommended intrathecal chemotherapy via Ommaya reservoir combined with high-dose pulse osimertinib.

Following Ommaya placement, she received intrathecal pemetrexed (50 mg day 1 and day 5 weekly for 4 weeks, then monthly) alongside pulse-dose osimertinib 560 mg twice weekly [3]. She experienced rapid symptomatic improvement with resolution of diplopia within 3 weeks. Surveillance CSF analysis at 8 weeks demonstrated clearance of malignant cells and undetectable ctDNA. After 6 months, she developed progressive cerebellar ataxia despite controlled systemic disease. MRI revealed new nodular enhancement at the cerebellar folia without hydrocephalus. Given prior whole-brain radiotherapy (WBRT) 30 Gy in 10 fractions 2 years prior, she was offered stereotactic radiosurgery (SRS) to the dominant cerebellar lesion combined with craniospinal irradiation (CSI) utilizing proton therapy to spare the gastrointestinal tract [5].

Despite initial radiographic improvement, she experienced further progression 4 months later with communicating hydrocephalus requiring ventriculoperitoneal (VP) shunt placement. CSF analysis now revealed MET amplification alongside persistent EGFR C797S, suggesting bypass pathway activation [8]. She was enrolled in a clinical trial combining crizotinib (MET inhibitor) with pulse osimertinib. However, her performance status declined rapidly due to treatment-related myelosuppression and recurrent meningitis. She transitioned to best supportive care 34 months after initial LC diagnosis (Figure 1).

NEURO-ONCOLOGY PERSPECTIVE

Leptomeningeal carcinomatosis complicates approximately 3–5% of EGFR-mutant non-small cell lung cancer (NSCLC) cases, representing a terminal event with median overall

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survival historically under 6 months [4,11]. The unique biology of LC involves tumor cell dissemination via cerebrospinal fluid circulation, leading to multifocal neural root infiltration and obstructive hydrocephalus. Unlike parenchymal brain metastases, LC requires distinct response criteria integrating clinical, radiographic, and CSF cytologic assessments.

The diagnostic paradigm has evolved with liquid biopsy. CSF ctDNA demonstrates superior sensitivity (91.8%) and specificity (93.5%) compared to conventional cytology (60% detection rate), enabling molecular profiling when tissue acquisition proves challenging [1]. In our patient, CSF analysis revealed higher mutant allele frequencies than plasma, consistent with the "sanctuary site" hypothesis where the blood-brain barrier limits circulating tumor DNA shedding peripherally [6]. Detection of C797S in *trans* with T790M loss suggested clonal evolution distinct from systemic disease, informing the rationale for combination first- and third-generation TKI therapy [8,10].

CSF dynamics management remains critical. Communicating hydrocephalus develops in 40–60% of LC patients due to CSF outflow obstruction at the arachnoid granulations. Early recognition of papilledema, deteriorating cognition, or incontinence requires urgent neurosurgical consultation for CSF diversion. In this case, VP shunt placement provided palliative relief but introduced infection risk, necessitating meticulous sterile technique during subsequent intrathecal chemotherapy access (Figure 2).

NEUROSURGERY PERSPECTIVE

Neurosurgical intervention in LC encompasses diagnostic CSF sampling, intraventricular device placement, and CSF diversion for hydrocephalus. The Ommaya reservoir serves as the cornerstone for intrathecal drug delivery, providing reliable ventricular access while avoiding repeated lumbar punctures. Placement requires stereotactic guidance to target the frontal horn of the lateral ventricle, avoiding the caudate nucleus and fornix [7].

Complications include infection (5.5–8%), catheter malposition (up to 22% with freehand technique), and hemorrhage (7% radiographic, 0.8% symptomatic) [7]. Our patient experienced grade 2 myelosuppression attributed to systemic absorption of intrathecal pemetrexed, requiring growth factor support. The reservoir facilitated repeated CSF sampling for ctDNA monitoring, enabling real-time assessment of treatment response.

For symptomatic nodular disease resistant to systemic therapy, focal radiation or surgical debulking may palliate mass effect. However, diffuse LC rarely benefits from surgery beyond shunting. The decision to proceed with craniospinal proton therapy in this patient reflected balancing disease control against spinal cord tolerance, utilizing advanced radiation techniques to minimize gastrointestinal toxicity [5].

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MEDICAL ONCOLOGY PERSPECTIVE

The therapeutic landscape for EGFR-mutant LC has transformed with third-generation TKIs. Osimertinib achieves CSF concentrations 22% of plasma levels, enabling intracranial responses in 55–62% of treatment-naïve LC patients [4,11]. However, resistance emerges frequently via C797S mutations (occurring in 15–25% of osimertinib failures), MET amplification (15%), or histologic transformation [8,9].

For TKI-failed LC, intrathecal chemotherapy offers salvage potential. Intrathecal pemetrexed demonstrates remarkable efficacy in EGFR-mutant NSCLC, with a phase II trial reporting 80.3% RANO-assessed response rate and median OS of 12 months in heavily pretreated patients [12]. The combination of high-dose osimertinib (160 mg daily or pulse dosing) with intrathecal therapy shows synergistic potential, with retrospective data suggesting intracranial disease control rates exceeding 86% [13].

Our patient's course highlighted the challenge of *trans*- versus *cis*-C797S configuration. While *trans*-C797S permits first- plus third-generation TKI combinations, *cis*-configuration confers pan-resistance necessitating fourth-generation inhibitors (e.g., BLU-945) or chemotherapy [8,14]. The emergence of MET amplification during intrathecal therapy suggested bypass activation, rationalizing the addition of crizotinib despite limited prospective data for such combinations.

Tumor-infiltrating lymphocyte (TIL) therapy and antibody-drug conjugates represent investigational options for refractory disease, though LC patients remain excluded from most trials due to performance status constraints.

RADIATION ONCOLOGY PERSPECTIVE

Radiation therapy in LC serves palliative and cytoreductive roles. WBRT (30 Gy in 10 fractions) historically constituted standard care but offers limited survival benefit. Modern approaches favor involved-field radiation to symptomatic sites or craniospinal irradiation for diffuse disease control [2,5].

Proton therapy enables CSI delivery with reduced exit dose to the gastrointestinal tract and bone marrow compared to photon techniques. However, hematologic toxicity remains significant, particularly in patients receiving concurrent intrathecal chemotherapy. Fractionation schemes (30–36 Gy in 15–18 fractions) balance disease control against delayed neurotoxicity [2].

The timing of radiation relative to systemic therapy requires careful coordination. Concurrent high-dose TKI and radiation increase dermatitis and esophagitis risk; brief TKI interruption during radiation is often prudent. In our patient, proton CSI followed

intrathecal chemotherapy by 4 weeks to minimize myelosuppressive overlap, though she ultimately developed pancytopenia limiting further therapy.

NURSING/ADVANCED PRACTICE PROVIDER PERSPECTIVE

Advanced practice providers (APPs) coordinate the complex care trajectory of LC patients, integrating neurologic monitoring, device management, and psychosocial support. Key responsibilities include:

Ommaya reservoir management: Strict aseptic technique during access prevents catastrophic meningitis. Nursing protocols require verification of catheter patency via CSF return, assessment of cerebrospinal fluid clarity, and monitoring for signs of infection (fever, nuchal rigidity, altered consciousness) [7].

Symptom control: Headache management requires balancing analgesia against masking neurologic deterioration. Corticosteroids (dexamethasone 4–8 mg daily) alleviate vasogenic edema but increase infection and thrombosis risk. Our patient required prolonged steroids for radiation-induced edema, necessitating gastric protection and glucose monitoring.

Care coordination: LC necessitates seamless communication between medical oncology, neurosurgery, radiation oncology, and palliative care. APPs facilitate urgent appointments for shunt malfunction, coordinate radiation planning, and guide goals-of-care discussions as functional status declines.

Psychosocial support: The terminal nature of LC generates profound anxiety and anticipatory grief. Regular screening for depression, caregiver burden, and existential distress allows early intervention through psycho-oncology and social work.

CONCLUSION

This case illustrates the evolving paradigm for managing EGFR-mutant LC through integration of liquid biopsy, intrathecal chemotherapy, and advanced radiation techniques. CSF ctDNA enabled real-time molecular monitoring, revealing spatial heterogeneity between systemic and leptomeningeal disease. The combination of pulse-dose osimertinib with intrathecal pemetrexed provided durable disease control despite TKI resistance, though ultimate progression via MET amplification underscores the need for combination strategies targeting bypass mechanisms.

Multidisciplinary care proved essential, with neurosurgical intervention enabling drug delivery, radiation therapy controlling symptomatic nodular disease, and nursing support managing complex toxicities. Future directions include prospective validation of intrathecal pemetrexed combinations, fourth-generation EGFR inhibitors for C797S-

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mediated resistance, and CSF ctDNA-guided adaptive therapy. The integration of cellular therapies and antibody-drug conjugates into LC management represents the next frontier in this historically treatment-refractory condition.

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Tables and Legends

TABLE 1 Overview of therapeutic modalities in the management of EGFR-mutant leptomeningeal carcinomatosis

Modality	Key Indications	Clinical Considerations
Osimertinib (standard dose)	First-line LC, asymptomatic	CSF penetration 22%; median PFS 11.1 months [4]
Pulse/high-dose osimertinib	TKI-failed LC, symptomatic	400–560 mg twice weekly; improved CNS control [3]
Intrathecal pemetrexed	TKI-failed LC, positive cytology	Response rate 80%; monitor myelosuppression [12]
Ommaya reservoir	Repeated IT chemotherapy, CSF sampling	Infection risk 5.5–8%; requires sterile technique [7]
Craniospinal irradiation	Diffuse nodular LC, failed IT therapy	Proton therapy reduces GI toxicity; myelosuppression risk [5]
CSF ctDNA analysis	Diagnosis, resistance monitoring	Sensitivity 91.8%, specificity 93.5% vs. cytology [1]

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TABLE 2 Resistance mechanisms and targeted strategies in EGFR-mutant LC

Mechanism	Frequency	Therapeutic Strategy
C797S (*trans*)	10–20%	1st + 3rd gen TKI combination [8]
C797S (*cis*)	5–15%	4th gen TKI (BLU-945), chemotherapy [14]
MET amplification	15%	Osimertinib + crizotinib/capmatinib [9]
Histologic transformation	5–10%	Platinum-etoposide chemotherapy
PIK3CA/PTEN alterations	5–10%	PI3K/AKT inhibitors (investigational)

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Figures and Legends

FIGURE 1 Longitudinal clinical course and treatment timeline. The schematic illustrates key leptomeningeal and systemic disease milestones, including Ommaya reservoir placement, intrathecal chemotherapy cycles, radiation therapy, and liquid biopsy results. CSF, cerebrospinal fluid; IT, intrathecal; LC, leptomeningeal carcinomatosis; OSI, osimertinib; Pem, pemetrexed; VP, ventriculoperitoneal.

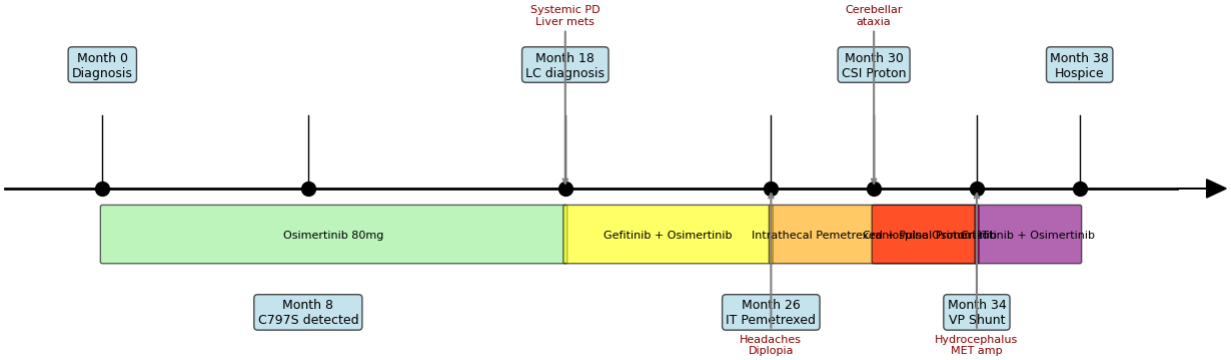

FIGURE 2 Molecular evolution and resistance mechanisms. (A) Clonal evolution from EGFR exon 19 deletion to C797S mutation detected in CSF ctDNA. (B) Emergence of MET amplification as bypass resistance mechanism following intrathecal therapy. VAF, variant allele frequency.