Acquired L718V/*TP53* co-mutation and discordant molecular pattern between plasmatic and cerebrospinal fluid in a bone and meningeal metastatic L858R+ non-small cell lung cancer: a case report

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Background: Osimertinib is approved in first line metastatic epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC). Acquired *EGFR* L718V mutation is a rare mechanism of resistance towards osimertinib in L858R+ NSCLC with potential sensibility to afatinib. This case reported an acquired *EGFR* L718V/TP53 V727M resistance co-mutation to osimertinib with discordant molecular pattern between plasmatic and cerebral fluid in a leptomeningeal and bone metastatic *EGFR* L858R mutant NSCLC.

Case Description: A 52-year-old female, diagnosed with a bone metastatic *EGFR* L858R-mutated NSCLC, was treated with osimertinib as second line treatment for a leptomeningeal progression. She developed an acquired *EGFR* L718V/*TP53* V272M resistance co-mutation after seventeen months of treatment. Discordant molecular status was observed between plasmatic (L718V+/*TP53*+/L858R+) and cerebrospinal fluid (CSF) (L718V–/*TP53*+/L858R+). Afatinib as third line did not prevent neurological progression.

Conclusions: Acquired *EGFR* L718V mutation mediate a rare mechanism of resistance to osimertinib. Some cases reported sensibility to afatinib in patients with *EGFR* L718V mutation. In this described case, afatinib had no efficacy against neurological progression. This could be explained by the absence of *EGFR* L718V mutation in CSF tumor cells and concomitant *TP53* V272M mutation as negative survival prognostic. Identify resistance mechanisms against osimertinib and develop specific therapeutic approaches remain a challenge in clinical routine.

Keywords: Osimertinib; *EGFR* L718V mutation; leptomeningeal metastasis; non-small cell lung carcinoma; case report

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Introduction

Epidermal growth factor receptor (*EGFR*) mutations occur in 11% of patients with a non-small cell lung cancer (NSCLC) (1). First- and second-generation EGFR tyrosine kinase inhibitors (TKIs) are major treatments in this population. Acquired *EGFR* T790M mutation occurs in 60% of patients treated with those EGFR TKIs (2,3). Osimertinib, a third-generation TKI, demonstrated clinical activity in T790M-positive *EGFR*-mutated NSCLC (4). Osimertinib was approved as a first-line treatment for metastatic *EGFR*-positive NSCLC with a 38.6-month median overall survival (5). Preclinical data suggested several mechanisms of resistance to first-line osimertinib, such *MET* amplification or secondary *EGFR* mutations (6,7). Studies assessing specific therapeutic approaches such TKIs combination are ongoing (8). We describe a rare case of a patient with a bone and leptomeningeal metastatic NSCLC who developed an acquired *EGFR* L718V/*TP53* V272M resistance co-mutation to osimertinib without sensibility to afatinib. Discordant molecular pattern in plasmatic and cerebrospinal fluid (CSF) is also described in this unique case. We present the following case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3861/rc).

Case presentation

A 52-year-old female, never smoker and without previous medical history, was diagnosed with bone metastatic *EGFR* L858R-mutated NSCLC in July 2019. According to guidelines, gefitinib (250 mg daily), a first-generation TKI, was administered without any adverse event (*Figure 1A*). Eleven months later, in June 2020, the patient developed intracranial hypertension symptoms (headache, diplopia, vomiting). CSF analysis showed hyperproteinorachia (0.49 g/L) and adenocarcinomatous cells (4%). Bone metastases and primary lung lesion did not progress. Molecular analysis identified *EGFR* L858R mutation without acquired T790M mutation in plasmatic and CSF analysis. Osimertinib (80 mg daily), as a second-line treatment, was started in combination with nineteen intrathecal methotrexate injections (15 mg biweekly) (*Figure 1B*). This treatment was well tolerated and led to neurological improvement with disappearance of tumor cells in CSF and normalization of proteinorachia.

Seventeen months later, in October 2021, neurological symptoms (cerebellar ataxia, diplopia, headaches and dysarthria) reappeared and CSF analysis confirmed progression of carcinomatous meningitis and high proteinorachia (8.66 g/L) while bone and lung lesion did not progress. Circulating plasmatic tumor cells DNA next-generation sequencing (NGS) analysis identified *EGFR* L718V (2152C>G) mutation [allelic frequency variation (AFV): 9%] and *TP53* V272M (814G>A) mutation (AFV: 2%) in conjunction with *EGFR* L858R mutation (AFV: 10%). In CSF, *EGFR* L718V mutation was not found while EGFR L858R mutation (AFV: 40%) and *TP53* V272M mutation (AFV: 33%) were found (*Figure 1C*).

Afatinib (40 mg daily), as a third-line treatment was started in December 2021 without any neurological clinical benefit. CSF analysis and thoracic CT-scan to evaluate afatinib effect could not be performed due to serious neurological degradation. The patient died in March 2022 of neurological progression.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Oral consent was obtained from the patient for publication of this case report and accompanying images.

Highlight box

Key findings

- Acquired *EGFR* L718V/*TP53* V272M resistance co-mutation against osimertinib in a patient with leptomeningeal and bone metastatic EGFR L858R-mutated non-small-cell lung carcinoma in association with a discordant molecular status between plasma and cerebrospinal fluid.

What is known and what is new?

- *EGFR* L718V mutation confers resistance to osimertinib.
- Co-mutation *EGFR* L718V/*TP53* V272M and discordant molecular status between plasma and cerebrospinal fluid could explain the lack of efficacy of afatinib.

What is the implication, and what should change now?

- Identify resistance mechanisms against third-generation tyrosine kinase inhibitors and develop specific therapeutic approaches.

Discussion

We report a rare case of an acquired *EGFR* L718V/*TP53* V272M co-mutation in a patient with a bone and leptomeningeal metastatic L858R-mutated NSCLC. Preclinical data suggest that acquired *EGFR* L718V mutation confers resistance to osimertinib (9). Five cases are

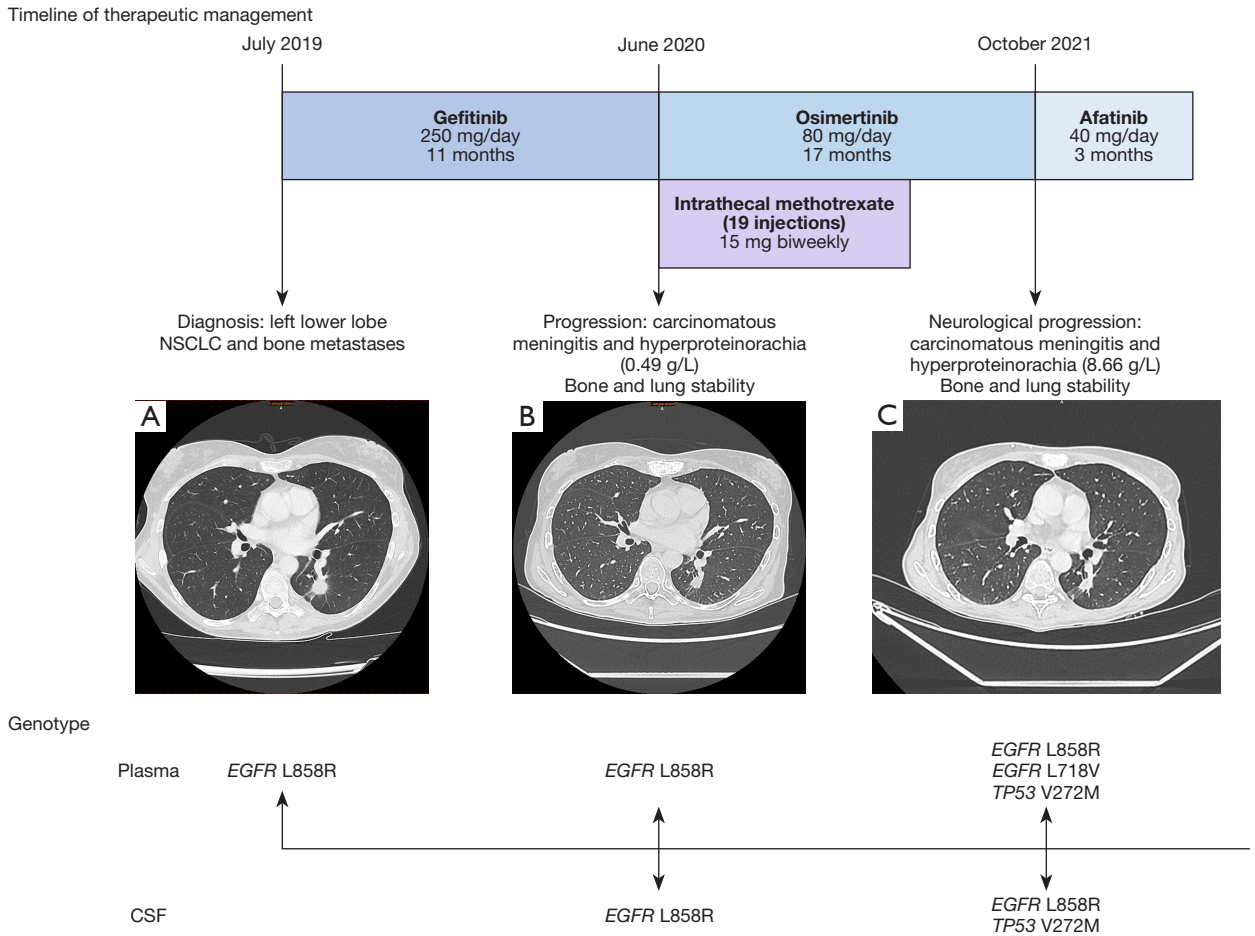

Figure 1 Timeline of therapeutic management and genotype data from each DNA analysis in plasmatic and cerebrospinal fluid according to the disease progression (A-C). NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; CSF, cerebrospinal fluid.

previously described in the literature, all with an acquired *EGFR* L718V resistance mutation to osimertinib and L858R+/T790M– status (10-13). The pathophysiological mechanisms remain unclear. *In vitro* studies suggested that L718V mutation induces a spatial conflict of EGFR that prevents osimertinib binding (9,11).

Resistance to osimertinib and sensitivity to afatinib were described in preclinical data and among the five patients treated with afatinib, four had clinical benefit with a disease stabilization (9,14). In this reported patient, afatinib had no efficacy against neurological progression. This could be explained by the absence of *EGFR* L718V mutation in CSF tumor cells. As observed by Zheng *et al.* liquid biopsy in CSF is more sensitive than in plasma to detect resistance alterations in leptomeningeal metastatic NSCLC with oncogenic driver mutation (15). As reported by Aredo *et al.* afatinib had a limited activity after progression under osimertinib (16). Also, Tamiya *et al.* observed low efficacy of afatinib for leptomeningeal carcinomatosis with a median progression-free survival of 2 months (17). The same authors described a low CSF penetration rate (1.7% compared to blood concentration rate) (18).

In this case, concomitant *TP53* V272M (exon 7) mutation could also explained afatinib resistance. Mutation in exon 7 in *TP53* is a negative survival prognostic factor in *EGFR*-mutated NSCLC, as reported in a phase III trial including 195 patients (19). No case of EGFR L718V/*TP53* co-mutation was reported in literature.

This case reported a rare resistance co-mutation *EGFR* L718V/*TP53* against osimertinib and a discordant molecular pattern between plasmatic and CSF. It suggested that EGFR TKI induced a molecular heterogeneity on

metastases and discordant clinical evolution. In routine practice, biopsies of the metastases that progressed should be performed to adapt the therapeutic strategy.

There is currently no therapeutic guideline in case of *EGFR* L718V mutation resistance to osimertinib. Combination of chemotherapy-bevacizumab and atezolizumab (20,21), or amivantanab a bispecific antibody targeting EGFR and MET, or lazertinib a third generation *EGFR* TKI could be therapeutic options. Studies are needed to evaluate these therapies after progression under osimertinib.

Conclusions

Acquired *EGFR* L718V/*TP53* co-mutation mediates resistance against osimertinib. Molecular pattern can be different between metastatic sites. Histologic analysis of progressive metastases is suggested to adapt the therapeutic strategy. Identify the resistance mechanisms against third-generation TKI and develop specific therapeutic approaches are a challenge in clinical routine.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3861/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3861/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Oral consent was obtained from the patient for publication of this case report and accompanying images.

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