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Case Report

An Unusual Case of Acquired AGK-BRAF Gene Fusion in Metastatic EGFR-mutant Lung Adenocarcinoma: A Case Report

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Abstract

This case report describes a 60-year-old male patient initially diagnosed with metastatic lung adenocarcinoma harboring an epidermal growth factor receptor (EGFR) exon 21 L858R mutation who subsequently developed a rare acquired AGK-BRAF fusion during the course of treatment. This case highlights the complexity of managing EGFR-mutant lung cancer with additional acquired genetic alterations, the potential role of these alterations in treatment resistance, and the importance of comprehensive genomic profiling in guiding personalized treatment strategies.

Keywords: AGK-BRAF fusion, epidermal growth factor receptor-mutant, nonsmall cell lung cancer

Introduction

Nonsmall cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases,[1,2] and nearly, half of patients present with distant metastasis at diagnosis.[3] Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have improved outcomes for patients with EGFR-mutant NSCLC;[4-10] however, acquired resistance limits long-term benefits.

While the EGFR T790M mutation accounts for approximately 60% of cases of resistance to first- and second-generation EGFR TKIs, other mechanisms of resistance have emerged, particularly with osimertinib.[11-13]

Recent studies have identified various acquired gene rearrangements as potential mechanisms, including BRAF fusions. *De novo* BRAF fusions are rare genetic alterations, representing approximately 4.3% of BRAF alterations in NSCLC.[14-16] These fusions typically retain the BRAF kinase domain while lacking the N-terminal inhibitory domain, resulting in constitutive Rapidly Accelerated Fibrosarcoma (RAF) protein dimerization and Mitogen-Activated Protein (MAP)-kinase signaling activation independent of Rat Sarcoma (RAS) activation.[17]

BRAF fusions have been reported to be the mechanism of acquired resistance to EGFR TKI therapy in approximately 2%

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of patients.[18] This finding opens up new potential therapeutic strategies, including the combined inhibition of EGFR and Mitogen-activated protein kinase kinase (MEK)[18] or the use of pan-RAF inhibitors.

This case report presents a 60-year-old male with EGFR-mutant lung adenocarcinoma who developed resistance to EGFR TKI therapy. Genetic profiling revealed a rare Acylglycerol Kinase (AGK)-BRAF fusion, highlighting the importance of comprehensive genomic testing in guiding treatment decisions.

Case Report

A 60-year-old male patient was initially found to have metastatic lung adenocarcinoma through incidental findings of one right lower lung nodule and several ground-glass opacities. He was then lost to follow-up for 5 years until this presentation, when he presented with a palpable mass in his right supraclavicular area. Subsequent investigations confirmed lung adenocarcinoma with an EGFR exon 21 L858R mutation and brain metastases.

Erlotinib and ramucirumab were given as frontline treatment after palliative radiotherapy for the brain metastases. Despite shrinkage of the initial lung tumors, disease progression was observed after 9 months of frontline treatment, with growth in both the right lower and upper lobe tumors. A biopsy of the right lower lung tumor revealed no detectable EGFR mutation by cobas EGFR mutation test, suggesting loss of the original driver mutation. He then underwent various treatments [Figure 1], including two lines of chemotherapy (cisplatin + pemetrexed and docetaxel) and further palliative radiotherapy for disease recurrence (whole-brain radiotherapy and right lower lung volumetric modulated arc therapy).

Despite treatment, his condition deteriorated, with nausea, vomiting, and signs of leptomeningeal disease. Multiple interventions were performed, including craniotomy to remove the brain metastases [Figure 2] and a short course of bevacizumab plus osimertinib. Next-generation sequencing of brain metastasis tissue revealed both a "loss of EGFR mutation" and a "gain of AGK-BRAF fusion" [Table 1], and he subsequently received trametinib monotherapy for 1 week. Transient stabilization of his mental status was observed for 2 weeks.

His course was further complicated by bloody urine and stool, with bladder [Figure 3a-c] and colon [Figure 4a-c] metastases identified. Malignant pleural effusion and bloodstream infection occurred, resulting in significant impairment of performance status. His family then decided to stop trametinib treatment and agreed to hospice care. The patient died 1 month after the discovery of the BRAF fusion.

Discussion

This case report aligns with recent findings that BRAF fusions are a potential mechanism of resistance to EGFR TKIs in EGFR-mutant NSCLC. While rare, the co-occurrence of EGFR mutations and BRAF fusions appears to be a recurrent event with significant treatment implications. BRAF fusions can mediate resistance to EGFR TKIs by activating the MEK-Extracellular signal-regulated kinases (ERK) pathway independently of EGFR signaling. Although BRAF fusions have been identified in approximately 2% of patients with acquired resistance to EGFR TKIs,[18] their impact on treatment outcomes is substantial due to tumor heterogeneity after heavy treatment.

Table 1: Next-generation sequencing report (by FoundationOne®CDx panel)

Detected alteration(s)	Variant allele frequency
BRAF AGK-BRAF fusion	-
PTEN loss exon 6–8	-
RB1 2107-2A>G	64.2%
TP53 G199V	72.3%

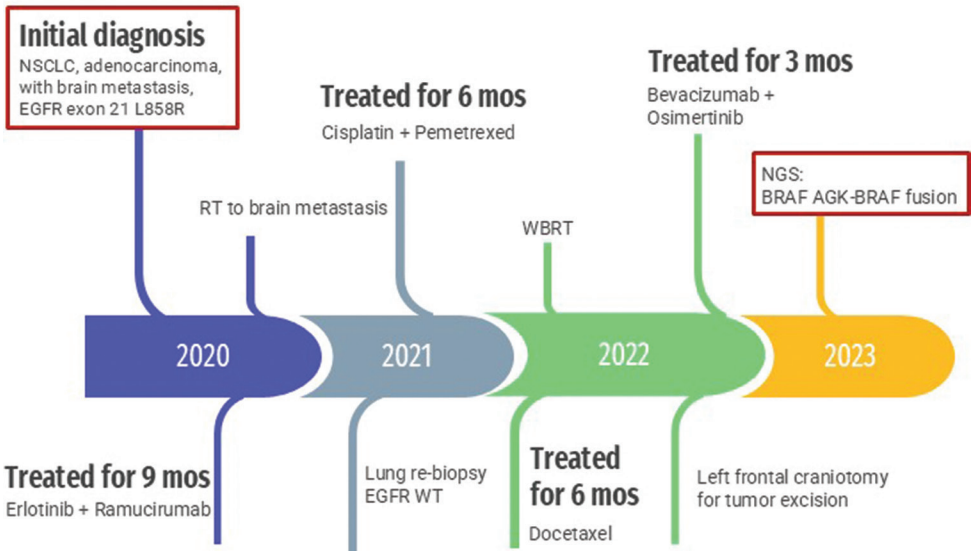

Figure 1: Timeline of treatment interventions before trametinib. NSCLC: Nonsmall cell lung cancer, EGFR: Epidermal growth factor receptor

BRAF alterations, including fusions and class 1 V600 mutations, impact cancer prognosis and treatment. Class 1 mutations exert strong activity by stimulating monomeric BRAF protein to drive downstream survival pathways, while fusions create hybrid proteins activating oncogenic pathways in a RAS-independent manner. Class 1 mutations respond well to BRAF and MEK inhibitors. Fusions are less common but are associated with complex treatment challenges due to unpredictable responses to standard therapies.[19-21] There are limited data on drug sensitivity profiles of tumors with BRAF fusion kinases due to their low prevalence and limited availability of cell lines harboring these alterations. BRAF fusions exhibit heterogeneous phenotypes and variable responses to MEK inhibition, as exemplified by trametinib. Vojnic *et al*. identified that BRAF rearrangements may be a mechanism of acquired resistance to EGFR inhibitors in four patients with EGFR-mutated lung cancer. *In vitro* studies demonstrated that induced AGK-BRAF fusion in various cell lines conferred resistance to osimertinib. The study further elucidated that a combination of trametinib and osimertinib synergistically inhibited proliferation in these cell lines.[18]

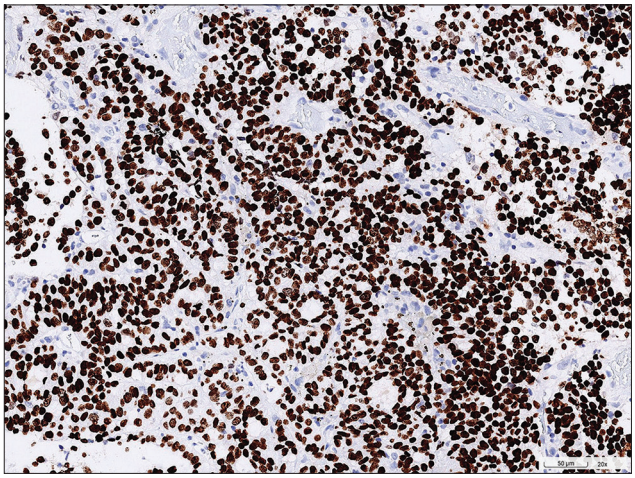

Figure 2: Thyroid transcription factor-1 (TTF-1) stain; brain tumor excision showed metastatic TTF1-positive adenocarcinoma cells with mixed cribriform and micropapillary patterns

Clinical evidence suggests the efficacy of MEK inhibitor monotherapy in patients with BRAF fusion-positive melanoma, and patients with metastatic melanoma harboring various BRAF fusions have been reported to respond to the MEK inhibitor trametinib.[14,22] MEK inhibition monotherapy has also been demonstrated to result in notable clinical responses in patients with RAF1 fusions in metastatic melanoma[23] and anaplastic pleomorphic xanthoastrocytoma with leptomeningeal dissemination.[24]

Two potential therapeutic strategies have emerged to address BRAF fusion-mediated resistance: combined MEK and EGFR inhibition and pan-RAF inhibition. The limited efficacy of currently Food and Drug Administration-approved BRAF inhibitors (e.g., vemurafenib and dabrafenib) against BRAF fusions underscores the need for novel therapeutic approaches. Preclinical studies of pan-RAF inhibitors such as LY3009120[25] and PLX8394[26] have yielded promising results, suggesting more effective targeting of BRAF fusions. *In vitro* studies have demonstrated a synergistic effect with combined MEK and EGFR inhibition in cell lines harboring both EGFR mutations and BRAF fusions,[18] potentially offering an immediate treatment strategy for patients presenting with this molecular profile.

In our case, identification of the AGK-BRAF fusion led to the use of trametinib, an MEK inhibitor. However, the limited clinical response highlights the need for further research into more effective treatment strategies for patients with this genetic profile and tumor heterogeneity. The rapid progression of disease in our patient, despite targeted therapy, emphasizes the aggressive nature of EGFR-mutant lung cancers with acquired BRAF fusions.

Our case underscores the critical role of serial genomic testing in identifying acquired resistance mechanisms and guiding subsequent treatment decisions. Future research should focus on developing more effective pan-RAF inhibitors, specifically targeting BRAF fusions and exploring combination therapies that

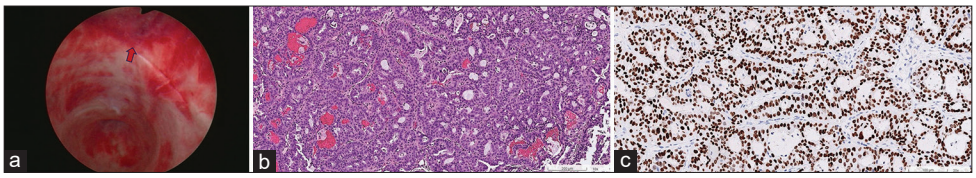

Figure 3: (a) Image of cystoscope, (arrow: metastatic lesion in bladder) (b) H and E stain, and (c) thyroid transcription factor-1 (TTF-1) stain; the bladder biopsy showed metastatic TTF1-positive adenocarcinoma cells with cribriform patterns

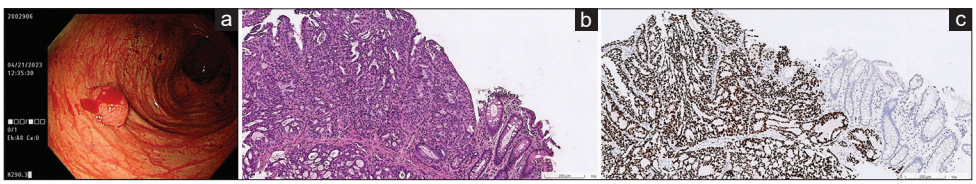

Figure 4: (a) Image of colonoscope, (b) H and E stain, and (c) thyroid transcription factor-1 (TTF-1) stain; the colon biopsy showed metastatic TTF1-positive adenocarcinoma cells with cribriform patterns

simultaneously target EGFR, MEK, and/or RAF pathways. In addition, efforts should be made to investigate potential biomarkers that could predict the development of BRAF fusion-mediated resistance, and clinical trials are needed to evaluate the efficacy of combined MEK and EGFR inhibition or pan-RAF inhibition in patients with EGFR-mutant NSCLC and acquired BRAF fusions.

In conclusion, this case report contributes to the growing body of evidence supporting BRAF fusions as a clinically relevant mechanism of acquired resistance to EGFR TKIs. It highlights the importance of comprehensive genomic profiling in guiding treatment decisions and the urgent need for novel therapeutic strategies to address this challenging resistance mechanism in EGFR-mutant NSCLC. Increased understanding of these complex genetic alterations may lead to the development of more effective, personalized treatment approaches that can significantly improve outcomes for patients with this difficult-to-treat subset of lung cancer.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflict of interest

There are no conflicts of interest.

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