CASE REPORT

Adenocarcinoma Harboring *EGFR-RAD51* Fusion Treated With Osimertinib: A Case Report

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ABSTRACT

EGFR mutations are among the most common driver mutations in lung adenocarcinoma. Rare alterations, such as the *EGFR-RAD51* fusion, respond to treatment with EGFR tyrosine kinase inhibitors but can be missed by limited genomic sequencing panels. Here, we report a case of metastatic lung adenocarcinoma in a never-smoker patient who initially did not have a targetable alteration identified on two different sequencing panels. The initial response to combination chemoimmunotherapy was short-lived. A rare *EGFR-RAD51* fusion was then identified using a more in-depth sequencing panel. The patient experienced a dramatic and durable response to osimertinib. This case highlights the rarity of *EGFR-RAD51* fusions, the efficacy of EGFR tyrosine kinase inhibitors, and the importance of a thorough search for targetable alterations in never-smokers with lung adenocarcinoma.

Keywords: Non–small cell lung cancer; EGFR fusion; TKI; Case report; NGS; Osimertinib

Introduction

Alterations in *EGFR* are common in NSCLC, with an incidence of more than 50% in never-smokers.[1] The *EGFR* alterations in NSCLC with the highest frequency are inframe deletions in exon 19 and point mutations in exon 21 (L858R), which lead to constitutive activation of the EGFR kinase domain. However, many other alterations exist, including atypical mutations and gene rearrangements. Here, we report a case of lung adenocarcinoma with a rare *EGFR-RAD51* fusion that responded dramatically to treatment with osimertinib.

Case Presentation

A 45-year-old man with no history of smoking presented with progressive back pain, chest discomfort, diplopia, and right eye ptosis. Imaging revealed a right cavernous sinus mass, innumerable bilateral pulmonary nodules, multifocal lymphadenopathy, and diffuse skeletal lesions. Left axillary lymph node biopsy revealed primary adenocarcinoma of the lung. The tumor proportion score for programmed death-ligand 1 (PD-L1) was less than 1%. Next-generation sequencing (NGS) performed on tissue using the Quest Diagnostics lung cancer panel did not detect any targetable alterations. Liquid biopsy using the Guardant360 CDx (Guardant, Redwood City, CA) revealed a KIT E69A variant of uncertain significance (Fig. 1).

He received one cycle of carboplatin and pemetrexed while awaiting NGS results, then was initiated on combination chemoimmunotherapy with carboplatin, pemetrexed, nivolumab, and ipilimumab once testing did not identify a targetable alteration. His condition progressively deteriorated—he began requiring supplemental oxygen, lost 10 kg, and had marked functional decline. Imaging before the third cycle of treatment revealed progressive disease with enlarging pulmonary infiltrates and new sites of bony metastases (Fig. 2).

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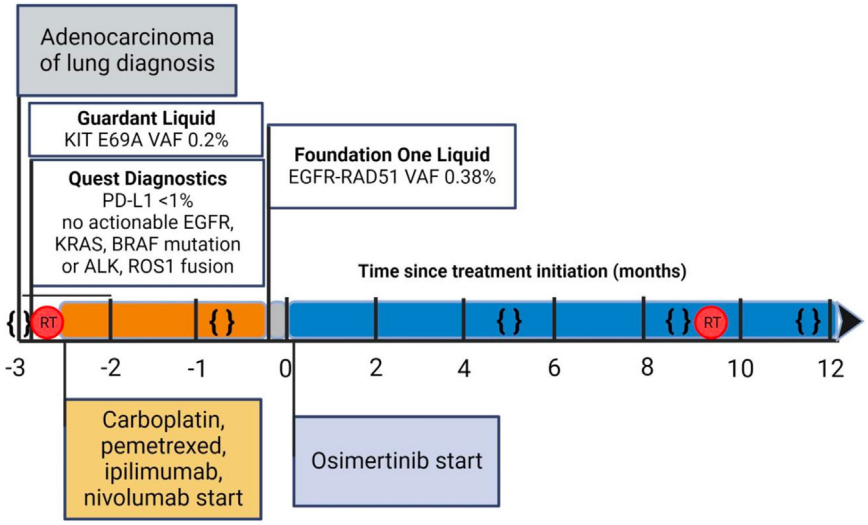

Figure 1. Swimmer plot illustration of the patient's treatment history and molecular profile, including palliative radiation treatment, chemoimmunotherapy until progressive disease, and treatment with osimertinib with partial response. { } denote CT scans during treatment. The light gray bar denotes a treatment holiday. CT, computed tomography; PD-L1, programmed death-ligand 1; RT, radiation therapy; VAF, variant allele frequency.

Repeat NGS was performed using the FoundationOne Liquid CDx (Foundation Medicine, Boston, MA) and revealed an *EGFR-RAD51* gene fusion with an allele frequency of 0.38%. He was switched from chemoimmunotherapy to osimertinib 80 mg daily. Within 1 month, he experienced dramatic symptom improvement. At 3 months, he returned to work and regained weight to baseline. Visual symptoms and cancer-related pain had resolved. Imaging revealed improvement in pulmonary nodularity, lymphadenopathy, and sclerosis of bony metastases. At 9 months, asymptomatic intracranial metastases were identified with stable systemic disease. He underwent gamma knife radiosurgery. Repeat FoundationOne Liquid CDx did not reveal acquired resistance mechanisms. *EGFR-RAD51* fusion was undetectable. No treatment-related adverse events, including pneumonitis, have occurred. At the last follow-up, approximately 1 year after initiation of osimertinib, imaging continued to reveal partial response and he remains on therapy to date.

Discussion

Reports of *EGFR* fusions are limited to case series and case reports. From a large commercial database of molecularly profiled patient tumors (Caris Life Sciences), we identified only two tumors, both NSCLC, harboring an *EGFR-RAD51* fusion detected by whole transcriptome sequencing, which highlights the rarity of these events. Konduri et al.[2] first described the *EGFR-RAD51* fusion in four patients. In preclinical studies, the EGFR-RAD51 protein activated downstream signaling through the MAPK and PI3K/AKT pathways, analogous to signaling by means of EGFR L858R. Growth in engineered cells expressing EGFR-RAD51 protein was inhibited by various EGFR tyrosine kinase inhibitors (TKIs) and therapeutic antibodies. Surprisingly, the autophosphorylation sites at the C-terminal tail of EGFR that are involved in activating downstream signaling were lost in the *EGFR-RAD51* fusion. However, the fusion product had less frequent turnover than the wild-type receptor owing to the lack of tyrosine 1045, which may account for its oncogenicity.[2]

The diagnosis of uncommon *EGFR* alterations can be complicated by limitations in the test selected. Many assays use an informed approach highlighting exons 18 to 21 in which mutations in *EGFR* most often occur. Such panels miss the *EGFR-RAD51* fusion because its breakpoint resides in intron 24. Clinicians may choose narrower assays because of differences in tissue availability, testing capabilities, and turnaround time. For example, RNA-based NGS testing is more effective in identifying fusions because of the lack of introns in mature RNA but requires higher-quality tissue samples. Here, the Guardant360 CDx only tests for single nucleotide variants, insertions, and deletions within the *EGFR* coding region but was chosen because of faster turnaround time and inadequacy of the tissue sample for RNA-based NGS. The FoundationOne Liquid CDx panel, which later identified the *EGFR-RAD51* fusion, includes intron coverage for the *EGFR* gene. In a study by Devarakonda et al.,[3] initial whole exome sequencing and RNA sequencing identified a known driver alteration in the RTK/RAS/RAF pathway in 65% of never-smokers with lung adenocarcinoma. Further analysis

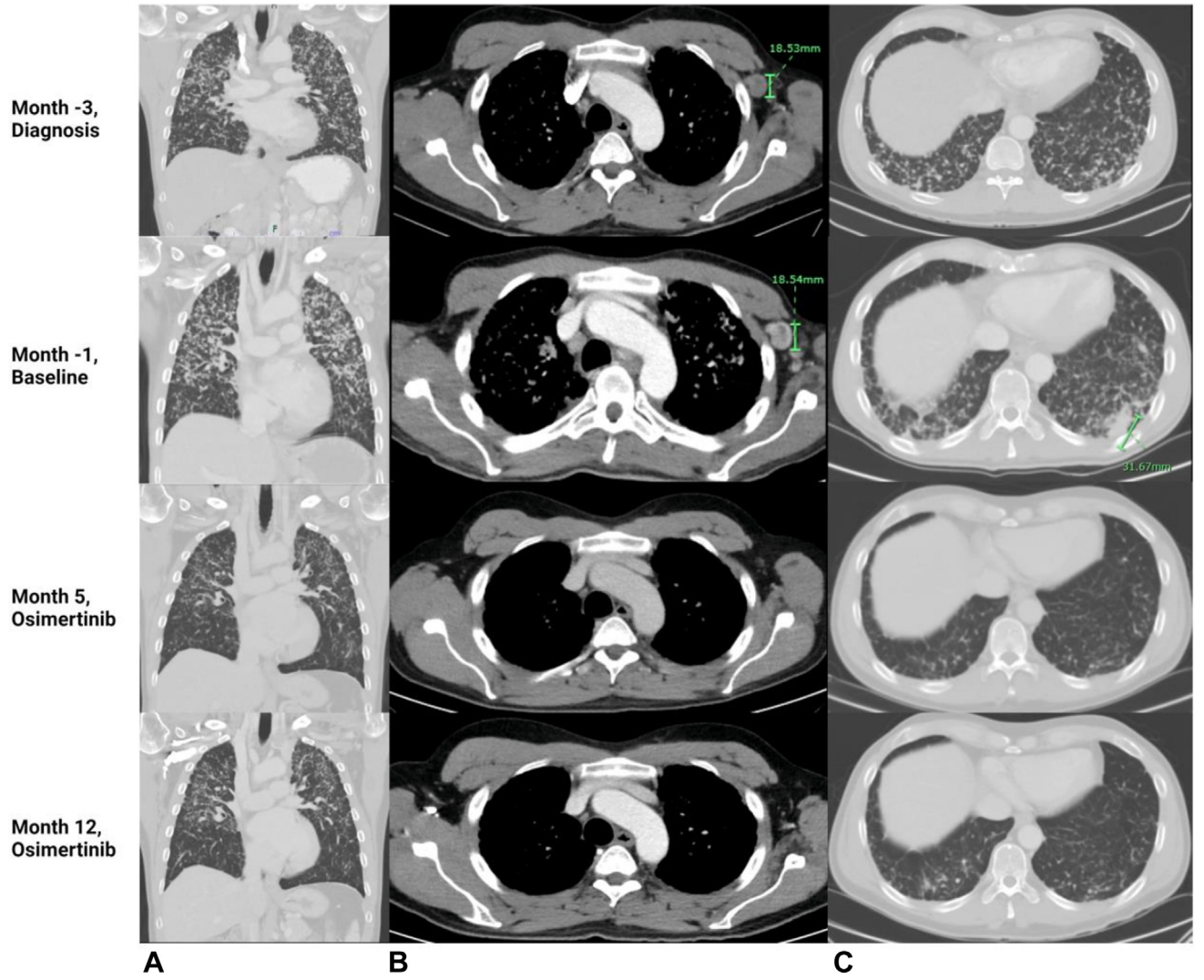

Figure 2. Computed tomography images of the (*A*) lung, (*B*) axillary nodes, and (*C*) lung bases at diagnosis, baseline (time of progression on chemoimmunotherapy), month 5 on osimertinib treatment, and month 12 on osimertinib treatment. Imaging revealed a reduction in diffuse lung parenchymal disease, left axillary adenopathy, and lung base nodules.

with fluorescent in situ hybridization and deep whole exome sequencing increased driver alteration detection to 81%.[3] Therefore, clinicians must understand the limitations of diagnostic modalities and consider more comprehensive testing in never-smokers with lung adenocarcinoma in which a driver mutation is not initially identified (Table 1).[4]

Unique *EGFR* alterations lead to different sensitivity profiles to EGFR TKIs and therapeutic antibodies. In the initial report of Konduri et al.[2] on the *EGFR-RAD51* fusion, four patients responded to erlotinib. A case series identified eight patients treated with EGFR TKIs, including gefinitib and erlotinib followed by osimertinib.[5]

Conclusion

We describe a case of metastatic lung adenocarcinoma with a rare *EGFR-RAD51* fusion not initially detected on more limited NGS panels, with a durable response to osimertinib after progression on chemoimmunotherapy. This case highlights the importance of a diligent search for rare but actionable genomic abnormalities, especially in never-smokers with lung adenocarcinoma. Clinicians must be aware of the limitations of often-used testing platforms and understand ways to broaden testing.

CRediT Authorship Contribution Statement

Sunny Y. Lai: Writing - original draft, Visualization.

Noah H. Richardson, Mya Tran: Writing - review & editing, Visualization.

Nasser H. Hanna: Writing - review & editing, Supervision.

Misty D. Shields: Conceptualization, Writing - review & editing, Visualization, Supervision.

Table 1. Strengths and Weaknesses of Common Molecular Testing Methods to Detect Fusions[4]

Test	Strengths	Weaknesses
DNA-based next-generation sequencing hybrid capture	• Can be performed on a limited tumor specimen • Cost-effective because of high throughput • Can determine the fusion partner and the exact breakpoint	• Unable to capture some fusions with a large intronic breakpoint • Does not provide information on transcription or expression
RNA-based next-generation sequencing	• Can capture transcribed fusions • Determines in-frame status in genes with multiple splice variants and transcriptional start sites	• Requires more or higher quality tissue than DNA-based next-generation sequencing • Highly sensitive to sample collection, fixation, and storage conditions
Immunohistochemistry	• Easy preparation • Inexpensive • Fast turnaround time • Does not require previous knowledge of the fusion partner	• Does not provide fusion partner or breakpoint information • False positives because of tissue-specific isoforms and endogenous expression of certain fusions in certain tissues
Break-apart fluorescence in situ hybridization	• Easy preparation • Inexpensive • Fast turnaround time • Does not require previous knowledge of the fusion partner	• Does not provide fusion partner or breakpoint information • Does not provide information on transcription or expression • False negatives because of the proximity of the target gene and fusion partner • Lack of validation for cutoff break-apart signaling for novel gene fusions

Disclosure

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The patient provided written consent for publication of this case report.

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