

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

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Abstract

Epidermal growth factor receptor (*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. We report a case of metastatic lung adenocarcinoma in a patient who is a never-smoker who initially did not have a targetable alteration identified on two different sequencing panels. 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, efficacy of *EGFR* TKIs, and importance of a thorough search for targetable alterations in never-smokers with lung adenocarcinoma.

Introduction

Alterations in *EGFR* are common in non-small cell lung cancer (NSCLC), with an incidence of >50% in never-smokers [1]. The *EGFR* alterations in NSCLC with the highest frequency are in-frame 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. 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 adenocarcinoma of lung primary. Tumor proportion score for PD-L1 was <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 revealed a KIT E69A variant of uncertain significance (**Figure 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 prior to the third cycle of treatment demonstrated progressive disease with enlarging pulmonary infiltrates and new sites of bony metastases (**Figure 2**).

Repeat NGS was performed using the FoundationOne Liquid CDx, 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 one month, he experienced dramatic symptom improvement. At three months, he returned to work and regained weight to baseline. Visual symptoms and cancer-related pain had resolved. Imaging demonstrated improvement in pulmonary nodularity, lymphadenopathy, and sclerosis of bony metastases. At nine 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

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adverse events, including pneumonitis, have occurred. At last follow-up, approximately one year from initiation of osimertinib, imaging continues 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. 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 via *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, due 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 utilize an informed approach highlighting exons 18-21 where mutations in *EGFR* most commonly occur. Such panels miss the *EGFR-RAD51* fusion because its breakpoint resides in intron 24. Clinicians may choose narrower assays due to differences in tissue availability, testing capabilities, and turnaround time. For example, RNA-based NGS testing is more effective in identifying fusions due to the absence 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 due to 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., 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 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**).

Unique *EGFR* alterations lead to different sensitivity profiles to *EGFR* TKIs and therapeutic antibodies. In Konduri's initial report of the *EGFR-RAD51* fusion, four patients responded to erlotinib [2]. A case series identified eight patients treated with *EGFR* TKIs, including gefitinib, and erlotinib followed by osimertinib [4].

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 commonly used testing platforms and understand ways to broaden testing.

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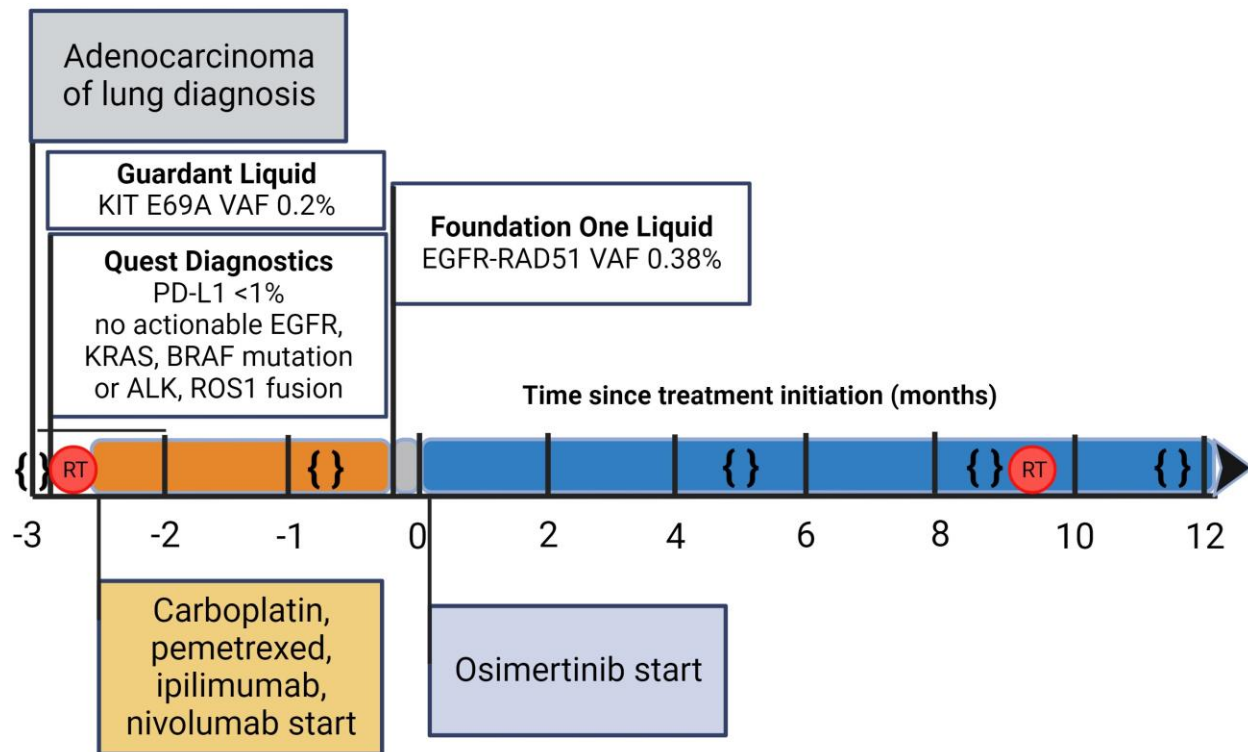


Figure 1: Swimmer plot illustration of the patient's treatment history and molecular profile, including palliative radiation treatment, chemoimmunotherapy until progressive disease, and treatment with osimertinib with partial response. { } denote CT scans during treatment. The light gray bar denotes treatment holiday. CT, computed tomography; RT, radiation therapy.

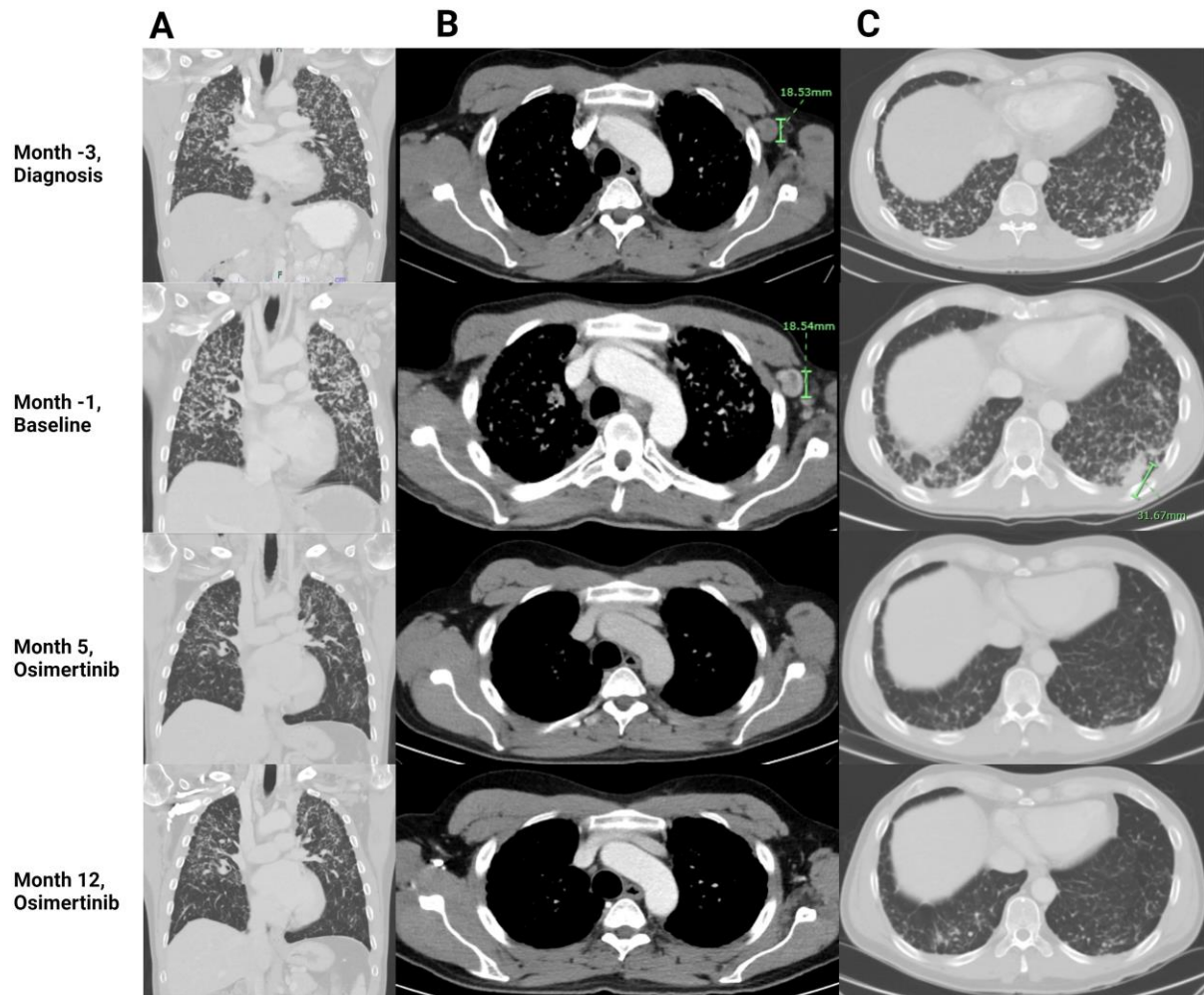


Figure 2: Computed tomography images of the (A) lung, (B) axillary nodes, and (C) lung bases at diagnosis, baseline (time of progression on chemoimmunotherapy), month five on osimertinib treatment, and month twelve on osimertinib treatment. Imaging revealed a reduction in diffuse lung parenchymal disease,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

Test	Strengths	Weaknesses
DNA-based next-generation sequencing hybrid capture	<ul style="list-style-type: none"> • Can be performed on a limited tumor specimen • Cost effective due to high throughput • Can determine the fusion partner and the exact breakpoint 	<ul style="list-style-type: none"> • Unable to capture some fusions with a large intronic breakpoint • Does not provide information on transcription or expression
RNA-based next-generation sequencing	<ul style="list-style-type: none"> • Can capture transcribed fusions • Determines in-frame status in genes with multiple splice variants and transcriptional start sites 	<ul style="list-style-type: none"> • Requires more or higher quality tissue than DNA-based next-generation sequencing • Highly sensitive to sample collection, fixation, and storage conditions
Immunohistochemistry	<ul style="list-style-type: none"> • Easy preparation • Inexpensive • Fast turnaround time • Does not require prior knowledge of the fusion partner 	<ul style="list-style-type: none"> • Does not provide fusion partner or breakpoint information • False positives due to tissue specific isoforms and endogenous expression of certain fusions in certain tissues
Break-apart fluorescence <i>in situ</i> hybridization	<ul style="list-style-type: none"> • Easy preparation • Inexpensive • Fast turnaround time • Does not require prior knowledge of the fusion partner 	<ul style="list-style-type: none"> • Does not provide fusion partner or breakpoint information • Does not provide information on transcription or expression • False negatives due to proximity of the target gene and fusion partner • Lack of validation for cut-off break apart signaling for novel gene fusions

Table 1: Strengths and weaknesses of common molecular testing methods to detect fusions. [5]

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CRedit Author Statement

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