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Effectiveness of EGFR-TKIs in a Patient with Lung Adenocarcinoma Harboring an *EGFR-RAD51* Fusion

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Abstract

Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (EGFR-TKIs) have become the first choice for patients with sensitive mutations and have significantly improved prognosis. *EGFR* exon 19 deletions and L858R mutation in exon 21 are the most common sensitive mutations in lung adenocarcinoma. With advances in detection technology, some rare variants of *EGFR* have been detected, including *EGFR* kinase domain duplications and *EGFR* fusions. Only a few reports have revealed the effectiveness of EGFR-TKIs in patients with these rare variants. In this study, we report a case of *EGFR-RAD51* fusion in lung adenocarcinoma that showed a response to icotinib; these findings provide additional support for the use of EGFR-TKIs for patients with these atypical variants. ***The Oncologist*** 2019;24:1027–1030

Key Points

- A young patient with lung adenocarcinoma harboring a rare *EGFR-RAD51* fusion who responded to icotinib with a PFS of longer than 15 months.
- All reported *EGFR-RAD51* fusions have the same breakpoints and show responses to EGFR-TKIs including icotinib, except for one patient who responded to chemotherapy.
- Although *EGFR* fusion is a rare *EGFR* variant type, the efficacy of EGFR-TKIs suggests the necessity for new detection technology, such as NGS, for patients with lung adenocarcinoma.
- The clinical usage of NGS could maximize the benefits of precision medicine in patients with cancer.
- The current case provides new evidence for the efficacy of icotinib in patients with the rare *EGFR-RAD51* fusion and *EGFR*-activating mutations.

Introduction

Lung cancer is the leading cause of cancer-related deaths. The main type of lung cancer is non-small cell lung cancer (NSCLC), which includes two major histological subtypes, adenocarcinoma and squamous cell carcinoma [1]. Genetic analyses have revealed driver genes in lung adenocarcinoma and have changed the treatment paradigm [2]. Epidermal growth factor receptor (*EGFR*) mutations are commonly associated with adenocarcinoma. The frequency of *EGFR* mutations differs between Western and Asia-Pacific regions (12% vs. 47%) [3], indicating that more patients with lung adenocarcinoma would benefit from EGFR-tyrosine kinase inhibitors (TKIs) in Asia than in other regions. Exon 19 deletions and L858R in *EGFR* are the most common variants with sensitivity to EGFR-TKIs [4]. Resistance mutations have also been identified, such as T790M and exon 20 insertions. Furthermore, rare genomic events can activate the kinase domain of EGFR, such as *EGFR* kinase domain duplications (EGFR-KDD) and *EGFR* rearrangements [5, 6]. Advanced detection technologies, such as next-generation sequencing (NGS), have facilitated the identification of rare variants. We present a case report of a patient with lung adenocarcinoma harboring a rare *EGFR-RAD51* fusion; treatment with icotinib resulted in a progression-free survival (PFS) of longer than 15 months. These results might help establish personalized treatment approaches for patients with rare *EGFR* fusions.

Patient Story

In a 26-year-old male patient with no smoking history or symptoms, the right lower lung exhibited a patchy appearance

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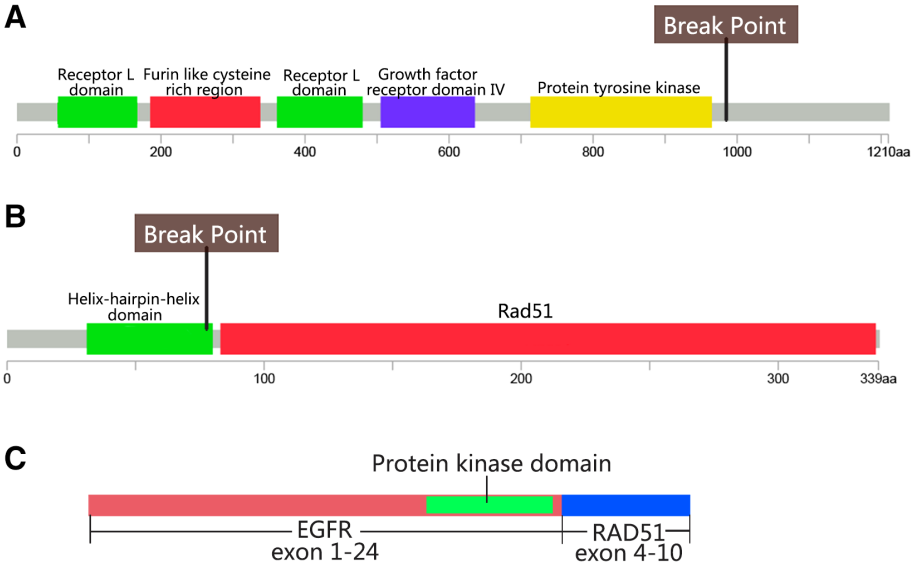

Figure 1. Schematic diagram of gene structure of *EGFR* and *RAD51*. Break points of *EGFR* and *RAD51* were shown in **(A)** and **(B)**. Schematic fusion protein was shown in **(C)**.

Table 1. Clinical characteristics of seven treated patients with *EGFR-RAD51* fusion lung adenocarcinoma

No	Age	Sex	Stage	Drug	Response	PFS, mo	Prior therapy	Concurrent alterations
1 [6]	35	F	IV	Erlotinib	PR	>8	No	*CDKN2A, CDKN2B, MYC*
2 [6]	21	F	IV	Erlotinib	PR	>5	RT	*CTNNB1, RANBP2, CDKN2B, TP53, CDKN2A*
3 [6]	38	M	IV	Erlotinib	PR	>6	CT	*RBM10, CHD4, MYC, MCL1, IKBKE, PIK3C2B, MDM4*
4 [6]	60	F	IV	Pemetrexed	PR	NA	RT+CT	*GRIN2A, ATR, ARID1A, FGF3, FGF4, CDKN2A, PDCD1LG2, CCND1, CD274, FGF19, EMSY, HGF, JAK2, CDKN2B*
5 [7]	48	M	IV	Erlotinib	PR	>5	No	*CDKN2A*
6 [8]	62	F	NA	Afatinib	PR	>6	CT + Nivolumab	NA
7	26	M	IV	Icotinib	PR	>15	CT	*TP53*

Abbreviations: CT, chemotherapy; NA, not available; PFS, progression-free survival; PR, partial response; RT, radiotherapy.

with an area of about 2.0 × 2.3 × 3.2 cm during a routine chest x-ray included in medical examination on October 24, 2016. An enhanced scan revealed that the density was not uniform, and the right oblique fissure and horizontal fissure exhibited pleural thickening. On November 25, 2016, the patient underwent thoracoscopic resection of the tumor in the right lower lobe and thoracoscopic electrocautery of pleural nodules. The postoperative pathology showed that the tumor in the right lower lobe was a 2 × 1.5 × 1.3 cm alveolar infiltrative adenocarcinoma involving the visceral pleura, invading the cartilage of the bronchial wall, invading the nerve and vessel wall, and without clear intravascular thrombosis. The chest wall nodules showed infiltrating adenocarcinoma components in fibers and adipose tissues. Surface nodules on the right middle lobe contained a few invasive adenocarcinoma components. The diagnosis was right lung adenocarcinoma (pT4NxM1, stage IV). The patient underwent thoracic perfusion with cisplatin and pemetrexed + cisplatin chemotherapy until March 2017. However, control of the pleural effusion and chest pain was poor.

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A surgical tissue sample was obtained for NGS using a panel of 47 cancer-related genes (OrigiMed, Shanghai, China) on January 11, 2017. *TP53* mutation (p.G244D) and *EGFR-RAD51* fusion were detected.

EGFR-RAD51 was a fusion of exons 1–24 of *EGFR* with exons 4–10 of *RAD51* (Fig. 1), resulting in the deletion of the *EGFR* C-terminal CBL binding domain, which is related to EGFR degradation. This fusion retains the complete kinase domain of EGFR and could activate downstream signaling pathways via MAPK and PI3K/Akt. *EGFR-RAD51* fusion cells are sensitive to the EGFR inhibitor erlotinib, afatinib, and the EGFR monoclonal antibody cetuximab [6].

In addition to this case, seven clinically treated *EGFR-RAD51* fusion cases have been reported (Table 1) [6–8]. All patients were diagnosed at stage IV, except for one patient with an unknown stage and wild-type EGFR at initial diagnosis but an *EGFR-RAD51* fusion during metastasis. All reported breakpoints of the *EGFR-RAD51* fusion are in intron 24 of

Table 2. Break points of EGFR fusion/rearrangement detected in the Chinese patients with lung adenocarcinoma

ID	Fusion/rearrangement	Reference transcript	Break points of EGFR
1	*EGFR-RAD51*	*RAD51*(NM_002875); *EGFR*(NM_005228)	intron24
2	*EGFR*-KDD	*EGFR*(NM_005228)	intron17, intron25
3	*EGFR*-KDD	*EGFR*(NM_005228)	intron17, intron25
4	*EGFR-ZNF713*	*EGFR*(NM005228); *ZNF713*(NM182633)	intron2
5	*EGFR-YAP1*	*EGFR*(NM_005228); *YAP1*(NM_006106)	intron26
6	*USP42-EGFR*	*USP42*(NM_032172); *EGFR*(NM_005228)	intron27
7	LINC01446-*EGFR*	LINC01446(NR_038371); *EGFR*(NM_005228)	intron15
8	*EGFR*-intergenic	*EGFR*(NM_005228)	intron25
9	*EGFR*-intergenic	*EGFR*(NM_005228)	intron7
10	*EGFR*-intergenic	*EGFR*(NM_005228)	intron7
11	*EGFR*-intergenic	*EGFR*(NM_005228)	intron15

Abbreviations: *EGFR*, epidermal growth factor receptor; ID, identification.

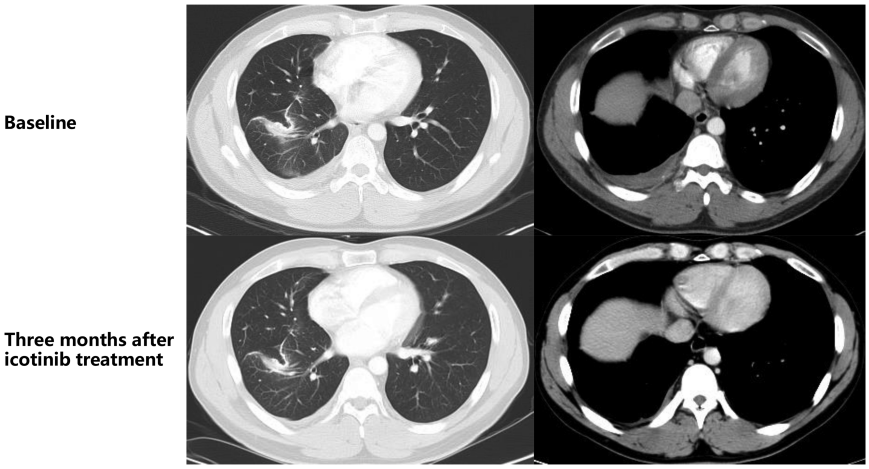

Figure 2. Imaging evaluation of the therapeutic effects of targeted therapy.

EGFR and intron 3 of *RAD51*, resulting in the fusion of *EGFR* exons 1–24 and *RAD51* exons 4–10. One patient showed a continuous response to chemotherapy. The other five patients showed partial responses to EGFR-TKIs, including erlotinib (4 patients) and afatinib (1 patient).

Fusions and rearrangements are rare genomic events in *EGFR*. They are relatively common (7.6%, 11/185) in glioblastoma, including *EGFR-SEPT14* and *EGFR-PSPH* fusions [9]. *EGFR*vIII (n = 65) generated by an intragenic rearrangement resulting in the deletion of exons 2–7 is a common rearrangement [10]. Raez summarized *EGFR* fusion based on publicly available genomic data and found a frequency of 0.05% in Foundation Medicine NSCLC data and 0.13% in MSK-IMPACT NSCLC data [8]. Using data from OrigiMed, we found an *EGFR* fusion/rearrangement frequency of 1.1% (11/989) in Chinese patients with lung adenocarcinoma. We further analyzed the break points of all *EGFR* fusion/rearrangements in OrigiMed (Table 2). Along with the reported *EGFR-RAD51* fusion and *EGFR*-KDD (patients 1–3 in Table 2), we found eight new *EGFR* rearrangements. In addition to the previously established breakpoints in *EGFR* exon 23 through intron 25 [6], we found three *EGFR* rearrangements with new partners and EGFR breakpoints in introns 2, 26, and 27 (patients 4–6 in Table 2). We also found one *EGFR* rearrangement with a lncRNA and four EGFR rearrangements involving intergenic regions, with breakpoints in *EGFR* introns 7, 15, and 25 (patients 7–11 in Table 2). These results emphasize the advantage of NGS for finding new variants, but their oncogenic potential and clinical significance need further exploration.

EGFR fusions are rare in NSCLC. Gene fusion detection techniques vary with respect to sensitivity and specificity [11, 12]. Immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and quantitative polymerase chain reaction (qPCR) have various limitations for the accurate discovery and detection of rare fusions. IHC and FISH yield false-positive and false-negative results. Break-apart FISH cannot assess the fusion partner of the target gene. Additionally, FISH is unrealistic for screening rare gene fusions, such as *EGFR* fusions, in clinical practice. qPCR can only detect known fusion types; its high specificity and low sensitivity limit its use for the discovery of new fusions and the screening of rare fusions. Targeted panel sequencing covering common fusion breakpoints located in intronic regions could provide information about known fusion types and could be helpful for finding new fusion types. Considered the efficiency of targeted therapies for some rare gene

fusions and the importance of screening multiple gene variants simultaneously in clinical practice, NGS might be the optimal choice in certain cases (e.g., for patients with lung adenocarcinoma).

Icotinib (Conmana, Betta Pharmaceuticals Co., Ltd., Hangzhou, China) is a self-developed first-generation EGFR-TKI and has been widely used in clinics in China [13]. A phase III ICOGEN trial proved its noninferiority to gefitinib in terms of PFS, and it was approved for patients with NSCLC by the China Food and Drug Administration [14]. The result of a network meta-analysis showed that icotinib had similar effectiveness to geftinib and erlotinib for the treatment of patients with *EGFR*-mutated NSCLC [15].

Patient Update

The imaging review on March 27, 2017, revealed pleural effusion and right interlobular pleural nodules. On March 28, 2017, oral icotinib was started. One week later, the chest pain was released. Three months later, chest CT showed a reduction in right interlobular pleural nodules and no pleural effusion, and the symptom of chest pain was significantly relieved (Fig. 2). The patient continued to use icotinib (as of June 13, 2018) with good disease control and no pleural effusion. The PFS was longer than 15 months.

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Glossary of Genomic Terms and Nomenclature

Fusion/Rearrangement: Recombination of two unlinked segments of human DNA, exhibited as sequencing reads uniquely aligned to two different genes or tow apart DNA segments.

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Collection and/or assembly of data: Xuemei Zhang
Data analysis and interpretation: Honglin Guo, Junping Shi
Manuscript writing: Honglin Guo, Junping Shi
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Disclosures

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