Case Report

EGFR-RAD51 gene fusion NSCLC responsiveness to different generation EGFR-TKIs: two cases and review of the literature

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Abstract: Epidermal growth factor receptor (*EGFR*) gene fusions represent an extremely rare aberration, occurring in approximately 0.05–0.13% non-small cell lung cancer (NSCLC) patients. *RAD51* is the most frequently involved partner gene in *EGFR* fusions, but other fusion partner genes have been described. To date, a considerable number of next-generation sequencing (NGS) panels still cannot detect these alterations due to the position of the breakpoint site, mainly involving intron 24 of *EGFR*. Current evidences show that such gene alteration is more likely to occur in lung adenocarcinomas of young, female, non-smoker patients. Also, brain metastases are frequently reported in these patients. Only very few cases in literature described clinical characteristics and outcomes of patients harboring *EGFR* gene fusions, reporting responses to 1st generation *EGFR* tyrosine kinase inhibitors (TKIs). Herein, we report the case of two young non-smoker females with metastatic NSCLC harboring *EGFR-RAD51* gene fusion, detected by FoundationOne DX1 assay, who responded to *EGFR* TKIs. The first patient initially received erlotinib, then switched to osimertinib for renal toxicity, while the second was treated with gefitinib. This is, to our knowledge, the first report describing response to the 3rd *EGFR* TKI osimertinib. Our experience highlights the need of a broader molecular profiling in young or never smoker NSCLC patients without detectable molecular aberration using standard NGS panels. Finally, further studies to assess the real prevalence of *EGFR* gene fusions and their spectrum of sensitivity to different *EGFR* TKIs are needed.

Keywords: Epidermal growth factor receptor (*EGFR*) gene fusion; *RAD51*; non-small cell lung cancer (NSCLC); tyrosine kinase inhibitor (TKI); case report

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Introduction

Epidermal growth factor receptor (*EGFR*) gene mutations account for around 15% of non-small cell lung cancer (NSCLC) in Caucasian patients (1). They most commonly occur as in-frame deletion in exon 19 or point mutation in exon 21 (L858R), conferring constitutive activation of *EGFR* tyrosine kinase domain. Following the implementation of *EGFR* tyrosine kinase inhibitors (TKIs) as the gold standard first-line therapy in this molecularly distinct subgroup of advanced NSCLC patients, testing for *EGFR* mutations has become standard practice, especially in non-squamous histology (1-5). The recent introduction of different next-generation sequencing (NGS) platforms has improved the turnaround time and widened the molecular testing of NSCLC, allowing to identify rarer genetic alterations capable of driving cancer proliferation. As part of them,

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EGFR gene fusions represent an extremely rare finding, with a prevalence of around 0.05–0.13% (6). The most frequent *EGFR* fusion partner gene is *RAD51*, but *PURB*, *ANXA2*, *KIF5B* and *SEPT14* have been reported as well (7-9). *RAD51* encodes for a protein involved in DNA-damage response and repair (DDR) mechanism and homologous recombination (HR). Breakpoints involve intron 24 of *EGFR* and intron 3 of *RAD51*, resulting in the fusion of *EGFR* exons 1–24 and *RAD51* exons 4–10. Interestingly, all NSCLC patients with *EGFR-RAD51* fusion responded to erlotinib (6). Few additional case reports described the role of *EGFR-RAD51* fusion in NSCLC patients, confirming its sensitivity to standard EGFR-TKIs (9-11). We present the following case series in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-888/rc).

Case presentation

Case #1

A 29-year-old non-smoker female was diagnosed in October 2019 with metastatic adenocarcinoma of the left lung (TTF-1+, Napsin-A+) following diagnostic assessment for dry cough and shoulder pain. Computed tomography (CT) scan showed secondary lesions involving lungs, bones, brain, soft tissues and lymph nodes. Programmed death ligand-1 (PD-L1) expression (clone SP263, Ventana) was negative (tumor proportion score, TPS <1%), and the baseline NGS performed on a nodal biopsy with the Oncomine Focus Assay—ThermoFisher Scientific (Kit RUO; Pleasanton, CA, USA) did not show gene aberrations.

The patient received the combination of chemotherapy (cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 every 3 weeks) and immunotherapy (pembrolizumab 200 mg every 3 weeks) as first-line treatment, obtaining clinical benefit and an objective partial response (PR) at CT scan imaging performed after the completion of induction phase (4 cycles). Maintenance treatment with pembrolizumab and pemetrexed was then started. A CT scan performed after 4 cycles showed progressive disease (PD) on lungs, brain and lymph nodes. Considering the maintained good performance status and the absence of symptomatic disease, the treatment was continued beyond progression and whole-brain radiation therapy (20 Gy/5 fractions) was performed.

The patient underwent a new biopsy on a left shoulder muscle metastatic nodule and a new molecular analysis was attempted using the same NGS panel. Again, no genetic aberration was detected. However, taking into account patient's young age and non-smoking status, a new biopsy on mediastinal lymph node was performed to obtain representative tumor tissue for FoundationOne DX1 panel which detected the presence of an *EGFR-RAD51* gene fusion. Concurrent cancer-related alterations were also found in the following genes: adenomatous polyposis coli (*APC*) loss; *SMAD* family member 4 (*SMAD4*_K340E); ataxia telangiectasia and Rad3-related protein (*ATR*_E1685); phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*, H450_P458del). The tumor mutational burden (TMB) was 10.09 Mut/Mb.

In light of existing literature, first-generation EGFR-TKI erlotinib (150 mg daily, then reduced to 100 mg daily due to recurrent grade 2 hyperbilirubinemia) was administered leading to a PR on all tumor sites, including brain, after only three weeks from treatment initiation (*Figure 1*). A progressive increase of serum creatinine (1.97 mg/dL) and worsening of glomerular filtration rate (33 mL/min according to Chronic Kidney Disease Epidemiology Collaboration, CDK-EPI) led to erlotinib discontinuation after two months of treatment. Renal biopsy showed severe chronic tubulointerstitial nephritis, consistent with karyomegalic nephropathy, probably related to prior chemo-immunotherapy. The third generation TKI osimertinib (80 mg daily) was then administered, with further tumor response at the subsequent restaging imaging. After 12 months from the beginning of EGFR-TKI, the treatment is still ongoing.

Case #2

In August 2019, a 37-year-old never-smoker woman was referred to the emergency room complaining of worsening dyspnea. The patient had no medical history except for autoimmune hypothyroidism. Upon admission, a chest CT scan showed massive pleural effusion with multiple pulmonary nodules spread to both lungs. Pleural effusion drainage and lung biopsy were performed. Based on histological examination and immunohistochemistry (TTF-1+, Napsin-A+, and cytokeratin 7+) assays the diagnosis was suggestive of pulmonary adenocarcinoma with mucinous pattern, PD-L1 (clone 22C3 pharmDx) positive (TPS 20%). Molecular analysis by using FoundationOne DX1 panel allowed to detect *EGFR-RAD51* fusion and tumor protein P53 (*TP53*_ E294) mutation; no other known cancer-related gene alterations were identified. The TMB was 2 Mut/Mb.

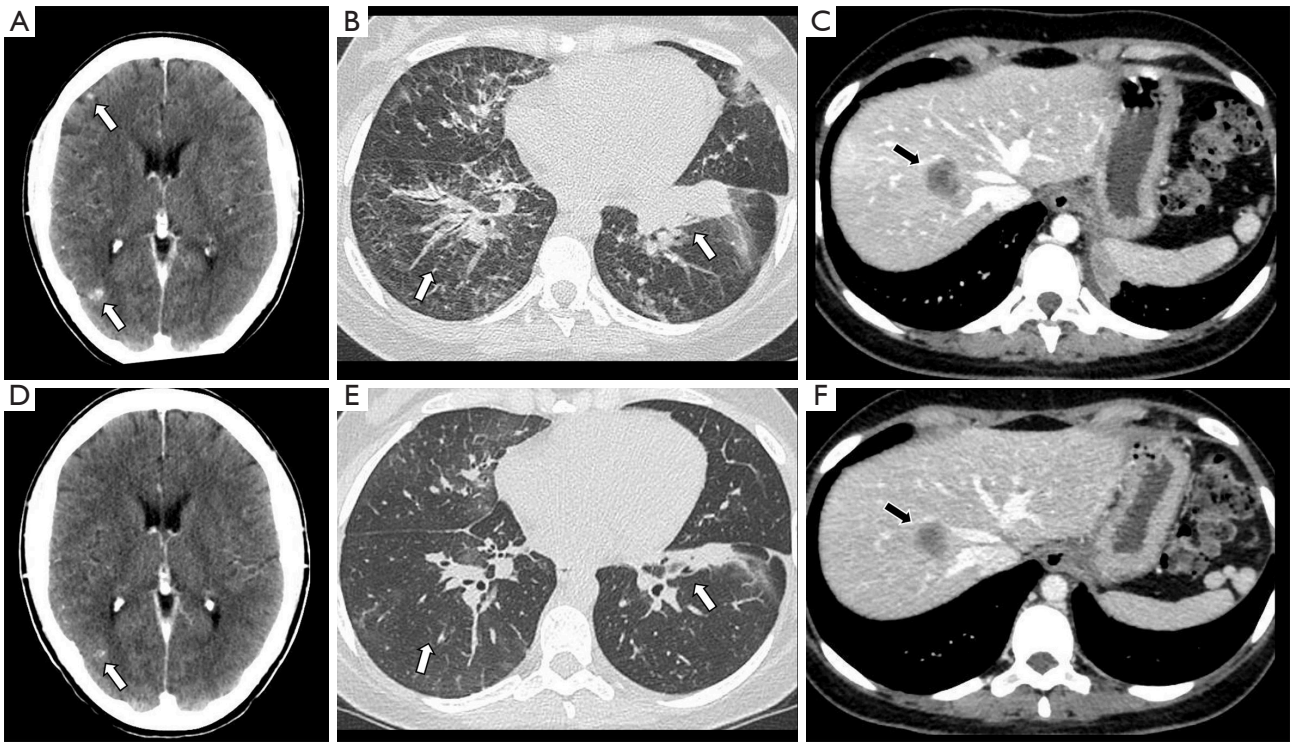

Figure 1 CT scans of case #1 performed before the initiation of the therapy with erlotinib (A-C) and after three weeks of treatment (D-F), showing PR on brain, lungs and liver lesions, see arrows. CT, computed tomography; PR, partial response.

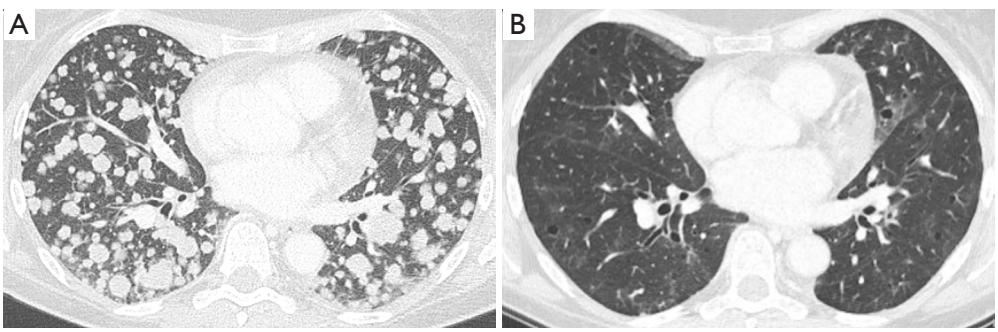

Figure 2 CT scans of case #2 performed before the initiation of the therapy with gefitinib (A) and after three months of treatment (B), showing CR. CT, computed tomography; CR, complete response.

The patient, therefore, started first-line treatment with first-generation EGFR-TKI gefitinib. Within few weeks, dyspnea improved considerably, and after three months a CT scan showed a complete response (CR) (*Figure 2*). The treatment was well tolerated, and no serious adverse event occurred (grade 2 skin rash and grade 1 diarrhea).

Unfortunately, after one year, in September 2020 a new CT scan showed PD (bilateral lung and single brain metastasis). The patient had chest pain and dyspnea. No new molecular assay on tissue or liquid re-biopsy by FoundationOne DX1 panel was performed because it was not available at that time. A customized gene sequencing panel was performed on liquid biopsy that confirmed the presence of *TP53* mutation along with hepatocyte growth factor (*HGF*) amplification. Single brain lesion was treated by stereotactic radiotherapy (27 Gy/3 fractions). Therefore, the patient started chemo-immunotherapy (cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 plus pembrolizumab

200 mg every 3 weeks) as second-line therapy. Clinical improvement in respiratory symptoms was observed during the first month from the beginning of the treatment. The first radiological assessment documented a PR, with a reduction of pulmonary nodules and pleural effusion. To date, the patient continues the treatment with excellent tolerance (only grade 1 asthenia and no immune-related adverse event) and no evidence of disease 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 Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Konduri *et al.* (6) first described *EGFR-RAD51* gene fusion in NSCLC, reporting a case series comprising four patients with NSCLC harboring this extremely rare aberration. They demonstrated in preclinical studies that *EGFR-RAD51* fusion creates active dimers and activates the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase/protein kinase B/Akt (PI3K/AKT) pathways to mediate downstream signaling. Surprisingly, *EGFR-RAD51* fusion lacks several autophosphorylation sites in the C-terminal tail of *EGFR*, which represent docking sites for adaptor proteins and play an important role in EGFR proliferation signaling. The preserved ability to activate downstream pathways of *EGFR-RAD51* fusion gene may thus be explained by the presence of tyrosine 845, another phosphorylation site within the kinase domain that is necessary for *EGFR* function and transformation in NSCLC (6). Moreover, the lack of tyrosine 1045, a binding site to mediate *EGFR* degradation, provides higher stability and lower degradation rate compared to *EGFR* wild type receptor.

EGFR-RAD51 gene fusion involves *EGFR* exons 1–24 and *RAD51* exons 4–10 through breakpoints in *EGFR* intron 24 and *RAD51* intron 3 (6). However, routinely used genetic assays usually search for aberrations between exons 18 and 21, which represent by far the most commonly altered sites in the *EGFR* gene. This explains why *EGFR-RAD51* fusion is often undetected.

To our knowledge, a total of 10 cases of patients harboring *EGFR-RAD51* fusion are reported in literature, included our two patients (6,9-12). All of them had adenocarcinoma histology. The majority were females (70%), young (median age: 36.5 years; range, 21–62 years), never or former light smokers (70%), and had brain metastases (70%). Coexisting tumor gene alterations and further patients' details are summarized in *Table 1*. Eight out of 10 patients received an EGFR-TKI as first- or further lines of treatment. All EGFR-TKIs

Table 1 Characteristics of patients harboring the *EGFR-RAD51* gene fusion

Patient No.	Ethnicity	Age/ gender	Smoking status	Histology	Disease sites	Other genetic alterations (including VUS)	Prior treatment	EGFR TKI	Best response
1	Caucasian	29/F	Never	ADC	Lungs; liver; bones; brain; soft tissues; lymph nodes	*APC* loss; *SMAD4* K340E; *ATR* E1685*; *PIK3CA* H450_P458del; *ERCC4* amplification; *CREBBP* amplification; *MSH6* T1243S; *CYP17A1* F384I; *INPP4B* A52S; *PTCH1* V619I; *EGFR* H1156P; *FANCA* V230I; *WHSC1* S808C; *ATR* H1294Y; *ATM* D894H; *JAK3* E183Q	PEM/MTA/ CDDP	ERL followed by OSI	PR
2	Caucasian	37/F	Never	ADC	Pleura; lungs; lymph nodes	*TP53* E294 *DDR1* P501L; *EPHB1* P419S; *RPTOR* S637F; *GRM3* A291T; *SMO* E740G; *HGF* amplification (at PD)	None	GEF	CR
3 (6)	Asian	35/F	Never	ADC	Bone; brain; adrenal gland breast; peritoneum; eye; lymph nodes	*CDKN2A* loss; *CDKN2B* loss; *MYC* amplification	None	ERL	PR

Table 1 (*continued*)

Table 1 (*continued*)

Patient No.	Ethnicity	Age/ gender	Smoking status	Histology	Disease sites	Other genetic alterations (including VUS)	Prior treatment	EGFR TKI	Best response
4 (6)	Caucasian	21/F	Current	ADC	Bone; brain; lymph nodes	*CTNNB1* T41A; *RANBP2* T951M; *CDKN2B* loss	None	ERL	PR
5 (6)	Caucasian	38/M	Former	ADC	Lungs; pleura; bone; lymph nodes	*RBM10* S570fs*133; *CHD4* D316H; *MYC* amplification; *MCL1* amplification; *IKBKE* amplification; *PIK3C2B* amplification; *MDM4* amplification	MTA/CDDP	ERL	PR
6 (6)	Caucasian	60/F	Never	ADC	Brain; lymph nodes	*GRIN2A* R1318W; *ATR* Q2408*; *ARID1A* P1484fs*10; *FGF3* amplification; *FGF4* amplification; *CDKN2A* loss; *PDCD1LG2* amplification; *CCND1* amplification; *CD274* amplification; *FGF19* amplification; *EMSY* amplification; *HGF* amplification; *JAK2* amplification; *CDKN2B* loss	MTA/ CBDCA	None	PR
7 (9)	Asian	36/F	Never	ADC	Lungs; bone; brain; pleura; pericardium	*EGFR-ANXA2* fusion; *ATR* exon 44 mutation; *BRCA2* exon 19 mutation	LOBA/MTA/ TEM/BEV	None	PR
8 (10)	Caucasian	62/F	Never	ADC	Brain; pleura	N.A.	1st-L: BEV/MTA/ CBDCA; 2nd-L: NIVO; 3rd-L: TAX	AFA	PR
9 (11)	Asian	26/M	Never	ADC	Pleura	*TP53* G244D	MTA/CDDP	ICO	PR
10 (12)	Asian	48/M	Former	ADC	Brain; lymph nodes	*CDKN2A* loss	None	ERL	PR

EGFR, epidermal growth factor receptor; VUS, variants of unknown significance; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; F, female; ADC, adenocarcinoma; *APC*, adenomatous polyposis coli; *SMAD4*, SMAD family member 4; *ATR*, ataxia telangiectasia and Rad3-related protein; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *ERCC4*, ERCC Excision Repair 4; *CREBBP*, cyclic adenosine monophosphate response element binding protein; *MSH6*, MutS Homolog 6; *CYP17A1*, cytochrome P450 family 17 subfamily A member 1; *INPP4B*, inositol polyphosphate-4-phosphatase type II B; *PTCH1*, protein patched homolog 1; *FANCA*, Fanconi anaemia, complementation group A; *WHSC1*, Wolf-Hirschhorn syndrome candidate 1; *ATM*, ataxia-telangiectasia mutated; *JAK3*, Janus Kinase 3; PEM, pembrolizumab; MTA, pemetrexed; CDDP, cisplatin; ERL, erlotinib; OSI, osimertinib; PR, partial response; *TP53*, tumor protein P53; *DDR1*, Discoidin Domain Receptor Tyrosine Kinase 1; *EPHB1*, Ephrin type-B receptor 1; *RPTOR*, Regulatory Associated Protein Of MTOR Complex 1; *GRM3*, Glutamate Metabotropic Receptor 3; *SMO*, Smoothened homolog precursor; *HGF*, hepatocyte growth factor; PD, progressive disease; GEF, gefitinib; CR, complete response; *CDKN2A*, cyclin dependent kinase inhibitor 2A; *CDKN2B*, cyclin dependent kinase inhibitor 2B; *MYC*, MYC Proto-Oncogene; *CTNNB1*, Catenin (Cadherin-Associated Protein) Beta 1; *RANBP2*, RAN Binding Protein 2; M, male; *RBM10*, RNA Binding Motif Protein 10; *CHD4*, Chromodomain Helicase DNA Binding Protein 4; *MCL1*, Myeloid Cell Leukemia Sequence 1; *IKBKE*, Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Epsilon; *PIK3C2B*, Phosphatidylinositol-4-Phosphate 3-Kinase Catalytic Subunit Type 2 Beta; *MDM4*, Mouse Double Minute 4; *GRIN2A*, Glutamate Ionotropic Receptor NMDA Type Subunit 2A; *ARID1A*, AT-rich interactive domain-containing protein 1A; *FGF3*, fibroblast growth factor 3; *FGF4*, fibroblast growth factor 4; *PDCD1LG2*, Programmed Cell Death 1 Ligand 2; *CCND1*, Cyclin D1; *CD274*, Programmed Cell Death 1 Ligand 1; *FGF19*, fibroblast growth factor 19; *EMSY*, EMSY Transcriptional Repressor, BRCA2 Interacting; *JAK2*, Janus Kinase 2; CBDCA, carboplatin; *ANXA2*, Annexin A2; *BRCA2*, Breast And Ovarian Cancer Susceptibility Protein 2; LOBA, lobaplatin; TEM, temozolomide; BEV, bevacizumab; N.A, not available; L, line; NIVO, nivolumab; TAX, docetaxel; AFA, afatinib; ICO, icotinib.

led to radiological tumor response (7 PRs + 1 CR). The remaining 2 patients were treated with chemotherapy and obtained a PR. In preclinical models, *EGFR-RAD51* cell lines treated with several EGFR-TKIs (erlotinib, afatinib and osimertinib), as well as *EGFR* monoclonal antibody (cetuximab), showed significant inhibition of tumor cell growth (6). However, in clinical practice, no previous data reported the sensitivity of NSCLC patients harboring *EGFR-RAD51* fusion to third-generation, irreversible EGFR-TKI osimertinib. The therapeutic implication of the involvement of *RAD51* as fusion partner gene has never been explored, but the role of poly-ADP-ribose polymerase inhibitors (PARPi) and other agents acting on DDR genes warrant investigation as therapeutic options for these patients, aside from EGFR-TKIs.

The current case series represents the first documented evidence of clinical activity of osimertinib and gefitinib in two NSCLC patients harboring *EGFR-RAD51* gene fusion. Considering its great intracranial activity and tolerability, the 3rd generation *EGFR* inhibitor could represent the preferred option, especially in case of brain metastasis. This work highlights the importance of employing genetic assays broad-panel NGS assays when standard panels do not show gene aberrations, especially in case of young and non-smoker patients with adenocarcinoma histology. Further studies and a routine use of wider molecular profiling would allow to assess the real prevalence of the *EGFR-RAD51* fusion, the outcome of patients treated with EGFR-TKIs, and the possible clinical and therapeutic implication of *RAD51* as fusion partner gene.

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Footnote

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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 Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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