Case Report

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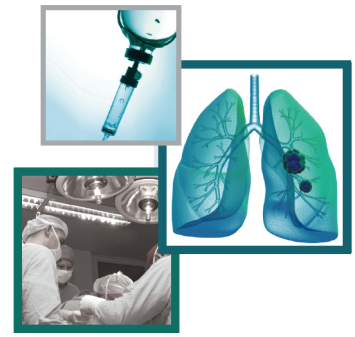

Exceptional response to afatinib in a patient with persistent G719A *EGFR*-mutant NSCLC

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Practice points

- Compound mutations in *EGFR*-mutant NSCLC is common.
- Optimal therapy in patients with compound mutations is not known.
- Osimertinib is effective against common activating *EGFR* mutations, the resistance mutation T790M and some uncommon mutations.
- Afatinib has demonstrated clinical benefit in patients with common, uncommon and compound *EGFR* mutations except T790M.
- More than one type of tyrosine kinase inhibitor targeting different clones may be required to control disease.
- Serial genomic profiling with next generation sequencing in patients with *EGFR*-mutant NSCLC is important to track clonal evolution during treatment.

We present a patient with metastatic NSCLC harboring a compound *EGFR* mutation with co-occurring G719A and T790M mutation. T790M mutation was treatment emergent mutation when patient was on early generation tyrosine kinase inhibitors. Initial Guardant 360 showed that G719A was the dominant clone. Following, osimertinib, the patient had only a radiographic disease stabilization and then developed both clinical and radiographic progression. On progression, T790M was undetectable but G719A continued to be the dominant clone. Subsequent administration of afatinib led to a clinical and radiological response. To our knowledge, this is the first case report describing co-occurrence of *EGFR* G719A and T790M mutations and the clonal evolution during treatment with anti-*EGFR* therapies.

Plain language summary: Drugs taken by mouth that target the *EGFR* gene are very effective in patients with NSCLC who have common mutations (changes) that affect the *EGFR* gene (known as 'sensitizing mutations'). However, some patients may have less common mutations that can cause their response to these drugs to vary. In rare cases, a patient may have two different *EGFR* mutations that affect their response to these drugs in different ways. In this Case Report we present a patient with advanced NSCLC who had both T790M (a common mutation) and G719A (an uncommon mutation). T790M was most likely a resistance mutation following treatment with gefitnib. Subsequent treatment with osimertinib gave short-term benefit and liquid biopsy (examination of fluid from the patient's body) carried out when the disease progressed showed the T790M clone had been eliminated but that the G719A mutation was still present. Treatment with afatinib then led to long-term treatment response. This case highlights the potential for using liquid biopsy for monitoring changes in mutations in *EGFR*-mutant NSCLC.

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Keywords: afatinib • compound mutations • *EGFR* mutation • liquid biopsy • mutations • next-generation sequencing • NSCLC • osimertinib • rare mutations • uncommon tyrosine kinase inhibitors

EGFR mutations are the most prevalent targetable genetic alterations in NSCLC with frequency varying from 10 to 15% in Caucasians to as high as 30–50% in Asians [1]. *EGFR* tyrosine kinase inhibitors (TKIs) are the established standard of care for first-line treatment of patients with *EGFR*-mutant advanced NSCLC. Five TKI's spanning three generations are currently approved by the US FDA [2–12]. Erlotinib and gefitinib are the first-generation reversible

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EGFR TKIs [2–7]; afatinib and dacomitinib are the second-generation irreversible pan-*EGFR* TKIs [8–11] and osimertinib is the third-generation irreversible *EGFR* TKI [12]. Mutations in exons 18–21 encompass most of the activating mutations on the tyrosine kinase domain are the most clinically and therapeutically relevant [13]. Clinical trials in *EGFR*-mutant NSCLC usually include patients harboring the canonical *EGFR* sensitizing mutations, exon 19 deletions (Del19) and L858R located on exon 21, which account for approximately 45 and 40% of patients with *EGFR*-mutant NSCLC, respectively [14,15]. Wide adoption of both tissue-based and blood-based next generation sequencing tests has resulted in identification of uncommon *EGFR* mutations of unclear clinical and biologic significance leading to considerable treatment challenges for clinicians. Patients with uncommon *EGFR* mutations are a heterogeneous group of patients which can account for approximately 7–23% patients with *EGFR*-mutant NSCLC [16]. These include exon 20 insertions (~6% of all *EGFR* mutations), G719X (~3%), L861Q (~1%), S768I (~1%) and exon 19 insertions (0.6%) [17–24]. Patients with uncommon *EGFR* mutations are usually excluded from clinical trials. G719X (including G719S, G719A, G719C and G719D), S768I and L861Q, on exons 18, 20 and 21, respectively, are referred to as the major uncommon mutations [25]. Although exon 20 insertions are the most common uncommon *EGFR* mutations, they are generally considered TKI resistant with a few exceptions [26,27]. Recently, two novel drugs have been approved in the treatment of *EGFR* exon 20 insertion-positive advanced NSCLC following progression on first-line therapy [28,29].

About 25% of all uncommon *EGFR*-mutant NSCLC, coexist with other independent common or uncommon *EGFR* mutations referred to as compound mutations [15,30]. Some of these compound *EGFR* mutations may be sub clonal in nature, in other words, variants only seen in a small proportion of tumor cells. In the context of compound mutations and considerable variability in therapeutic efficacy of *EGFR* TKI therapies to different mutations, it is important to identify if a given mutation is TKI sensitive. Osimertinib is the preferred first-line TKI in patients with advanced NSCLC harboring Del19, L858R and the TKI resistance gatekeeper mutation T790M [12]. There is limited data on the efficacy of TKIs in patients with uncommon *EGFR*. Afatinib and osimertinib have both demonstrated varying degrees of efficacy against uncommon *EGFR* mutations whereas early generation TKI have limited efficacy. A pooled analysis of patients participating in the Phase III LUX-Lung 3 and 6 trials, and the Phase II LUX-Lung 2 trial, demonstrated efficacy of afatninb [24]. Of the 75 patients with uncommon *EGFR* mutations, 18 harbored G719X, 16 had L861Q and eight patients had S768I mutations. The objective response rates (ORR) were 78, 56 and 100%, and the median progression-free survival (PFS) was 13.8, 8.2 and 14.7 months, respectively. Based on these findings, afatinib was FDA approved in patients with *EGFR*-mutated NSCLC with uncommon and common sensitizing mutations. A recent Phase II study (KCSG-LU15-09) demonstrated comparable efficacy of osimertinib in patients with uncommon EGFR mutatnt NSCLC [31]. The ORR for G719X (n = 19), L861Q (n = 9) and S768I (n = 8) were 53, 78 and 38%, respectively. The median PFS was 8.2, 15.2 and 12.3 months, respectively. However, early generation TKI have limited efficacy against G719X, and L861Q mutations with combined ORR of 20% [32]. Activity of osimertinib or afatinib in patients with compound mutations, especially co-occurring T790M and G719A compound mutations is not well characterized.

We present a patient with recurrent metastatic NSCLC who developed T790M mutation following early-generation *EGFR* TKI. Guardant360 testing also showed co-occurring G719A mutation with a higher allelic fraction. Following osimertinib, the patient had radiographic stabilization of disease before progression. Guardant360 testing at progression, showed that T790M was not detectable anymore but G719A was persistent. Subsequent administration of afatinib led to a quick clinical and radiographic partial response that is ongoing at 12-month follow-up.

Case report

A 52-year-old Caucasian female who never smoked developed non resolving cough and pleuritic left chest pain in 02/2002. Chest CT showed 4.5 × 3.6 cm left supra-hilar mass. Bronchoscopy biopsy confirmed moderately differentiated adenocarcinoma. There was no evidence of disease in the hilar or mediastinal lymph nodes (LN) by CT scan. She received four cycles of neoadjuvant chemotherapy with carboplatin, gemcitabine and thalidomide on a clinical trial (NCT002818270). In 07/2002 she underwent thoracoscopic left upper lobe lobectomy with mediastinal LN dissection. Pathology confirmed moderately differentiated adenocarcinoma (4.5 × 3.5 × 2.5 cm) with no LN involvement. Final staging was IIB (AJCC 6th edition). In April 2004 she was found to have multiple enlarging sub-centimeter pulmonary nodules in the left lower lobe on serial CT scans. In June 2004, she underwent CT-guided thoracoscopic biopsy which confirmed recurrence of lung adenocarcinoma. Immuno-peroxidase stain for *EGFR* was positive. In July 2004, she was started on gefitinib which at the time was approved for relapsed

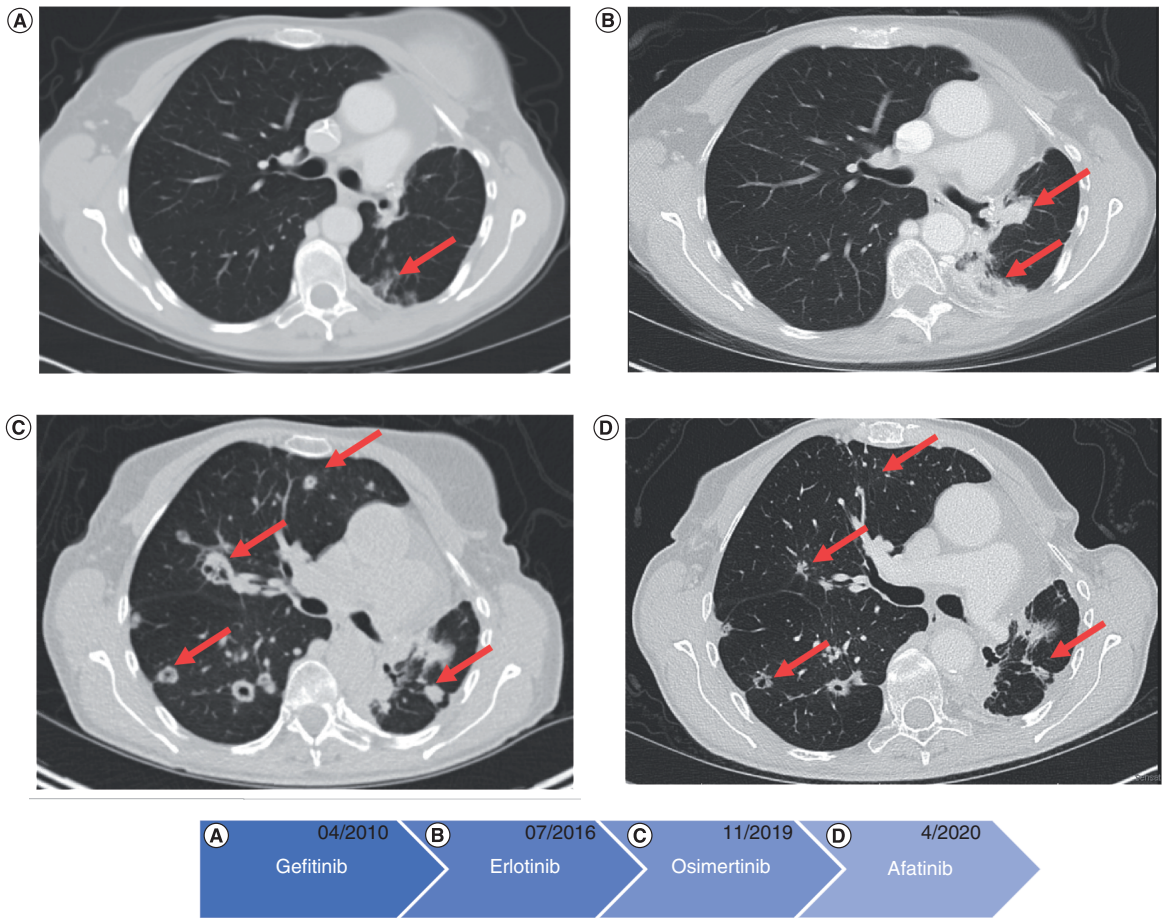

Figure 1. Serial CT scan axial sections at same level showing evolution of cancer captured at the time of progression on treatments. (A) Progression on gefitnib in April 2010. **(B)** Progression on erlotinib in July 2016. **(C)** Progression on osimertinib in November 2019. **(D)** Response on afatinib in April 2020.

NSCLC irrespective of *EGFR* mutation. The patient achieved prolonged stable disease on gefitinib by response evaluation criteria in solid tumors (RECIST version. 1.1.) until February 2010 when there was progressive disease (PD) noted in left lower lobe pulmonary nodules and pre-carinal LN. Therapy was switched to erlotinib with good partial response until June 2015 before radiographic PD in multiple nodules in the left lobe and mediastinal LN. Due to minimal symptoms, erlotinib was continued until July 2016. Guardant 360 cfDNA testing at this time revealed *EGFR* T790M (0.7% cfDNA) and *EGFR* G719A (7.1% cfDNA) mutations. In August 2016 therapy was switched to osimertinib. The patient had stable disease until November 2019 when she experienced symptomatic progression (worsening dyspnea, cough, fatigue) and radiographic progression with several new sub centimeter nodules in both lobes and new left supraclavicular LN enlargement. Biopsy of the left supraclavicular LN ruled out histologic transformation and showed recurrent adenocarcinoma. There was not enough tissue for molecular testing on the tumor biopsy sample. Guardant 360 cfDNA testing showed persistent G719A mutation (6.4% cfDNA) but T790M was not detectable. PD-L1 assay by Ventana SP263 showed tumor proportion score <1%. In November 2019, therapy was switched to afatinib. Within a few weeks, the patient noticed remarkable symptomatic improvement. Restaging scan after 2 months of therapy showed good PR that is sustained at 12-months follow-up (Figure 1). Informed consent was obtained from the patient to share this information.

Discussion

Compound *EGFR* mutations are seen in up to approximately 25% of *EGFR* mutant NSCLC and are associated with less favorable prognosis [15,30]. Published data suggests that the ORR of afatinib in patients with compound mutations is 77% with median duration of response of 16.6 months [10]. This clinical benefit is comparable with

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that observed against common EGFR mutations (Del19/L858R). Overall, afatinib offers clinically meaningful benefit in patients with most compound mutations except for T790M [30]. There is limited efficacy data of other EGFR TKIs against compound mutations. Patients with uncommon *EGFR* mutations and compound mutations are often excluded from clinical trials. T790M is typically a treatment emergent mutation following first-generation EGFR inhibitors seen in approximately 60% of patients [33]. Osimertinib is the preferred treatment in *EGFR* exon 19 deletion, L858R mutation and T790M mutation [12]. G719X is considered to be an uncommon non canonical activating *EGFR* mutation given high response rates with *EGFR* TKI. The ORR of osimertinib in patients with G719X mutations is approximately 53% with a median PFS of 8.2 months [31] whereas for afatinib ORR 63–78% with median PFS of 13–17 months [24,34]. Compound mutations with co-occurring of G719X and T790M is exceedingly rare, and the optimal therapy is not known. In this patient, initial treatment with osimertinib produced only modest disease control, probably only in a tumor sub clone that harbored T790M. Despite the previously demonstrated clinical activity of osimertinib in patients with G719X mutations, in this patient with G719A which was a dominant clone, was sensitive to afatinib producing both radiological and clinical response.

Based on available data, afatinib or osimertinib should be considered as a frontline treatment option for patients with treatment-naive metastatic NSCLC with major uncommon mutations. In patients with compound mutations, known clinical activity of second or third generation TKIs for each of the mutations should be considered. Given the rarity of compound mutations and the lack of comparative data for optimal TKI therapy, the final treatment plan needs to be individualized based on individual patient characteristics, physician preference, tolerability and access to drugs. Intracranial activity is also an important consideration, given a high prevalence of uncommon *EGFR* mutations in brain metastasis samples of patients with advanced NSCLC [35]. Although both osimertinib and afatinib are active in the central nervous system in patients with common *EGFR* mutations, there is limited data on their activity in patients with brain metastases harboring uncommon mutations.

Conclusion

In summary, this case report highlights two important observations. First, the patient responded to afatinib after osimertinib, inverting the usual canonical treatment sequence. Second, this underscores the importance of serial genomic profiling of in *EGFR* mutated NSCLC to monitor clonal evolution during treatment. At last, clinical trials in patients with uncommon *EGFR* mutations and compound mutations are needed.

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Informed consent disclosure

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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