Clinical Case Report

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Successful treatment of a lung adenocarcinoma patient with a novel EGFR exon 20-ins mutation with afatinib

A case report

Yangyang Cai, MB, Xu Wang, MD, Ye Guo, MM, Chao Sun, MM, Yinghui Xu, MD, Shi Qiu, MM, Kewei Ma, MD*

Abstract

Rationale: Comprehensive genomic profiling for non-small cell lung cancer (NSCLC) is likely to identify more patients with rare genetic alterations, including uncommon epidermal growth factor receptor (EGFR) gene mutation.

Patient concerns: A 63-year-old Chinese woman who had never smoked visited our lung cancer clinic due to a chronic cough.

Diagnosis: The patient was diagnosed with lung adenocarcinoma by transbronchial lung biopsy. An EGFR mutation (exon 20 insertion H773_V774insH, D770_N771insG, V769_D770insASV, D770_N771insSVD) was detected in the biopsy specimen by quantitative real-time PCR.

Interventions: The patient was treated with osimertinib first, and the progression-free survival (PFS) was 4.4 months. After the disease progressed, the second genetic test of pleural effusion suggesting the EGFR exon 20-ins mutation site changed to A767delinsASVD only. Then the patient was treated with afatinib with informed consent.

Outcomes: The treatment of afatinib in this patient was successful, PFS was 7.4 months.

Lessons: To our knowledge, EGFR exon 20-ins mutation A767delinsASVD has never been reported, and the successful treatment of afatinib may provide a new therapeutic option for this type of exon 20 insertion mutations.

Abbreviations: CT = computed tomography, EGFR = epidermal growth factor receptor, EGFR-TKIs = tyrosine kinase inhibitors of epidermal growth factor receptor, MA = mutation abundance, NGS = next generation sequencing, NSCLC = non-small cell lung cancer, SD = Stable Disease, TKI = tyrosine kinase inhibitor.

Keywords: afatinib, EGFR exon 20-ins mutation, EGFR-TKI, lung cancer

1. Introduction

Epidermal growth factor receptor (EGFR) gene mutations are frequently seen in patients with lung adenocarcinoma who are nonsmokers and females. They are reported in approximately 10% to 30% of adenocarcinomas of the lung worldwide.[1–3] EGFR mutation occurs mainly in exons 18 to 21, in which exon 19 deletion and exon 21 L858R point mutation are known as sensitive mutation and confer a favorable response to tyrosine kinase inhibitor (TKI) therapy. However, the clinical significance and implications of rare mutation in the EGFR are still unclear. These mutations include exon 20-ins mutation, which accounts for 4% to 10% of all EGFR mutation.[4–6] Generally, EGFR exon 20-ins mutation are resistant to 1st TKIs of epidermal growth factor receptors (EGFR-TKIs), in addition to A763_Y764insFQEA,[3,7–9] and the efficacy of 2nd or 3rd EGFR-TKIs in patients with EGFR exon 20-ins mutant lung adenocarcinoma is not clear. Most patients choose chemotherapy. We report a case of A767delinsASVD in EGFR exon 20-ins mutation, which has never been reported in any previous study and performs an efficacy test with the second generation TKI afatinib.

2. Case report

A 63-year-old Chinese woman who had never smoked visited our lung cancer clinic in March 2017 due to a chronic cough. Computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) revealed a mass in the left lower lobe, left pleural metastasis and left malignant pleural effusion (Fig. 1). The patient was diagnosed with lung adenocarcinoma by transbronchial lung biopsy, cT3N2M1 stage IV. An EGFR

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Cancer and Stem Cell Center, First Affiliated Hospital, Jilin University, Changchun, Jilin, P.R. China.

* Correspondence: Kewei Ma, The Jilin University First Hospital, No. 71, Xinmin Street, Changchun, Jilin 130021, P.R. China (e-mail: makw@jlu.edu.cn).

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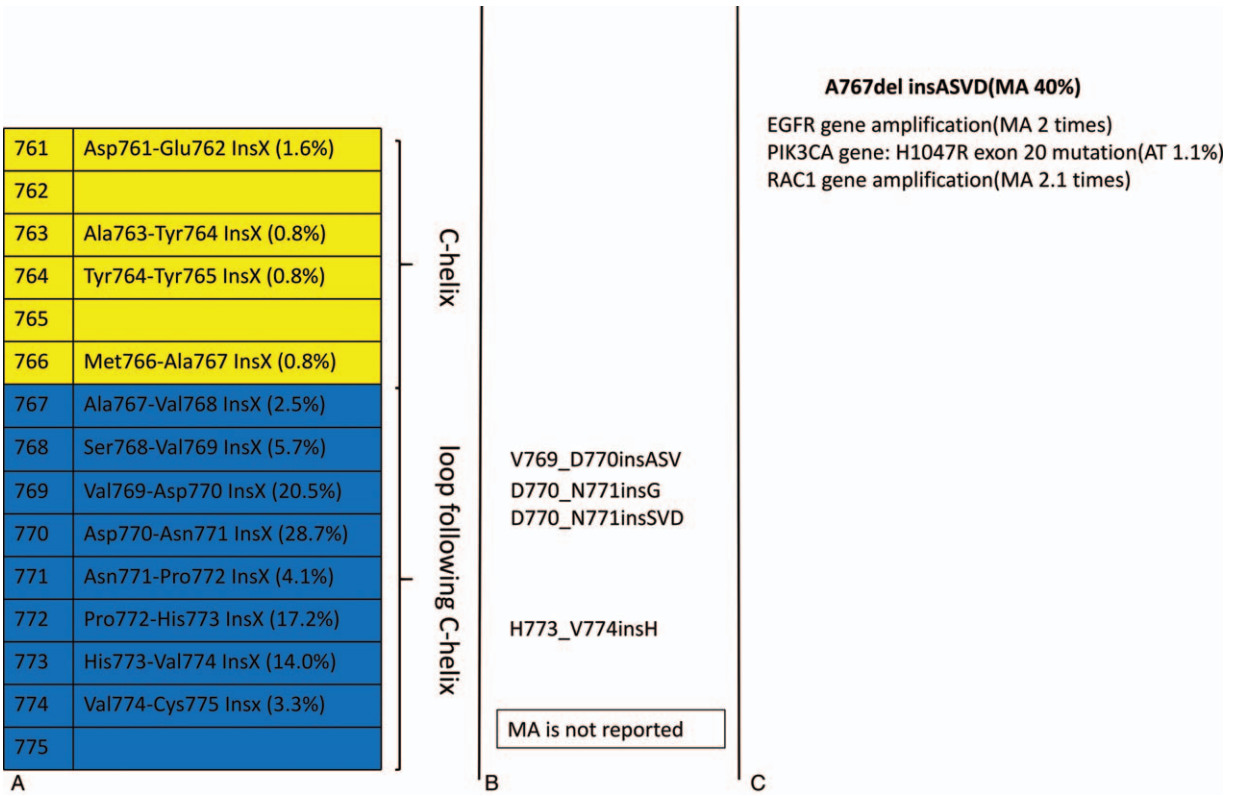

Figure 1. Insertion site of EGFR exon20 insertion mutants. (a) Previous reported Exon 20 insertion mutations. Prevalence of each mutation spectrum (noted as insX to represent all known insertions within those residues) by amino acid position is indicated in parentheses. (b) Gene analysis and MA from sequential tumor biopsy specimens by quantitative real-time PCR before treated with osimertinib. (c) Gene analysis and MA; amplified gene shows only AT from pleural effusion by NGS of the whole-exome after treatment with osimertinib. AT = amplification time, EGFR = epidermal growth factor receptor, MA = mutation abundance, NGS = next generation sequencing.

mutation (exon 20 insertion H773_V774insH, D770_N771insG, V769_D770insASV, D770_N771insSVD) was detected in the biopsy specimen by quantitative real-time PCR (mutation abundance (MA) from pleural effusion is not reported). Patient has no intention of chemotherapy. Daily oral doses of 80 mg of osimertinib were given starting at the end of March 2017. Two months later a CT scan revealed the disease was stable. Then, 4.4 months later, the patient felt chest tightness, tumor progression was observed, and a massive malignant pleural effusion, which was revealed to be adenocarcinoma through exfoliocytology examination. PFS was 4.4 months. Genetic testing of the pleural effusion by next-generation sequencing (NGS) of the whole exome, suggesting exon 20-ins was still present, but the insert site was A767del insASVD, along with EGFR gene amplification, PIK3CA gene: H1047R exon 20 mutation, RAC1 gene amplification (the site and prevalence of EGFR exon 20 insertion mutation is shown in Fig. 1, according to Hiroyuki Yasuda[4]). From the end of August 2017, the patient was treated with afatinib (40 mg/day), with informed consent. During this treatment, the primary tumor decreased in size and pleural effusion was significantly reduced. Efficacy evaluation is Stable Disease (SD). Disease developed again, as shown by a CT scan, in March 2018. PFS was 7.4 months (Fig. 2).

3. Discussion

EGFR mutations occur mainly in exon 18 to 21.[10] Exon 20 insertion mutations account for 4% to 10% of all EGFR mutation.[3,4,7] Most of these mutations lie near the end of the C-helix within the N-lobe of the kinase, after residue M766 and have been reported up to C775, but a small subset map to the middle of the C-helix (affecting amino-acids E762 to Y764)[4,7]. D770_N771insSVD and V769_D770insASV are the most frequent of all EGFR exon 20-ins mutation.[8,9] The clinical and pathological characteristics of EGFR exon 20-ins mutation are similar to classic EGFR mutation, are nonsmoker status, female sex, Asian and adenocarcinoma histology.[1,2,5–7,11–14]

Currently, response to the 1st generation EGFR TKI therapy for these patients has been explored in small retrospective studies ranging from 2 to 49 patients.[2–6,8,9,11,12,15,16] These studies demonstrate mixed results with regard to objective response rate to the 1st generation EGFR-TKI, as well as progression-free survival and overall survival. Unlike EGFR exon 19 deletions and L858R–bearing tumors, most NSCLCs with EGFR exon 20-ins mutation (except A763_Y764insFQEA) don't respond radiographically or clinically to the 1st generation EGFR-TKIs, such as gefitinib or erlotinib. Traditionally, V769_D770insASV is thought to be resistant to EGFR TKIs, but Naidoo[9] reported a patient with V769_D770insASV mutation who exhibited a partial response to EGFR TKI, with a prolonged TTP of 20 months and an OS of 24 months; however, there is only one paper associated with this incident. In a compilation of data on the treatment of EGFR exon 20-ins mutation, response to 1st generation EGFR-TKIs (except A763_Y764insFQEA and V769_D770insASV) ORR was only 5% to 8%,[3,4,7,8] and the PFS was only 1.4 to 2.5 months.[4,6,9,15,16]

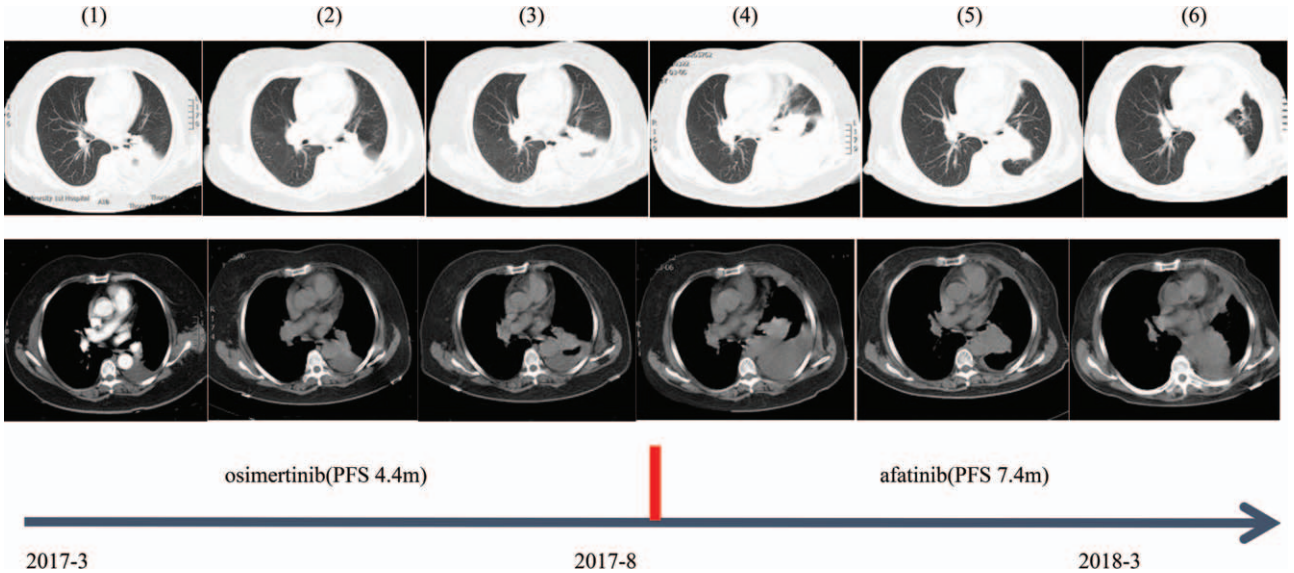

Figure 2. Patient clinical course including treatment history and relevant imaging studies. (1) At baseline before osimertinib, showing left pulmonary lesion and left pleural effusion. (2) At 1.5 months of osimertinib, with an SD response. (3) At 2.5 months of osimertinib, with an SD response. (4) At 4.4 months of osimertinib, lung and left pleural effusion progression. (5) At 4.0 months of treatment with afatinib, left pulmonary lesion was stable disease and the pleural effusion was significantly reduced. (6) At 7.4 months of treatment with afatinib, with progressed disease with left pulmonary lesion and stable pleural effusion. SD = Stable Disease.

First generation EGFR-TKIs do not appear to make a meaningful contribution to the total treatment of NSCLCs with EGFR exon 20-ins mutation (except A763_Y764insFQEA). Thus, most patients with EGFR exon 20-ins mutation spend the majority of their treatment time receiving chemotherapy. Many doctors would advocate chemotherapy as standard first-line therapy for patients with advanced lung adenocarcinoma harboring an EGFR exon 20-ins mutation. Jarushka Naidoo et al[9] reported an ORR of 63% to platinum doublet chemotherapy compared to an ORR of 27% in patients treated with erlotinib. Geoffrey R. Oxnard et al[6] reported that 17 patients with EGFR exon 20-ins mutation received combination chemotherapy, the ORR was 58%, and the median TTF was 5.9 months. The survival analysis showed that these patients (threated with chemotherapy only or together with the 1st generation EGFR-TKI) have an OS similar to that of patients with wild-type EGFR mutation (median 16.5 and 20.0 months), and both were shorter than that of common EGFR mutation (median 33.0 months).

We recommended that our patient use chemotherapy, but the patient refused. Although there are some studies that have reported a good response from V769_D770insASV, most reports identified it as resistant to EGFR TKIs, and at first, there were 4 mutations detected in our patient, including exon 20 insertion (H773_V774insH, D770_N771insG, V769_D770insASV, D770_N771insSVD). To target EGFR mutation, including EGFR T790M mutation, multiple EGFR-TKIs have been developed. These include 2nd generation EGFR-TKIs, afatinib, and dacomitinib, as well as 3rd generation EGFR-TKIs, osimertinib, and rociletinib. However, only a few studies were performed on patients with exon 20 insertion. In a combined post hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 report of 600 patients given afatinib, 23 patients had exon 20 insertion mutation, 2 patients had objective responses (8.7%, 95% CI 1.1–28.0), and median PFS was only 2.7 months (95% CI 1.8–4.2).[17] Four patients with EGFR 20-ins mutation were treated with chemotherapy (ORR 0%, PFS 5.2 months). Toshiyuki Hirano et al[3] performed MTS assays with or without EGFR-TKIs, using cells harboring four representative EGFR exon 20 insertion mutation, namely, A763_Y764insFQEA, Y764_V765insHH, A767_V769dupASV, and D770_N771 insNPG. Afatinib potently inhibited the growth of cells harboring EGFR A763_Y764insFQEA. Of the other three EGFR-TKIs including erlotinib, afatinib, and rociletinib, osimertinib most effectively inhibited Ba/F3 cell growth. Then, they biologically confirmed the efficacy and therapeutic window of osimertinib for EGFR exon 20 insertion mutation. Although these mutations are different from that in our case report, it may be a good reference point, so we tried the 3rd generation EGFR-TKI osimertinib first, and the PFS was 4.4 months. The efficiency may be better than the 1st generation EGFR-TKIs.

After the disease progressed, and the second genetic test with pleural effusion, suggesting exon 20 insertion mutation was still present was done, the insertion site changed to A767delinsASVD, and its MA increased to 40%. It is interesting that the second genetic result of EGFR exon 20-ins mutation was different than the first one. There are 2 possibilities for this change: first, it may be due to the spatial heterogeneity of primary and metastatic tumor samples;[18,19] second, it may belong to the new drug-resistant mutation. For the second gene mutation test we used NGS for the whole exon, and we also found there were other genetic mutation, such as EGFR gene amplification, H1047R exon 20 mutations in PIK3CA gene and RAC1 gene amplification. It has been reported that concurrence of EGFR amplification and sensitizing mutation indicate a better survival benefit from EGFR-TKI therapy in lung adenocarcinoma patients.[20–23] PIK3CA mutation frequently coexists with EGFR mutation in non-small cell lung cancer (NSCLC) and often suggest poor prognosis.[24–26] In addition, overexpression of RAC1 has been reported in lung cancer, and RAC1 can activate EGFR signaling, which promotes cell proliferation, survival, and cancer metastasis in NSCLC cells.[27,28] As far as we know, these mutations are not

clear driver mutation such as the EGFR exon 20-ins mutation. It is worth noting that as far as we know, A767delinsASVD has neither been reported in any articles nor retrieved from the Catalogue of Somatic Mutation in Cancer (COSMIC). The patient still declined chemotherapy, so we replaced the previous treatment with afatinib. PFS was 7.4 months without obvious side effects and the efficacy evaluation is SD. This is the first report of a rare case with A767delinsASVD, and the successful treatment of afatinib may provide a new therapeutic option for this type of exon 20 mutation. The underlying biology accounting for A767delinsASVD of EGFR exon20 should be studied further.

In conclusion, our report presented a rare case with A767delinsASVD, which has never before been reported, and the successful treatment of afatinib may provide a new therapeutic option for this type of exon 20 insertion mutation, especially for patients who decline or are not suitable for chemotherapy. In addition to that, for the EGFR 20 insertion mutation, the different genomic variants confer diversity in biologic behavior and response to targeted therapies, and the mechanism of this is still not clear. In light of increasing knowledge of the function and structural differences between rare subtypes of EGFR exon 20-ins mutation variants, further studies are needed to examine the differential responses to EGFR TKIs and the overall survival in patients who harbor these mutations.

Author contributions

Resources: Shi Qiu.
Supervision: Yinghui Xu.
Validation: Chao Sun.
Visualization: Ye Guo.
Writing – original draft: Yangyang Cai, Xu Wang.
Writing – review & editing: Kewei Ma.
Kewei Ma orcid: 0000-0003-2987-576X.

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