Rare T263P epidermal growth factor receptor extracellular domain mutation of advanced non-small cell lung cancer with benefit of the first-line afatinib in a Vietnamese male patient

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Abstract

Background: A T263P mutation is one of the rare EGFR mutation, located in 7p11.2, a change in the amino acid residue at position 263 in the epidermal growth factor receptor protein where L-threonine has been replaced by L-proline. This missense mutation in the EGFR extracellular (EC) domain is poor-known about EGFR EC domain mutations in lung cancer. Purpose: In this study, we firstly reported a patient with advanced lung adenocarcinoma haboring a rare EGFR mutations of T263P alone who benefited from first-line treatment with afatinib in Vietnam. Results: This patient achieved a partial response and had a progression-free survival of 5 months. After disease progression, this patient was subsequently administered several chemotherapy regimens and had an overall survival of 17 months. Conclusion: NSCLCs with rare T263P mutation reveal the response to afatinib, however prognosis is often poor.

Introduction

Epidermal growth factor receptor (*EGFR*) mutations are one of the most common oncogenic driver event in non-small cell lung cancer (NSCLC) [1, 2]. Classical activating mutations (exon 19 deletions and the *L858R*point mutation) comprise the vast majority of *EGFR* mutations and are well defined as strong predictors for good clinical response to*EGFR* tyrosine kinase inhibitors (*EGFR* TKIs). The*EGFR* TKIs compete for ATP binding sites on the tyrosine kinase region, leading to inhibition of persistent phosphorylation, inhibiting intracellular transmission, and reducing proliferation, adhesion, invasion and metastasis, and accelerated cell death process. However, low frequent mutations including point mutations, deletions, insertions and duplications occur within exons 18–25 of the *EGFR* gene in NSCLC and are associated with poorer responses to *EGFR* TKIs [3, 4].

Although there are now many highly sensitive methods to detect rare*EGFR* mutations in NSCLC patients, the understanding of the molecular biology of those rare mutations was still limited. Although the most clinical trials did not conducted these mutations, 7% to 23% of NSCLC patients harboring uncommon *EGFR* mutations [5]. These mutations represent a highly heterogeneous group with almost 600 variants were identified. Up to 25% of all uncommon *EGFR* mutation–positive tumors coexist with other *EGFR* mutations within the same tumor (called "compound mutations" or "co-mutations"). The next-generation sequencing (NGS), a highly sensitive technique is more likely to explore uncommon mutations, including *EGFR* mutations. Therefore, more and more rare mutations will be identified in the future [6].

T263P mutation is one of the rare *EGFR* mutation, located in 7p11.2, a change in the amino acid residue at position 263 in the epidermal growth factor receptor protein where L-threonine has been replaced by L-proline. Missense mutations in the *EGFR*extracellular (EC) domain are found in 10% to 15% of glioblastomas [7]. However, little is known about EGFR EC domain mutations in lung cancer. Therefore, we reported the

clinical and paraclinical features, outcome of the advanced NSCLC haboured *EGFR* mutation of *T263P* in a Vietnamese male.

CASE REPORT

A male 59-year-old patient presented with dry cough for months and hospitalized at Department of Medical Oncology at our hospital in April 2020. There was no personal medical history, but he has consumed the smoke of over 5 cigarettes per day for 30 years. Clinical examinations showed performance status ECOG 1 with dyspnea on exertion, no hemoptysis. Enhanced chest computed tomography (CT) scan revealed a tumor with a 5x3.2 cm in diameter in the left pulmonary lower lobe (Figure 1A) and bilateral multi-nodules (Figure 1B). There was no report of brain metastasis or metastasis of any organs. Histopathological result of needle core biopsy showed lung pulmonary adenocarcinoma, NOS. Immunohistochemical result was positive for TTF-1. The result of tumoral NGS showed a rare mutation of *EGFR* gene as *T263P* . Based on CT scan and brain magnetic resonance imaging (MRI), he was diagnosed of lung adenocarcinoma staged IV according to the 8thedition of the American Joint Committee on Cancer (AJCC).

Despite of limited reports about *EGFR* EC domain mutations in lung cancer, we initiated administration of afatinib as the second EGFR TKIs at a dose of 40 mg/day and closely clinically observed. After 2 months of treatment, patient experienced of cough relief and no presence of dyspnea without report of grades 3-4 toxicities. Chest CT scan showed a partial response both in the primary tumor (Figure 2A) and metastatic nodules (Figure 2B). However, patient was hospitalized for weight loss and dyspnea after 3 months later. Imaging showed a progressive disease on bilateral lung nodules but no brain metastasis. A tumoral biopsy was repeated and reported of no hispathological type change and NGS test of the second cancer tissue did not reveal other mutations nor resistant mutation as *T790M* . We decided to treated patient with pemetrexed/carboplatin chemotherapy for three cycles and patient experienced a decreased complain. A CT scan revealed a partial response and we continued more three cycles of double platinum-based chemotherapy before maintained as pemetrexed monotherapy. However, after only 3 maintainable cycles, patient developed pulmonary progressive disease and docetaxel was administered at that time. Patient had stable disease for more than 4 months before progressive disease and experienced palliative care.

As of the last follow-up, progression-free survival for first-line afatinib was 5 months and patient had died in September 2021 with an overall survival of 17 months from April 2020 to September 2021, for a lung cancer patient of rare *EGFR T263P* mutation in our hospital.

Discussion

EGFR TKI has become the first-line recommended treatment for advanced NSCLC patients with sensitive *EGFR* mutation [8]. However, the most clinical trials revealed the efficacy of *EGFR* -TKIs have been conducted in advanced NSCLC patients harboring common *EGFR* mutations [9-11]. In this report, we presented a*EGFR* rare mutation, *T263P* mutation, which is a missense mutations in the *EGFR* EC domain. The *EGFR* typically contains an extracellular domain, a transmembrane domain, and an intracellular kinase domain. This mutation is a change in the amino acid residue at position 263 in the epidermal growth factor receptor protein where L-threonine has been replaced by L-proline. Interestingly, the previous researches almost reported the appearance of rare mutations in extracellular domain of *EGFR* gene in cases of glioblastoma, one of them was T263P mutation and reported to be sensitive to erlotinib, however there are only a few reports about this mutation on NSCLC in the litterature [7, 12]. A retrospective study in lung cancer showed that *EGFR* EC domain mutations were more likely to be combination with *EGFR* KD mutations [13]. A report of Choong-kun Lee*et al.* , a case of non-small cell lung cancer with a missense mutation in extracellular domain of EGFR as *T263P* or*Thr263Pro* , combining with *G719A* mutation (co-mutation) in the same tumor. Elortinib was administered in that case, but the patient presented drug resistance to the first generation TKI with a PFS of less than 4 months [14]. However, other report of co-mutation between EC *EGFR* mutation and common mutation (*L858R* mutation) and *MET* amplification showed that patietnt experienced a good PFS for more than 19 months with erlotinib plus capmatinib after early resistance to first-line Osimertinib [15].

In our case, we firstly reported the *T263P* -mutant patient without co-mutations, he experienced partial response and achieved a PFS for nearly 5 months with the 2nd generation TKI as afatinib. Although some reports suggest that afatinib is more effective than first-generation TKIs in *T263P* mutations because afatinib is an irreversible ErbB family blocker (*EGFR* ,ErbB family) that potently inhibits signaling from all ErbB family receptor homodimers and heterodimers [14, 16], the prognosis of *EGFR* EC mutation seems to be worse than with other sensitizing *EGFR*mutations [17, 18]. One question is, how does the treatment effectiveness compare between afatinib and platinum-based combination chemotherapy? More case reports as well as preclinical trials are needed to further investigate treatment strategies for patients harboring *EGFR T263P* mutation.

Conclusion

Non-small cell lung cancer carrying the *EGFR T263P* gene mutation alone or combined with sensitizing *EGFR* mutations is rare in clinical practice, the mechanism of resistance is complex to first generation tyrosine kinase inhibitors, and has a poor prognosis. Afatinib is effective in treating patients with rare genetic mutations and in particular the case of *T263P* mutation. The assessment of response closely, early detection when the disease progresses to have appropriate further treatment.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of details of his medical cases and any accompanying images.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

Kien Hung Do should be considered the major author. He is the participated directly in diagnosis, treatment, and follow up of the patients, performed literature review, and assisted in drafting of the components of the case report, and assisted in formatting the presented material. He should be considered the major author.

Tu Anh Do Duc and Thanh Le took part in the diagnostic and treatment consultant and, assisted in literature review.

Tai Van Nguyen performed follow up of the patient, took illustrated figures, literature review, assisted in drafting of the components of the case report.

Chu Van Nguyen performed the diagnostic consultant of the HE stains and immunohistochemical staining and testing of gene mutation, literature review, and assisted in drafting of the components of the case report, and assisted in formatting the presented material.

Data Availability

All data analysed during this case reports are included in this article. Further enquiries can be directed to the corresponding author.

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Figure 1: Illustrated pictures demonstrated revealed a tumor in the left pulmonary lower lobe (Fig 1A) and bilateral multi-nodules (Fig 1B) on Enhanced chest computed tomography (CT) scan.

Figure 2: Photomicrographs of CT scan showed a partial response both in the primary tumor and metastatic nodules after TKi treatment by the first-line afatinib (Fig 2A and 2B, respectively) for more 2 months.