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CASE REPORT

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Rare *T263P* epidermal growth factor receptor extracellular domain mutation of advanced non-small cell lung cancer in a Vietnamese male patient

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Abstract

T263P mutation is one of the rare *EGFR* mutations located on chromosome 7p11.2, which is a change in amino acid residue at position 263 of the epidermal growth factor receptor protein, where L-threonine has been replaced by L-proline. This missense mutation in the extracellular EGFR domain is not well-known in lung cancer. In this study, we first report a patient with advanced lung adenocarcinoma harbouring only a rare T263P *EGFR* mutation who benefited from first-line afatinib therapy in Vietnam. The patient achieved a partial response with a time-to-treatment failure of 5 months. The patient subsequently received several chemotherapy regimens as the disease progressed, with overall survival of 17 months. Non-small cell lung cancer with a rare T263P *EGFR* mutation responds to afatinib but has a poor prognosis. Further studies are needed to determine the efficacy of targeted therapies in this specific population.

KEYWORDS
extracellular *EGFR* mutation, NSCLC, *T263P* mutation

INTRODUCTION

Epidermal growth factor receptor (*EGFR*) mutations are one of the most common oncogenic drivers in non-small cell lung cancer (NSCLC).[1,2] Classical activating mutations (exon 19 deletions and *L858R* point mutations) account for the vast majority of *EGFR* mutations and are well-defined as strong predictors of favourable clinical response to *EGFR* tyrosine kinase inhibitors (*EGFR* TKIs). However, low-frequency mutations including point mutations, deletions, insertions and duplications occur in exons 18–25 of the *EGFR* gene in NSCLC and are associated with a diminished response to *EGFR* TKIs.[3,4] In clinical trials of advanced NSCLC patients with *EGFR* mutations, only 7%–23% of patients were reported with uncommon *EGFR* mutations.[5] The next-generation sequencing (NGS) is a highly sensitive method that is more likely to discover uncommon mutations, including *EGFR* mutations. Consequently, the number of rare mutations to be discovered will increase in the future.[6]

Missense mutations in the extracellular *EGFR* domain (*EC-EGFR*) are found in 10%–15% of glioblastomas.[7] The prevalence of *EC-EGFR* mutations in NSCLC is less than 0.4%,[8] and little is known about *EGFR-EC* domain mutations in lung cancer. We therefore report the clinical and paraclinical features and outcome of a Vietnamese male patient with advanced NSCLC harbouring *EC-EGFR* mutation.

CASE REPORT

A 59-year-old male patient was admitted to the Department of Medical Oncology I at our hospital in April 2020 after several months of nonproductive cough. There was no personal medical history, but he has smoked more than 5 cigarettes per day for 30 years. Clinical examinations revealed an ECOG 1 performance status with exertional dyspnea and no hemoptysis. Contrast-enhanced computed tomography (CT) of the chest revealed a tumour measuring 5 × 3.2 cm

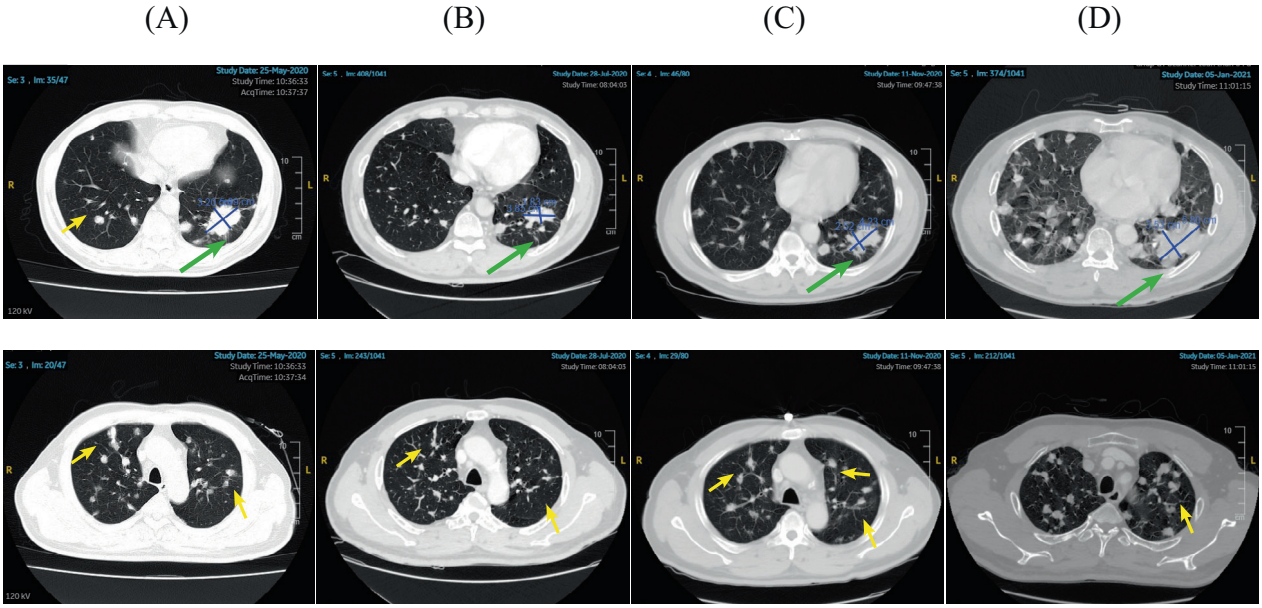

FIGURE 1 Enhanced chest computed tomography scans showed the following: (A) Before treatment: primary tumour in the left pulmonary lower lobe (green arrow) and bilateral multinodules (yellow arrows). (B) Two month after the use of afatinib: partial response. (C) Five months after the use of afatinib: progressive disease both in primary tumour and bilateral pulmonary nodules. (D) progression disease after 2 months of chemotherapy.

in diameter in the left lower lobe (Figure 1A, upper panel) and bilateral multinodules (Figure 1A, lower panel). There were no reports of brain metastasis or metastasis of any organs. Histopathological results of a core biopsy showed lung pulmonary adenocarcinoma. We performed NGS in liquid biopsy because small tissue biopsy was insufficient for genetic testing. NGS testing is performed by a platform such as MiniSeq, Illumina, USA with Massively parallel DNA sequencing by Next Generation Sequencing technology. The lung cancer gene panel includes 7 genes including *EGFR*, *ALK*, *ROS1*, *BRAF*, *KRAS*, *NRAS*, and *PIK3CA*. The result of liquid biopsy genetics showed that the rare mutation of *EGFR* gene was *T263P* (NM_005228.4:c.787A>C), and the mutation frequency was 7.0% according to the NGS method. Based on imaging and pathological findings, he was diagnosed of staged IV lung adenocarcinoma according to the 8th edition of the American Joint Committee on Cancer (AJCC).

Despite limited reports of *EGFR*-EC domain mutations in lung cancer, our patient received afatinib at a dose of 40 mg/day and was closely clinically observed. After 2 months of treatment, he had reduced cough, no dyspnea, and no grade 3–4 toxicities. Chest CT scans showed partial responses according to response evaluation criteria in solid tumours version 1.1 (RECIST) in both the primary tumour (Figure 1B, left panel) and the metastatic nodules (Figure 1B, right panel). However, our patient was hospitalized 3 months later with weight loss and dyspnea. Imaging showed disease progression in bilateral pulmonary nodules but no brain metastases (Figure 1C). A tumoral biopsy was performed and there were no changes in histopathological pattern, and NGS testing of this sample showed the same *T263P* mutation and did not reveal other mutations or resistance mutations. We decided to treat the patient with three cycles of pemetrexed/carboplatin chemotherapy, after which he felt less discomfort. CT scans showed stable disease, but 2 cycles later, the patient developed pulmonary progression (Figure 1D), and docetaxel was administered at that time. The patient had been in stable disease for more than 4 months before disease progression and was given vinorelbin monotherapy 3 months later before palliative care.

At the last follow-up, the duration of first-line afatinib treatment was approximately 5 months, the patient died in September 2021, and the overall survival from April 2020 to September 2021was 17 months for a rare T263P *EGFR*-mutated lung cancer.

DISCUSSION

EGFR-TKIs are recommended as first-line therapy for advanced NSCLC patients with sensitive *EGFR* mutation. However, most clinical studies demonstrating the efficacy of *EGFR* TKIs were conducted in advanced NSCLC patients with common *EGFR* mutations.[9–11] In this report, we present a rare *EGFR* mutation, the *T263P* mutation, which is a missense mutation in the EC domain of EGFR. The *EGFR* typically contains an extracellular domain, a transmembrane domain, and an intracellular kinase domain. This mutation is a change in amino acid residue at position 263 in the epidermal growth factor receptor protein, in which L-threonine has been replaced by L-proline. Interestingly, previous studies have also reported rare mutations in the extracellular domain of *EGFR* gene in cases of glioblastoma, one of which

TABLE 1 Effectiveness of tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer harbouring *T263P* mutation in the literature.

Author, year	Number of patients	Age/sex	ECOG	Pathology	Stage	Gene method evaluations	EGFR mutations	Treatment	Response treatment	Toxicity	Follow-up
C-K Lee et al.[13]	1	NG	NG	NG	NG	NGS	*T263P* and *G719A*	Erlotinib	No response	NG	PFS: 3.9 months
Wang et al.[14]	1	61/female	3	AC	IVB	NGS	*T263P, L858R, and MET* amplification	Brain RT, ossimertinib then chemotherapy	No response to osimertinib	NG	
								Then erlotinib plus capmatinib	PR to erlotinib plus capmatinib	No AEs	PFS > 19 months
Our study	1	59/male	1	AC	IVB	NGS	*T263P*	Afatinib, then chemotherapy	PR to afatinib	No grade 3 or above	TTF: 5 months OS: 17 months

Abbreviations: AC, adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NG, not given; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PR, partial response; RT, radiotherapy.

was the *T263P* mutation, which has been reported to be sensitive to erlotinib, but there are few reports in the literature about this mutation in NSCLC.[7,12]

The *T263P* mutation rarely occurred in NSCLC, accounting for only 0.02% (2/10100) of NSCLC according to a retrospective study by Guo R et al.[8] To the best of our knowledge, only two cases of *T263P*-mutant NSCLC with treatment descriptions have been reported in the published literature (Table 1). Choong-kun Lee et al. reported a case of NSCLC with a missense mutation in the extracellular domain of EGFR as *T263P* or *Thr263Pro*, accompanied by a *G719A* mutation (co-mutation) in the same tumour. In that case, erlotinib was given, but the patient developed resistance to the first-generation TKI, with a PFS of less than 4 months.[13] However, Wang et al. showed a successful response to erlotinib plus capmatinib in a patient with co-mutation of EC *EGFR* mutation, common mutation (*L858R* mutation), and *MET* amplification after early resistance to first-line Osimertinib.[14] It should be noted that in these two cases, *T263P* mutation was combined with intracellular domain *EGFR* mutation. This is also true in *EC-EGFR* mutations, a retrospective study of lung cancer showed, that *EGFR*-EC domain mutations were more likely to be combined with *EGFR*-intracellular kinase mutations.[8]

In our case, we report, for the first time, a patient with *T263P* mutation without co-mutation, who experienced a partial response and whose time-to-treatment failure with a second-generation TKI was nearly 5 months. In vitro, the study by Choong-kun Lee et al. demonstrated that the cancer cells with *T263P* mutation were shown to be unresponsive to gefitinib but were sensitive to afatinib.[13] Although some reports suggested that afatinib is more effective than first-generation TKIs in *T263P* mutation, since afatinib is an irreversible ErbB family (*EGFR*, ErbB family) blocker that potently inhibits signalling from all ErbB family receptor homodimers and heterodimers,[13–15] the prognosis of *EC-EGFR* mutation appears to be worse than that of other sensitizing *EGFR* mutations.[16,17] One question that remains is to establish how afatinib compares to platinum-based combination chemotherapy. Further case reports and preclinical studies are needed to further investigate treatment strategies for patients with *EGFR T263P* mutation.

In conclusion, non-small cell lung cancer with *EGFR T263P* mutation alone or combined with sensitizing *EGFR* mutations is rare in clinical practice. Afatinib is effective in treating patients with rare *EGFR* mutations, especially in the case of the *T263P* mutation. Further studies are needed to determine the efficacy of targeted therapies in this specific population.

AUTHOR CONTRIBUTIONS

Kien Hung Do should be considered the major author. He 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. Tu Anh Do Duc and Thanh Le took part in the diagnostic and treatment

consultancy and assisted in literature review. Tai Van Nguyen and Phuong Thi Bich Nguyen took part in the diagnostic and treatment consultancy, performed follow up of the patient, took part in the creation of the figures, assisted in the literature review, assisted in drafting of the components of the case report. Chu Van Nguyen performed the diagnostic consultancy 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.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

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