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【 CASE REPORT 】

Successful Treatment of Lung Adenocarcinoma with Epidermal Growth Factor Receptor Compound Mutations Involving Exon 19 Deletion and Exon 20 Insertion by Afatinib

Tomoyuki Ikeuchi, Hirokazu Tokuyasu and Soichiro Ishikawa

Abstract:
A 70-year-old woman was referred to our hospital after a nodular shadow was noted on chest X-ray. Chest computed tomography showed a pulmonary mass in the right upper lobe, and brain magnetic resonance imaging revealed a right-sided frontal lobe tumor. A histological examination of a transbronchial lung biopsy specimen revealed adenocarcinoma with epidermal growth factor receptor mutations involving both exon 19 deletion and exon 20 insertion. After stereotactic radiotherapy for brain metastasis, the patient was treated with afatinib, which resulted in a complete response. We observed a case in which a patient had non-small cell lung cancer with compound *EGFR* mutations involving both exon 19 deletion and exon 20 insertion mutations that responded well to afatinib therapy.

Key words: afatinib, complete response, compound mutation, exon 19 deletion, exon 20 insertion

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Introduction

Epidermal growth factor receptor (*EGFR*) mutations have been identified in approximately 45% of non-small cell lung adenocarcinomas (1), and exon 20 insertion mutations have been reported to account for 5.8% of all *EGFR* mutations in Japan (2). As a whole, EGFR tyrosine kinase inhibitors (TKIs) are ineffective treatment options for patients who have lung cancer with exon 20 insertion mutations (3). Compound *EGFR* mutations are defined as the combination of two or more independent mutations in the *EGFR* tyrosine kinase domain (*TKD*). The frequency of compound *EGFR* mutations in *EGFR*-mutation-positive lung adenocarcinoma has recently been reported to be 24.6% (4). However, it is extremely rare for combination mutations to involve both exon 19 deletion and exon 20 insertion. In addition, the response to EGFR TKIs in patients with compound mutations has been uncertain.

We experienced a case in which a patient had non-small cell lung cancer (NSCLC) with compound *EGFR* mutations involving both an exon 19 deletion and exon 20 insertion mutations. A good response to afatinib therapy was observed.

Case Report

In June 2016, a non-smoking 70-year-old woman with ulcerative colitis was referred to our hospital after a nodular shadow was noted on right-side chest X-ray. Her Eastern Cooperative Oncology Group performance status was 0. The levels of tumor markers, including carcinoembryonic antigen, cytokeratin 19 fragment, and pro-gastrin-releasing peptide, were normal. Chest computed tomography (CT) revealed a 2.3-cm pulmonary mass in the right upper lobe (Fig. 1). Brain magnetic resonance imaging (MRI) revealed a 1-cm right-sided frontal lobe tumor (Fig. 2). ^{18}Fluorine fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) revealed the intense accumulation of FDG in the right lung tumor. Adenocarcinoma was confirmed by a histological examination of transbronchial lung biopsy specimens that had been obtained from the pulmonary mass.

Department of Respiratory Medicine, Matsue Red Cross Hospital, Japan
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Correspondence to Dr. Hirokazu Tokuyasu, tokuun3200@yahoo.co.jp

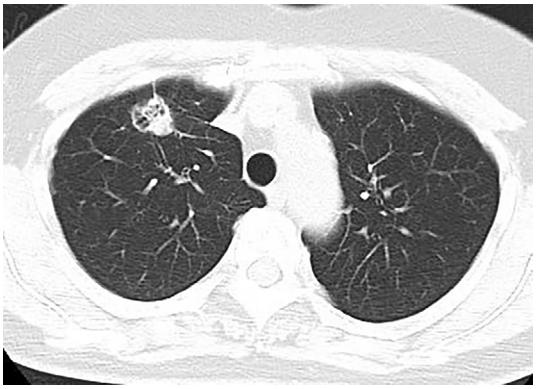

Figure 1. **Computed tomography showing a pulmonary mass in the right upper lobe.**

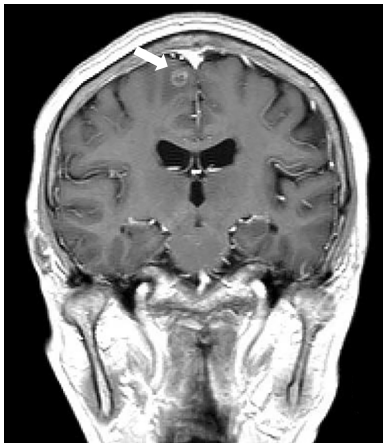

Figure 2. **Brain magnetic resonance imaging showing a 1-cm right-sided frontal lobe tumor (arrow).**

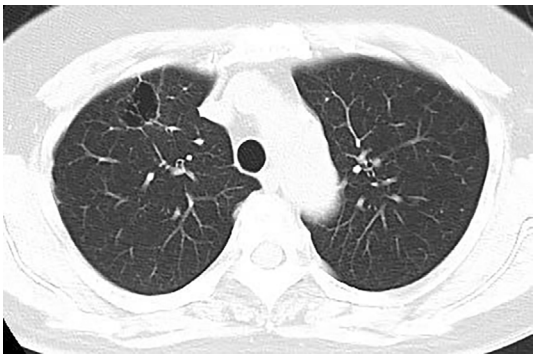

Figure 3. **Chest computed tomography showing the disappearance of the pulmonary lung tumor two months after starting treatment with afatinib.**

This case was therefore diagnosed as lung adenocarcinoma, clinical T1bN0M1b, stage IV.

The Roche cobas® EGFR Mutation Test v2 (Roche Molecular Systems, South Branchburg, USA) confirmed the concurrent exon 19 deletion mutation and exon 20 insertion mutation (detectable EGFR exon 20 insertion gene mutations: V769_D770insASV, D770_N771insG, D770_N771 insSVD, H773_V774insH). After stereotactic radiotherapy for the brain metastasis, treatment with afatinib was initiated (40 mg/day) at the beginning of August 2016. After 20 days, afatinib was reduced to 30 mg/day because her stool had been bloody for 2 days. At the end of September 2016, chest CT showed the disappearance of the pulmonary lung tumor (Fig. 3). Brain MRI did not reveal any other metastases, and PET/CT showed no abnormal findings in September 2017, indicating a complete response (CR) following treatment with afatinib.

Discussion

The two most common *EGFR* mutations, exon 19 deletion and exon 21L858R, account for roughly 90% of all *EGFR*-mutation-positive NSCLC tumors (5-7). The remaining 10% include a heterogeneous group of molecular alterations within exons 18-21; these have been termed uncommon mutations (8). Exon 20 insertion mutations belong to a group of relatively rare uncommon mutations (Table) (3, 9-17). A review of the Wellcome Trust Sanger Institute's Catalogue of Somatic Mutations in Cancer (COSMIC) database showed that, of 7,066 unique samples from NSCLCs with identified *EGFR* mutations, only 114 (1.6%) contained exon 20 insertion. However, exon 20 insertion mutations have been reported to account for 5.8% of all *EGFR* mutations in Japan (2). Of the exon 20 insertion mutations that have been described to date, almost all occurred in the 14 amino acids of the N-lobe of EGFR, encompassing residues Glu762 to Cys775. Publications have reported 51 variants of exon 20 insertion mutations occurring in these 14 amino acids (18). Unlike common *EGFR* mutations, the crystal structure of exon 20 insertion mutations does not alter the adenosine triphosphate (ATP) binding pocket that is required for kinase activity. Instead, these mutations form a wedge at the end of the C-helix that promotes the active kinase conformation but does not increase the affinity for EGFR TKIs (19). An analysis of approximately 20 representative EGFR exon 20 insertion mutations was carried out using *in vitro* systems, and in almost all cases, this mutation was shown to be an oncogenic driver mutation (19). However, whether or not this is true *in vivo* is unclear. In addition, D770_N771insG as detected by the cobas v2 kit was not examined in this report. Therefore, the EGFR exon 20 insertion in our case might not have been an oncogenic driver mutation.

Clinical evidence regarding common *EGFR* mutations has been obtained in prospective trials: an objective response rate (ORRs) of approximately 60% and a median progression-free survival (mPFS) of 9-13 months were observed in cases of lung cancer with common *EGFR* mutations treated with EGFR TKIs, such as gefitinib, erlotinib, and afatinib (5, 20-25). However, *EGFR* exon 20 insertion mutations are generally associated with insensitivity to available EGFR TKIs. Several studies on the EGFR TKI treatment response of NSCLC with EGFR exon 20 insertions

Table. Efficacy of EGFR TKIs in Patients with Non-small-cell Lung Cancer with EGFR Exon 20 Insertion.

Reference	EGFR exon 20 insertions/ total lung cancers tested (%)	EGFR exon 20 insertions/ all EGFR mutations (%)	TKI solo treatment (n)	Objective response rate (%)	PFS with EGFR TKI (months)	Median OS (months)
(9)	7/332 (2.1%)	7/54 (13.0%)	2 (Gef)	0	N/A	N/A
(10)	13/515 (2.5%)	13/253 (5.1%)	2 (Gef)	0	1.6	N/A
(11)	N/A	3/222 (1.4%)	3 (Gef or Erl)	0	1.0	1.5
(12)	N/A	7/119 (5.9%)	4 (2; Gef, 2; Erl)	0	N/A	N/A
(13)	27/1,086 (2.5%)	27/294 (9.2%)	8 (Erl)	0 (n=0/5)	2.4	16.5
(14)	33/1,500 (2.2%)	33/367 (9.0%)	2 (Erl)	0	N/A	>48 (n=15)
(15)	41/1,047 (3.9%)	41/1,047 (3.9%)	19 (Erl or Gef)	5.3 (n=1/19)	N/A	N/A
(16)	46/1,882 (2.4%)	N/A	11 (Erl)	27 (n=3/11)	2.5	26
(3)	N/A	23/600 (3.8%)	23 (Afa)	8.7 (n=2/23)	2.7	9.2
(17)	29/3,910 (0.74%)	29/1,560 (1.9%)	29 (Erl or Gef or Ico)	6.9 (n=2/29)	1.9	12.9

EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor, PFS: progression-free survival, OS: overall survival, PR: partial response, Gef: gefitinib, Erl: erlotinib, Afa: afatinib, Ico: icotinib, N/A: not available

have been published, but these have included relatively few patients (Table). The average ORR and mPFS in those studies were 4.8% (range: 0-27%) and 2 months (range: 1-2.7 months), respectively. Naidoo et al. reported an ORR of 27%, the best among these studies (16). They identified the insertion sequence variant A763_Y764insFQEA in one patient out of three who showed a partial response. Yasuda et al. reported that this variant is highly sensitive to EGFR TKIs *in vitro* (19). This sequence variant accounts for approximately 7% of all reported EGFR exon 20 insertions (2). However, this sequence variant was undetectable with the commercially available mutation screening approach we used in the present case.

Furthermore, the EGFR exon 20 insertion variants that commercially available mutation screening approaches can detect have been traditionally thought to confer resistance to EGFR TKIs (26). Kobayashi and Mitsudomi reported the *in vitro* sensitivities of Ba/F3 cells expressing each EGFR mutation to various TKIs (2). In that study, the inhibition concentration 50% (IC_{50}) value of gefitinib was 4.8 and 26 nM for the common mutations delE746_A750 and L858R, respectively. In contrast, the IC_{50} value of afatinib was 72 and 86 nM for V769_D770insASV and D770_N771insSVD, respectively. Although we were unable to identify the exon 20 insertion sequence variant in our case, afatinib might have been effective to some extent.

The majority of compound *EGFR* mutations comprise one common mutation and an uncommon partner mutation (4). In a 2006 study, 7 (6.9%) of 102 *EGFR*-mutation-positive cases were *EGFR* compound mutations (27). Kim et al. reported that an *EGFR* compound mutation was detected in 15 (24.6%) of 61 cases of *EGFR*-mutation-positive lung adenocarcinoma in 2016 (4). In this case, we observed a combination mutation involving exon 19 deletion and exon 20 insertion that had previously only been reported in two cases (17). The detection rate of *EGFR* compound mutations has gradually increased year after year, and between-study differences in detection rates may be attributed to progress in sequencing technology and the sources of sequencing templates.

The efficacy of EGFR TKIs in patients with compound mutations has remained uncertain. A good response to afatinib was evident in our patient who had lung adenocarcinoma with *EGFR* compound mutations involving both exon 19 deletion and exon 20 insertion. Chen et al. treated two cases of *EGFR* compound mutations involving both 19 deletion and exon 20 insertion and one case involving exon 21L 858R and exon 20 insertion by EGFR TKIs and reported that each case showed an increased PFS of more than six months (17). Compared with patients whose combination mutations only involve uncommon mutations, those whose combination mutations include both an uncommon and a common mutation have shown a higher response rate (83% vs. 29%), longer mPFS (12.7 vs. 4.9 months), and longer median overall survival (24.7 vs. 12.3 months) after gefitinib treatment (28). These results suggest that common mutations might play a primary role in objective responses to EGFR TKIs.

The authors state that they have no Conflict of Interest (COI).

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