계명의대학술지 제33권 2호
Keimyung Med J
Vol. 33, No. 2, December, 2014

A Case of Patient with Lung Adenocarcinoma with Double Rare EGFR Mutation of G719C and L861Q

Jin Tak Yun, M.D., Gi Jun Kim, M.D., Shin Young Kim, M.D., Joon Won Jeong, M.D., Suk Young Park, M.D., Young Jun Yang, M.D., Ji Chan Park, M.D.

Department of Internal Medicine, Daejeon St. Mary's Hospital, The Catholic University of Korea College of Medicine, Daejeon, Korea

Abstract

The vast majority of epidermal growth factor receptor (EGFR) gene mutations are detected in lung adenocarcinoma. EGFR mutations are the strongest predictor of response to EGFR tyrosine kinase inhibitor (TKI) treatment in patient with advanced non-small cell lung cancer. Of these, exon 19 deletions and exon 21 L858R point mutations account for more than 80% of mutations detected in tumor with EGFR mutations, which called classical EGFR mutations, and double mutations mainly composed of classical and uncommon EGFR mutations are reported to be present in 13% of total EGFR mutations. But there has been no report to date of patient with double mutation of TKI sensitive uncommon EGFR mutations (G719C and L861Q). We experienced a case of patient with lung adenocarcinoma with double mutation of G719C and L861Q, the first case on our literature review, and showing partial response to TKI treatment.

Key Words : Adenocarcinoma, EGFR tyrosine kinase inhibitor, Lung cancer, Mutation

Introduction

The vast majority of epidermal growth factor receptor (EGFR) gene mutations are detected in lung adenocarcinoma. EGFR mutations are the strongest predictor of response to EGFR tyrosine kinase inhibitor (TKI) treatment in patient with advanced non-small cell lung cancer (NSCLC). EGFR-TKI therapy for NSCLC with EGFR mutation shows a significantly higher response rate, longer progression-free survival and better quality of life when compared with platinum-doublet chemotherapy [1].

EGFR Mutations were found in 10% to 20% of

Corresponding Author: Suk Young Park, M.D., Division of Oncology, Department of Internal Medicine, Daejeon St. Mary's Hospital, The Catholic University of Korea College of Medicine, 64 Daeheung-ro, Jung-gu, Daejeon 301-723, Korea
Tel : +82-42-220-9821 E-mail : sypark1011@hotmail.com

Caucasian patients and in 30% to 60% of Asian patients with NSCLC [2]. EGFR mutations occur more frequently in NSCLC of women, never smokers, and those with adenocarcinoma cell type [2]. Activating mutations in EGFR occur in exon 18 to 21, and most of the mutations in exon 18, 19 and 21 are regarded as sensitive mutations for EGFR-TKI [3]. Of these, exon 19 deletions and exon 21 L858R point mutations account for more than 80% of mutations detected in tumor with EGFR mutations [3], which called classical EGFR mutations.

There are other EGFR mutations, such as amino acid substitutions in E709, G719, S768, L861, and others. The number of these mutations are small and their influences on the effectiveness of EGFR-TKI have not been fully elucidated [2]. These small populations of EGFR mutations are collectively named 'uncommon mutation of unkown clinical significance' [2].

Double mutations mainly composed of classical and uncommon EGFR mutations are reported to be present in 13% of total EGFR mutations [2,4]. Double mutations of uncommon EGFR mutations are known to be very rare and Wu *et al*. reported 12 cases (32/627, 5.1%) [2].

But there has been no report to date of patient with double mutation of EGFR-TKI sensitive uncommon EGFR mutations (G719C and L861Q). We experienced a case of patient with lung adenocarcinoma with double rare EGFR mutation of G719C and L861Q, the first case on our literature review, and showing partial response to EGFR-TKI treatment.

Case Report

A 61-year-old man who was ex-smoker (20PY) referred our hospital with problem of abnormal chest X-ray finding. He had past history of hypertension and no family history of lung cancer. Chest computed tomography (CT) revealed a 3.3-cm lung mass in right lower lobe, superior segment. Bronchoscopic examination showed no endobronchial lesions. A positron emission tomography/computed tomography (PET/CT) scan revealed a lung mass in RLL superior segment with increased uptake of fluorodeoxyglucose (FDG)(SUVmax 7.1) and bone metastasis in T3, T10, T11, T12 vertebrae and right 12^{th} & left 3^{rd} rib. TNM staging was T2aNOM1b (Fig. 1A-1D). Percutaneous needle aspiration biopsy from tumor of the right lower lobe showed adenocarcinoma, consistent with lung primary (Fig. 2). EGFR mutation analysis was performed. Results showed that exon18 G719C and exon21 L861Q mutation were positive by PCR & pyrosequencing method.

Gefitinib (Iressa®) 250 mg daily was started in August 2013. After six week of gefitinib treatment, PET/CT scan showed decreased size of primary lung cancer and decreased uptake of fluorodeoxyglucose (FDG) in both lung and metastatic bone lesions. During a year, with treatment of gefitinib, the tumor response to gefitinib was partial response (Fig. 1E-1H) and the patient had been tolerable with some acne-like eruption.

Discussion

In the original reports by Lynch *et al.* [5] and Paez *et al*. [6], only one mutation per tumor was detected. However subsequent studies demonstrated the presence of more than one mutation per tumor sample, so called double mutant tumor.

Wu *et al.* [2] reported on a large group of lung cancer patients with uncommon EGFR mutations of

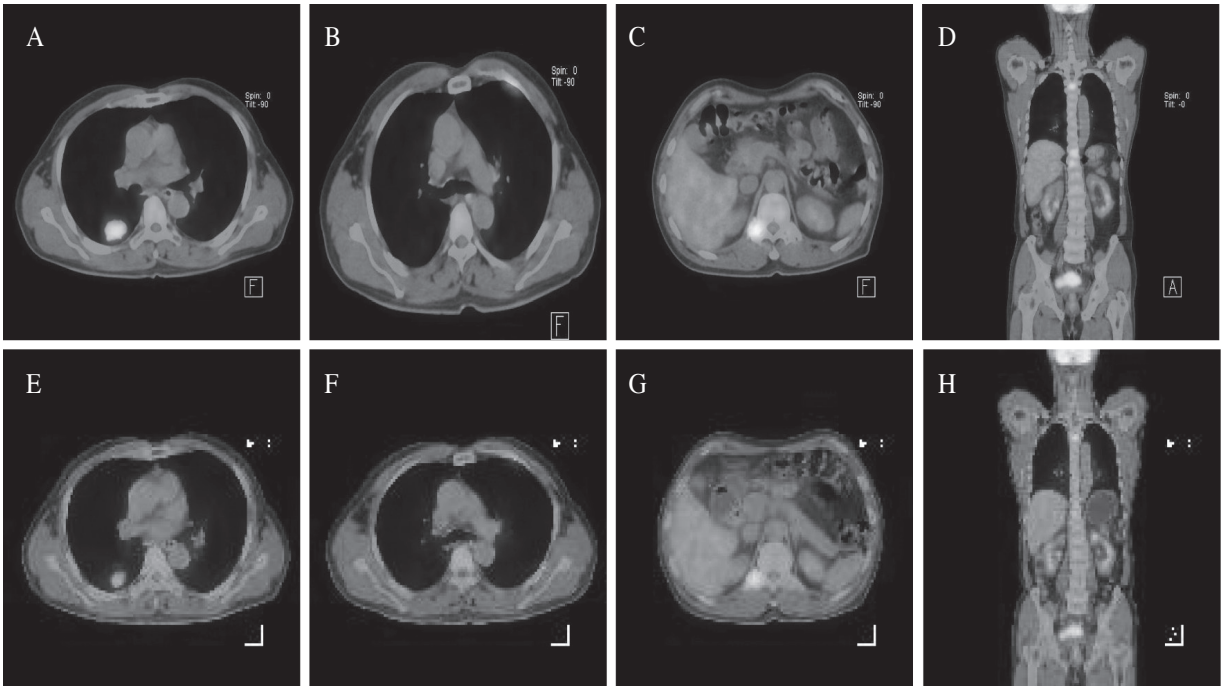

Fig. 1. A-D: PET/CT shows FDG uptake (A: RLL mass, B: left 3rd rib, C: right 12th rib, D: thoracic vertebrae). E-H: Six weeks later, PET/CT shows decreased intensity of FDG uptake (E: RLL mass, F: left 3rd rib, G: right 12th rib, H: thoracic vertebrae).

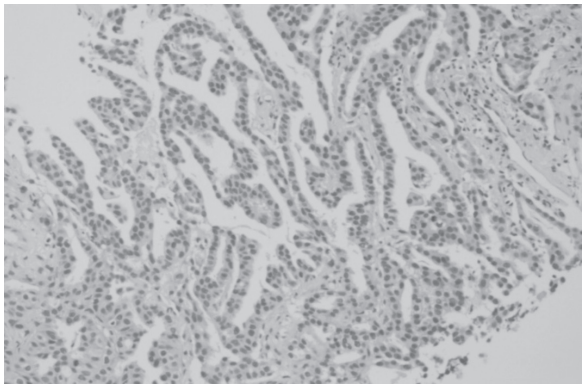

Fig. 2. Percutaneous needle aspiration biopsy from tumor of right lower lobe shows moderately differentiated adenocarcinoma of lung (×200).

unkown clinical significance and their association with treatment of EGFR-TKI. They reported two cases of uncommon mutations located in both G719 and L861. One case had double uncommon mutations of G719D and L861Q and response to TKI was partial response. Other case had double uncommon mutations of G719S and L861Q and response to EGFR-TKI was stable disease [2].

G719 and L861 are a minor portion of the total EGFR mutations and known to be associated with favorable effectiveness of EGFR-TKI, which is a little worse compared with well-known classical EGFR mutations, such as exon 19 deletion and exon 21 L858R [2].

Summary

We report a case of patient with double mutation of TKI sensitive uncommon EGFR mutations (G719C and L861Q). In our case, good

response to EGFR-TKI was expected because both mutations are sensitive to EGFR-TKI, especially *in vitro* sensitivity of 719C to EGFR-TKI was reported to be very high, but the response was similar with that of single mutation [6]. Double uncommon EGFR mutations of G719C and L861Q seem to be unique, the first case on our literature review, and needs to be added to data base for further study later.

Conflict of Interest

The authors report no conflict of interest in this work.

References

1. Tomonaga N, Nakamura Y, Yamaguchi H, Ikeda T, Mizoguchi K, Motoshima K, *et al*. Analysis of intratumor heterogeneity of EGFR mutations in mixed type lung adenocarcinoma. *Clin Lung Cancer* 2013;**14**:521-6.
2. Wu JY, Yu CJ, Chang YC, Yang CH, Shin JY, Yang PC. Effectiveness of tyrosine kinase inhibitors on 'uncommon' epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer. *Clin Cancer Res* 2011;**17**:3812-21.
3. Takagi Y, Nakahara Y, Hosomi Y, Hishima, T. Small-cell lung cancer with a rare epidermal growth factor receptor gene mutation showing 'wax-and-wane' transformation. *BMC Cancer* 2013;**13**:529.
4. Pallis AG, Voutsina A, Kalikaki A, Souglakos J, Briasoulis E, Murray S, *et al*. Classical' but not 'other' mutations of EGFR kinase domain are associated with clinical outcome in gefitinib-treated patients with non-small cell lung cancer. *Br J Cancer* 2007;**97**:1560-6.
5. Lynch TJ1, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al*. Activating mutations in the epigermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;**350**:2129-39.
6. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, *et al*. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;**304**:1497-500.