Case Report

Exon 19 L747P mutation presented as a primary resistance to EGFR-TKI: a case report

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Abstract: Active mutations of the *EGFR* gene have been proved to predict the activity of *EGFR*-TKI. The most common mutations are the exon 19 deletion and exon 21 point mutation, both of which are sensitive to *EGFR*-TKI. However, rare *EGFR* mutations or complex mutations still exist, and data of which are scarce and controversial. Their response to *EGFR*-TKI remains uncertain. We presented a patient diagnosed with stage IV lung adenocarcinoma who was found to have the *EGFR* mutation in exon 19 (*L747P*) before any treatment. The disease progressed 2 months after the chemotherapy containing cisplatin and pemetrexed, and erlotinib was administered, but there was no response found. This *EGFR*-TKI naïve patient failed to achieve the desired effect with the therapy of *EGFR*-TKI. *L747P* may be associated with primary resistance to EGFR-TKI in this case.

Keywords: *EGFR* 19 mutation; adenocarcinoma; lung

Submitted Feb 22, 2016. Accepted for publication Apr 29, 2016.
doi: 10.21037/jtd.2016.05.95
View this article at: http://dx.doi.org/10.21037/jtd.2016.05.95

Introduction

It has been reported that patients with non-small cell lung cancer (NSCLC) that harbor activating mutations of the *EGFR* gene may be sensitive to the *EGFR*-TKI therapy which has been proved to improve response and survival rate, therefore, clinical screening for *EGFR* gene has been widely performed for patients with NSCLC. *EGFR* mutation testing usually focuses on common mutations like the exon 19 deletion and exon 21 point mutation, both of which are sensitive to *EGFR*-TKI. However, beyond the identification of classic *EGFR* mutations, there are still rare or complex mutations which may or may not benefit from *EGFR*-TKI therapy. Up to now, we have little knowledge of rare or complex mutations, and the results in this field remain limited and controversial. Studies with large numbers of patients harboring these mutations need to be performed (1).

Case presentation

A 61-year-old Chinese male with a smoking history of 30 years (12 pack-years) began to cough associated with a large number of white sticky sputum since August 2014. CT scan of the chest showed that the right lower lobe consisted of a nodule (2.5 cm × 1.8 cm) (*Figure 1A*) and the mediastinal lymph nodes along with the right hilar lymph nodes enlarged. PET-CT showed that both the nodule in the right lung and the enlarged lymph nodes were related with high SUV (*Figure 1B*), and multiple bone metastases were revealed. After a percutaneous lung biopsy, the pathological diagnosis demonstrated that the nodular lesion was lung adenocarcinoma of the right lower lobe (invasive tiny papillary carcinoma) (*Figure 2*). The tumor markers, CEA, CA125, CYFRA211 and NSE elevated with values of 14.59 ng/mL, 58.96 U/mL, 6.48 ng/mL and 21.73 ng/mL, respectively. The patient was finally diagnosed with stage IV lung adenocarcinoma for multiple vertebra and rib metastases.

Genetic testing was performed using a paraffin slice from the tissue specimen by means of first-generation sequencing technique (Sanger) for the detection of *EGFR* gene 18, 19, 21, *K-ras* gene, *B-raf* gene, *ALK* gene, *ROS1* gene. As

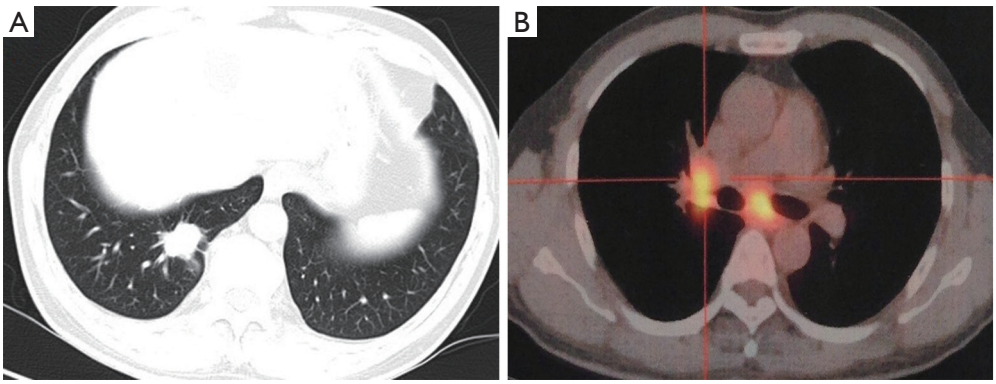

Figure 1 The medical image materials of the lungs on the first time the patient was diagnosed. (A) The computerized tomographic scan showed that the right lower lobe consisted of a nodule (2.5 cm × 1.8 cm); (B) the PET-CT image showed that the mediastinal lymph nodes and the right hilar lymph nodes enlarged and both were related with high SUV.

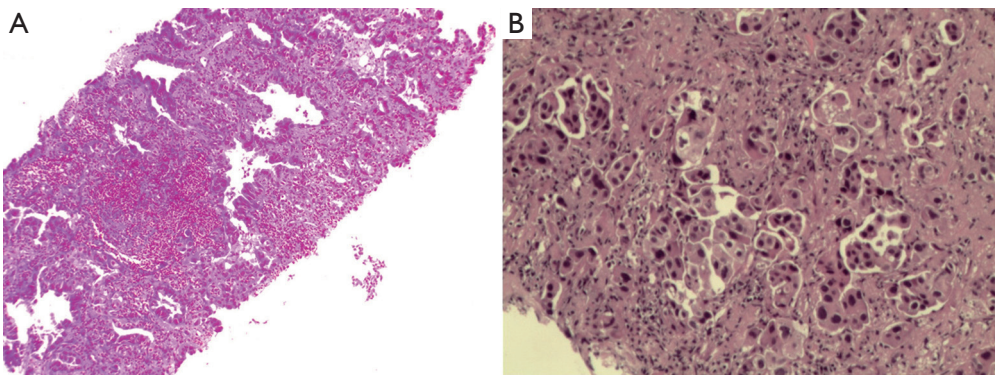

Figure 2 Histology of the primary tumor—an invasive tiny papillary adenocarcinoma (HE, A: 40×; B: 100×).

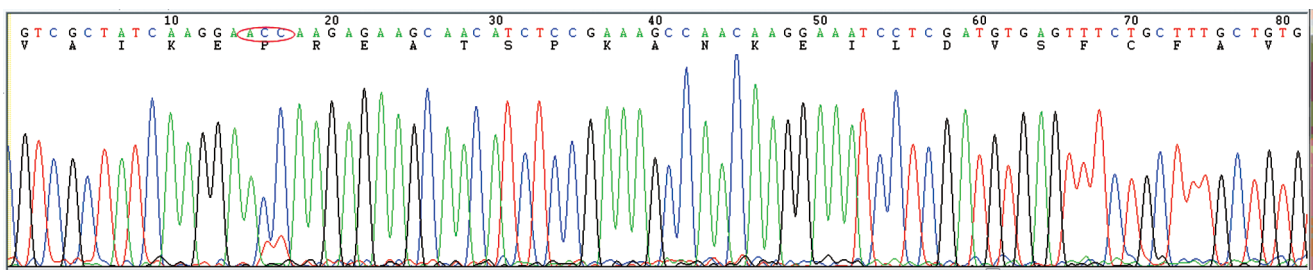

Figure 3 Gene sequencing results of the primary tumor. It showed the *EGFR* mutation *L747P* in exon 19.

shown in *Figure 3*, *L747P* was found in exon 19.

A platinum doublet was chosen as a first-line therapy according to the existing treatment protocol in 2009. Six cycles of combination chemotherapy containing cisplatin and pemetrexed was administered at 3-week intervals. The CT scan of the chest indicated that the lesion in the right lower lobe remained almost the same as before. The tumor markers as mentioned above returned to the base-line value, except NSE with values of 21.1 ng/mL out of normal range. The patient was judged as having a stable disease. After 2-month observation, the patient began to cough again with the right chest pain. The CT scan of the chest suggested that multiple small nodules could be seen in both lung fields (*Figure 4A*). The levels of the tumor markers increased significantly. The disease progressed obviously, and EGFR-TKI was chosen as a second-line therapy. He received the

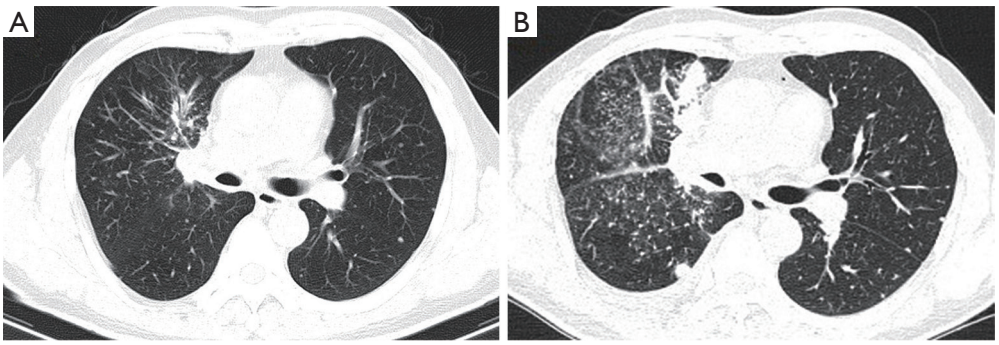

Figure 4 Computerized tomographic scan of the lungs before and after erlotinib was treated. Metastatic nodules in (B) were much more than those in (A).

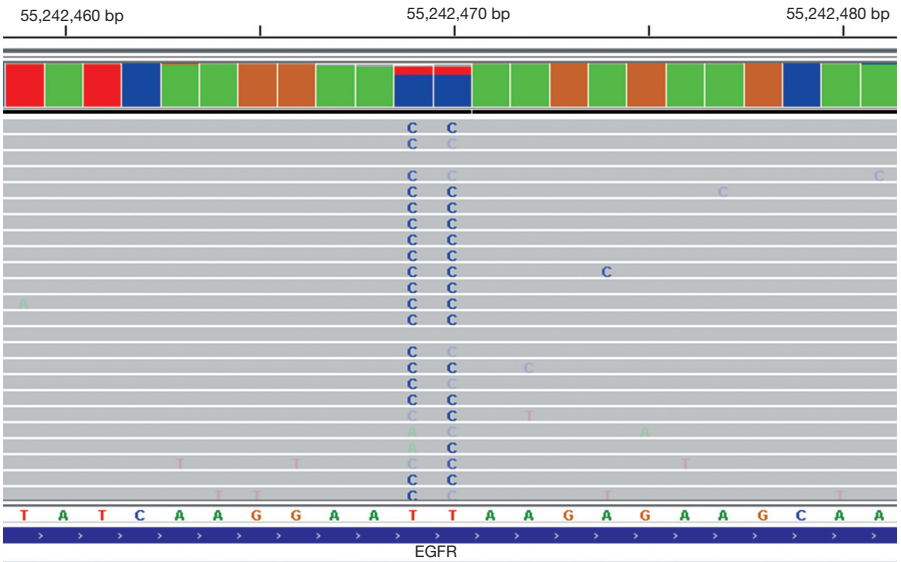

Figure 5 Gene sequencing (using whole blood as sample by means of ctDNA detection method) results of the tumor after 1-month treatment with erlotinib. It showed the *EGFR* mutation *L747P* in exon 19.

erlotinib therapy at a dose of 150 mg/d administered orally for 1 month. After that, the CT scan of the chest showed that much more metastatic nodules were found in both lungs (*Figure 4B*). The concentration of the tumor markers continued to rise rapidly. Obviously, the disease did not stop progressing, and erlotinib failed to achieve the desired response.

In order to study whether there were some changes of gene mutation after using chemotherapy and *EGFR*-TKI, we performed genetic testing again using a whole blood sample by means of next-generation sequencing (NGS) technique (ctDNA detection method). As shown in *Figure 5*, *L747P* missense mutation was found in *EGFR* exon 19, and the mutation abundance was 79.50%. This gene sequencing was consistent with the first-generation gene sequencing result in the primary tumor tissue.

Discussion

Previous studies have shown that exon 19 deletion and exon 21 point mutation of *EGFR* are sensitive to *EGFR*-TKI in patients with advanced NSCLC. Most of the deletions in exon 19 encompass the amino acids from codons L747-750 (LRE fragment) which activate *EGFR* and respond to *EGFR*-TKI, while the other deletions which do not involve any of the LRE fragment are reported to have a worse response (2). This may be because that the LRE deletion mutation can significantly change the conformation of a

protein in this region from the initial to the "active dimer" state and can keep the state longer (3).

Recently, some mixed insertion/substitutions are found in exon 19. A few patients with the *L858R-EGFR*-activating mutation that acquired the secondary *L747S* mutation after treatment to gefitinib and became resistant to gefitinib subsequently have been reported. Further researches have shown that a dose escalation of gefitinib or a switch to erlotinib, both ways increase a dose of reversible TKI, would lead to beneficial clinical effects in these *L858R-L747S*-mutant patients (4,5). The mechanisms of these secondary mutations resistant to *EGFR*-TKI may be associated with the BIM up-regulation and the mitochondrial apoptosis pathway. As the *L858R-L747S* attenuates both the up-regulation of BIM and apoptosis, a dose escalation of reversible TKI would change the situation of TKI resistance (6).

Intense researches in NSCLC have identified two major mechanisms of resistance to *EGFR*-TKI: secondary resistance mutations and "oncogene kinase switch" systems (7). The *EGFR T790M* mutation as the most common secondary resistance mutation is the first identified mechanism of acquired resistance to *EGFR*-TKIs. Other secondary mutations (*D761Y*, *L747S*) seem to be rare (4-6,8).

We presented a patient diagnosed with stage IV lung adenocarcinoma who was found to have the *EGFR* mutation in exon 19 (*L747P*). After the first-line chemotherapy, the patient was judged as having a stable disease. Two months later, the disease progressed and the erlotinib was chosen as the second line therapy. However, the disease did not stop progressing. In recent studies in China, two patients with lung adenocarcinoma harboring *L747P* mutation before any treatment were found to be resistant to *EGFR*-TKI (9,10). Besides, a recent study in Japan showed that *L747S* mutation associated with *EGFR*-TKI resistance was detected in some NSCLC patients, none of whom had ever received *EGFR*-TKI (11). In our study, we performsed next-generation sequencing (NGS) by means of ctDNA detection method and *L747P* missense mutation was found in exon 19 of *EGFR*. We indicated that the patient failed to achieve the desired effect after using erlotinib because of harboring *L747P* mutation in exon 19 of *EGFR*.

Conclusions

We reported a patient with advanced NSCLC who had the *EGFR* mutation *L747P* in exon 19. This *EGFR*-TKI naïve patient failed to achieve the desired effect with the therapy of TKI. *L747P* may be associated with primary resistance. Because data are limited and results may vary, the mechanism of the *L747P* mutation resistance to *EGFR*-TKI needs further investigation.

Acknowledgements

The authors would like to thank Guangzhou Burning Rock Clinical Lab Co., Ltd for the next-generation sequencing using whole blood as sample by means of ctDNA detection method.

Funding: This work was supported by Jiangsu Provincial Special Program of Medical Science (BL2012023), and Clinical Medical Center of Suzhou.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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Cite this article as: Wang YT, Ning WW, Li J, Huang JA. Exon 19 L747P mutation presented as a primary resistance to EGFR-TKI: a case report. J Thorac Dis 2016;8(7):E542-E546. doi: 10.21037/jtd.2016.05.95