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CASE REPORT

Non-small cell lung cancer harboring a rare *EGFR* L747P mutation showing intrinsic resistance to both gefitinib and osimertinib (AZD9291): A case report

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Abstract

The most common *EGFR* mutations in non-small cell lung cancer are exon 19 deletions and exon 21 point mutations, which are both sensitive to *EGFR*-tyrosine kinase inhibitors. However, rare *EGFR* mutations do exist and how these mutations respond to tyrosine kinase inhibitors is not well understood. A Chinese woman diagnosed with stage IV lung adenocarcinoma harbored a rare *EGFR L747P* (2239-2240 TT > CC) mutation, and treatment with gefitinib and osimertinib failed to achieve the desired effect. Herein, possible correlations between gene analysis and the outcomes of subsequent treatment are discussed.

Background

Lung cancer is the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases.[1] *EGFR* is one of the earliest identified driver mutations.[2] Approximately 47–54% of patients diagnosed with advanced NSCLC in China harbor *EGFR* mutations.[1] Exon 19 deletions and exon 21 *L858R* mutations account for approximately 45% and 40% of all *EGFR* mutations, respectively,[3] while other mutations are rare. Inhibiting *EGFR* signaling is an effective molecular target therapy. Gefitinib, erlotinib, and afatinib have been approved as first-line-therapy for advanced NSCLC patients harboring *EGFR* activating mutations.[4–6] Patients with *EGFR* mutations, particularly those with exon 19 deletions or *L858R* mutations, are sensitive to tyrosine kinase inhibitors (TKIs). However, 20–30% of *EGFR* mutated patients develop resistance to gefitinib/erlotinib within three months,[7] and almost all patients with activating *EGFR* mutations initially responsive to *EGFR*-TKIs acquire resistance after 8–16 months of therapy. T790M has been identified as an important marker of acquired TKI resistance.[8] Nearly 50–60% of patients with advanced NSCLC have secondary mutations with *T790M* after developing *EGFR*-TKI resistance.[8,9] Although osimertinib has been used to treat T790M mutated patients, the choice of subsequent treatments after resistance to first generation TKIs remains a major challenge.

In this report, we present the case of a patient with lung adenocarcinoma harboring a rare type of mutation in *EGFR* exon 19: *L747P* (2239-2240 TT > CC). The patient developed intrinsic resistance to both gefitinib and osimertinib, and underwent various subsequent treatments, including anti-angiogenesis and anti-PD-1 monoclonal antibody therapy after rapid progression of pulmonary and bone metastases.

Case Report

A 54-year-old non-smoking Chinese woman underwent chest computed tomography (CT) screening, which revealed a nodule in her left upper lung and an enlarged lymph node in the ipsilateral mediastinum and hilum. After physical examination, abdominal CT, single photon emission CT bone scan, and magnetic resonance imaging (MRI) of the head, no signs of distant metastasis were observed. A left upper lung lobectomy and lymphadenectomy was conducted, and postoperative diagnosis of moderate-poorly differentiated adenocarcinoma of the left upper lung with mediastinal lymph node metastasis was made. Immunohistochemistry showed that the tumor cells were negative for ALK-Ventana and ROS-1 (Fig 1a–c), but positive (≥ 50%) for PD-L1 (Fig 1d). Genetic analysis of *EGFR* by amplification refractory mutation system showed an exon 19 deletion.

Postoperative chemotherapy was administered with four cycles of pemetrexed (500 mg/m^2 IV day 1) and cisplatin (75 mg/m^2 IV, split over three days), followed by radiotherapy to the mediastinum and bronchial stump (50.40 Gy in 1.8 Gy fractions). Four months later, multiple metastases in the thoracic vertebrae were detected via positron emission tomography-CT (PET-CT).

Oral gefitinib treatment was immediately administered at a daily dose of 250 mg, with concurrent radiotherapy (45 Gy in 3 Gy fractions) to the eighth thoracic vertebra. One month after commencing gefitinib treatment, chest CT revealed that the patient had asymptomatic multiple pulmonary metastasis and MRI revealed new vertebral metastatic lesions. Gefitinib treatment was continued for another three months, until the patient complained of exacerbating back pain. A chest CT and spinal MRI revealed that the metastatic nodules in her lungs (Fig 2a) and progressive metastatic lesions in her vertebra (Fig 2b) had increased in number and size. As a result, gefitinib treatment was discontinued.

Next-generation sequencing (NGS) analysis with a panel covering 390 cancer-related genes was performed, and a rare mutation of *EGFR L747P* in exon 19 was found in both the pretreatment surgical formalin-fixed paraffin embedded (FFPE) and plasma (ctDNA) samples, and a *TP53 Q331* mutation at exon 9 was detected in the FFPE sample. Second-line oral afatinib was administered, but was discontinued two weeks later because of intolerable diarrhea and mucosal ulceration.

Erlotinib (oral 150 mg daily) and bevacizumab (7.5 mg/kg IV every 21 days) were then administered with concurrent radiotherapy at the vertebrae (40 Gy in 2 Gy fractions) and pelvis (51 Gy in 3 Gy fractions). The patient achieved stable disease for seven months until chest CT revealed a soft tissue mass in the right hilum (Fig 2d) and enlarged nodules in the left residual lung (Fig 2c). PET-CT also revealed high 18-F fluorodeoxyglucose (FDG) uptake nodules in the left residual lung. Resection of the enlarged nodules was performed, and postoperative diagnosis of poorly differentiated adenocarcinoma was made showing tumor cells negative for ALK-V, ROS-1, and PD-L1 (Fig 1e). Further NGS analysis was performed on the FFPE sample, which revealed *EGFR L747P* and *TP53 Q331* mutations, *MYC* amplification, and a high tumor mutation burden (TMB). As a result, oral osimertinib was administered in place of erlotinib and bevacizumab. In the second month of oral osimertinib treatment, PET-CT showed increased 18F-FDG uptake in the right hilar lymph node

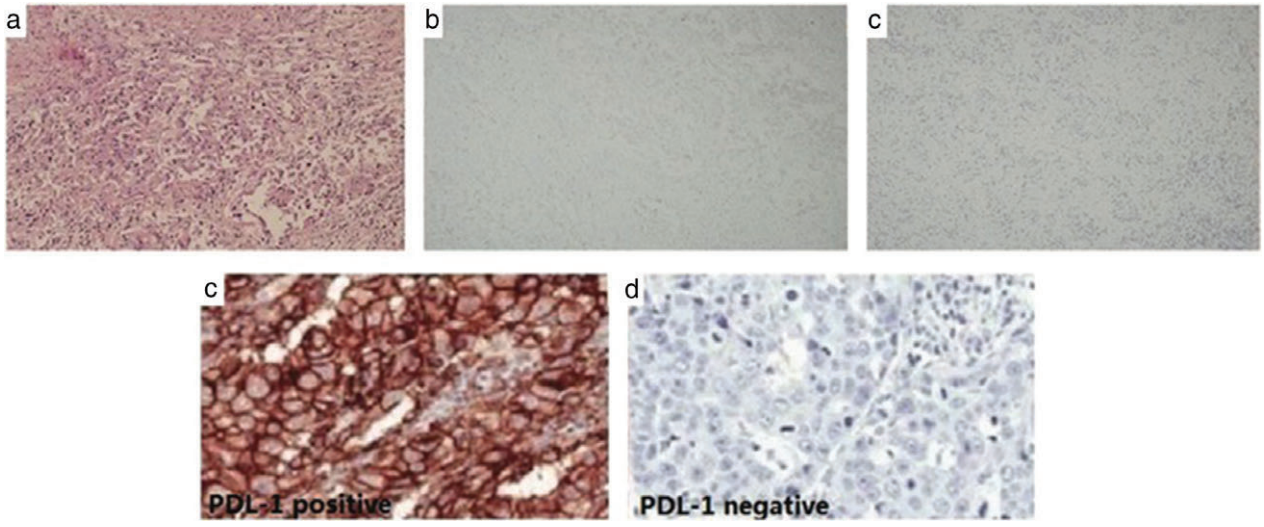

Figure 1 (**a**) Histology of the primary tumor: poorly differentiated adenocarcinoma (HE100X); immunohistochemistry: (**b**) ALK-V (–), (**c**) ROS-1(–) (100X); (**d**) PD-L1 positive in the primary tumor sample (pretreatment surgical sample); (**e**) PD-L1 negative in the metastatic tumor.

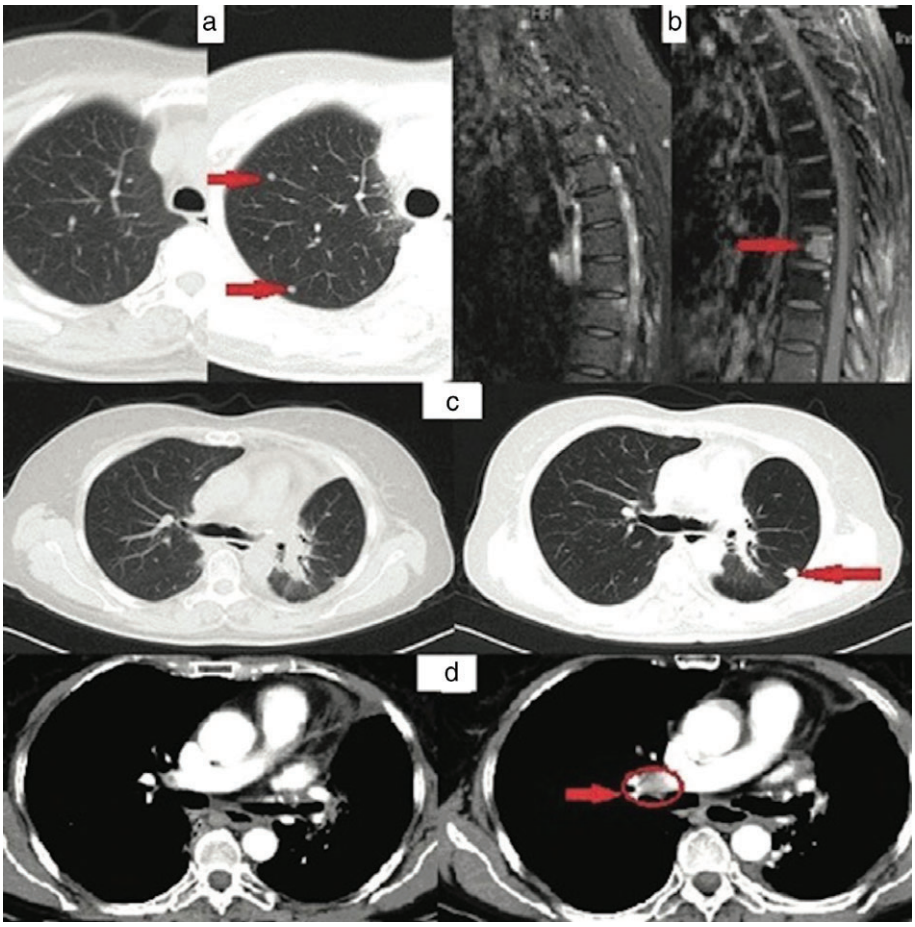

Figure 2 Computed tomography (CT) scan of the lungs before and after gefitinib treatment: (**a**) the metastatic nodules in the patient's lungs and (**b**) progressive metastatic lesions in the vertebra increased in number and size. CT scan of the lungs before and after erlotinib plus bevacizumab: (**c**) showing the enlarged nodule of the left residual lung and (**d**) new soft tissue in the right hilar lymph node.

(standardized uptake value 7.64) (Fig 3a,b), indicating disease progression, thus osimertinib was discontinued. Because PD-L1 was positive in the first FFPE and a high TMB was observed in the second surgical FFPE sample, a pembrolizumab plus cisplatin-pemetrexed regimen was administered for three cycles until increased 18F-FDG uptake in the right pleural mass (max standardized uptake value 6.6) (Fig 3c,d) was observed in a PET-CT scan, suggesting disease progression. Thus, abraxane and carboplatin were administered.

Discussion

Resistance to *EGFR*-TKIs can be categorized into primary or acquired resistance. Primary resistance refers to the immediate inefficacy of *EGFR*-TKIs, while acquired resistance is progression of the disease after a duration of clinical benefit. Acquired resistance to TKIs in patients with advanced NSCLC harboring sensitive *EGFR* mutations has been well documented;[10,11] however, knowledge of primary TKI resistance is limited.

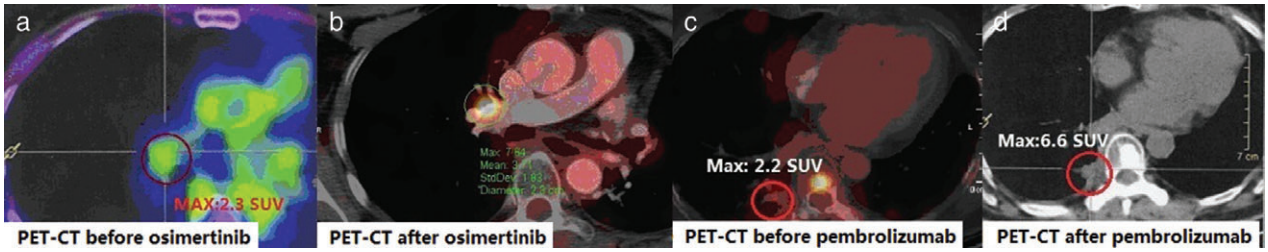

Figure 3 Positron emission tomography-computed tomography (PET-CT) taken (**a**) before and (**b**) two months after osimertinib administration, demonstrating higher 18F-fluorodeoxyglucose (FDG) uptake in the right hilar lymph node (standardized uptake value [SUV] 7.64) after treatment. PET-CT taken (**c**) before and (**d**) after three cycles of pembrolizumab plus cisplatin-pemetrexed, showing increasing 18F-FDG uptake of the right pleural mass (max SUV value 6.6) after treatment.

In our case, the patient showed rapid resistance to gefitinib. None of the existing mechanisms for primary resistance were found, such as somatic *T790M* mutation and germline T790M polymorphism, germline *EGFR V843I* mutation, or deletion polymorphism in BIM.[12–17] Instead, NGS revealed a rare primary *EGFR* mutation, *L747P* in exon 19 within the pretreatment tumor, implying close correlation with the rapid resistance to gefitinib.

EGFR L747P mutations have been observed in very few *EGFR*-TKI naive NSCLC patients. Two patients exhibited resistance and disease progression during gefitinib or erlotinib treatment, suggesting that this *L747P* mutation is associated with resistance to first generation TKIs.[18,19] *EGFR L747P* mutation also correlated with primary resistance to gefitinib in our case.

Another noteworthy finding in our case is that the *EGFR L747P* mutation was resistant to osimertinib treatment. To our knowledge, this is the first case to report the efficacy of the third generation TKIs in an NSCLC patient harboring this rare mutation. Osimertinib has achieved an objective response rate of 61% and progression-free survival (PFS) of 9.6 months in patients with *T790M*-induced TKI resistance. In addition, osimertinib is associated with a response rate of 21% among patients without detectable *T790M* and a lower rate (11%) among patients who were T790M-negative and had received a TKI immediately before AZD9291.[20] Eberlein *et al.* suggested certain *NRAS* mutations (*E63K, G21V*) or *NRAS* gain are the most frequent genetic modifications able to drive resistance to osimertinib. Furthermore, in their transgenic models, a combination of osimertinib with selumetinib or aurora kinase B inhibitor AZD1152-HQPA made osimertinib-resistant tumors more sensitive.[21] Thress *et al.* reported that 11 out of 15 NSCLC patients acquired *EGFR C797S* mutations after developing osimertinib resistance, and hypothesized that *EGFR-C797S* is a mediator of acquired resistance to osimertinib.[22] In our case, the patient harbored an *L747P* mutation and exhibited no response to osimertinib. Because of the rarity of this mutation, the relationship between *L747P* mutations and osimertinib resistance requires further study.

The patient in our case harbored a primary *TP53 Q331* mutation in exon 9 concurrent with the *EGFR L747P* mutation. A *TP53* mutation in exon 9 shows an association with increased *SOX2* expression.[23] *SOX2* amplification is reported to correlate with resistance to icotinib in *EGFR-T790M* negative patients.[10,24] However, the impact of the *TP53* mutation on resistance to TKIs in this case is unclear.

MYC amplification was another genetic alteration found in this patient, which appeared in the metastatic tumor after osimertinib treatment. We could not evaluate whether *MYC* conferred resistance to first-line TKI therapy in this case because of the lack of corresponding data to compare with NGS data obtained after treatments. The association of *MYC* amplification with resistance to the third generation TKIs has not previously been reported and thus requires further evidence to clarify.

In this case, combined erlotinib and bevacizumab possibly enhanced the responsiveness of TKIs in *L747P*-mutated NSCLC. The combination therapy of erlotinib and bevacizumab following gefitinib resistance achieved PFS of seven months. Upregulation of the *EGFR* signaling pathway enhances the production of angiogenic factors, including *VEGF*, and dual blockade of *VEGF* and *EGFR*, resulting in additive anti-tumor activity,[25,26] and may prove to be an alternative treatment in advanced NSCLC with resistance to first generation TKI.[27] Because of the patient's intolerance to afatinib, the efficacy of subsequent second generation TKIs cannot be evaluated in this case. Data has shown the effectiveness of an afatinib/cetuximab regimen for patients with tumor progression after *EGFR*-TKI treatment.[28] However, re-administering first and second generation TKIs after gefitinib failure is not a standard practice and needs to be validated.

The patient in our case showed 50% positivity of PD-L1 in the primary tumor and high TMB in the metastatic tumor, both relating to clinical benefit from treatment with antibodies directed against the PD-1 immune checkpoint receptor.[29,30] However, despite treatment with pembrolizumab and cisplatin-pemetrexed, the disease was still out of control with PFS of barely four months. Although activation of the oncogenic *EGFR* pathway may enhance the susceptibility of lung cancer to PD-1 blockade in animal models,[31] recent data suggests that patients with *EGFR* mutations have a lower response rate to PD-1 inhibitors compared with patients without these genetic alterations.[32] The unfavorable outcome of the PD-1 inhibitor in this case is not comparable with other series because it was administered as fourth-line therapy, which is not a standard treatment, and our patient harbors a rare *EGFR* mutation.

In conclusion, the results of this case suggest that the rare *EGFR L747P* mutation in exon 19 confers resistance to both the first generation TKI gefitinib and the third generation TKI osimertinib, while combined bevacizumab and erlotinib showed efficacy for disease control. It is necessary to seek strategies to overcome *L747P* associated TKI resistance.

Disclosure

No authors report any conflict of interest.

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