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CASE REPORT

A promising response to osimertinib in a patient with erlotinib-resistant lung adenocarcinoma with an uncommon EGFR mutation

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SUMMARY

Most patients with non-small cell lung cancer with common epidermal growth factor receptor (EGFR) mutations respond dramatically to EGFR tyrosine kinase inhibitors (TKIs), but data are limited on the response of tumours with uncommon mutations. We present the case of a 68-year-old man with stage IV lung adenocarcinoma with an uncommon EGFR mutation in exon 21 (L861Q). The disease progressed 2 years after he started erlotinib (150 mg daily). Using a transbronchial lung biopsy, we detected additional mutations in exon 20 (T790M) and exon 21 (L858R). He was treated with osimertinib (80 mg daily) and achieved a partial remission. This case demonstrates the value of repeating a biopsy after EGFR-TKI therapy in patients with uncommon EGFR mutations.

BACKGROUND

Lung cancer is the leading cause of death worldwide.[1] Cytotoxic chemotherapies such as platinum-based regimens were once the primary therapeutic option for non-small cell lung cancer (NSCLC), but their efficacy is limited. The prognosis of advanced NSCLC depends on the presence of driver mutations. Epidermal growth factor receptor (*EGFR*) mutations are the most common driver mutations.[2] Many patients with *EGFR* mutations have benefitted from EGFR tyrosine kinase inhibitors (EGFR-TKIs).

Recent research has focused on acquired resistance to first-generation or second-generation EGFR-TKI therapy. The resistance is caused by a T790M gatekeeper mutation in over half of all patients.[3 4] A third-generation EGFR-TKI, osimertinib, is considered effective in the patients with T790M.[5] However, most of the studied patients have had common *EGFR* mutations, such as exon21 L858R or exon 19 deletions. The sensitivity to EGFR-TKI of tumours with uncommon mutations has not been sufficiently studied.[6] In addition, we have little evidence that T790M is found in tumours from patients with uncommon mutations after initial treatment with EGFR-TKI. Re-biopsy of patients with uncommon mutations after EGFR-TKI therapy may be necessary to detect any newly acquired mutations. The acquired T790M mutations might be present as a minor clone before treatment, or they might evolve during the course of EGFR-TKI treatment.[7] In this report, we discuss the case of a patient with an uncommon *EGFR* mutation who became resistant to erlotinib after acquiring the T790M mutation, but then responded to osimertinib therapy.

CASE PRESENTATION

A 68-year-old man with a smoking history (8 pack-years) presented with exertional dyspnoea since 2013. A CT scan of the chest revealed a nodule (2.8 cm×1.4 cm) in the right lower lobe and pleural effusion. The mediastinal, hilar and supraclavicular lymph nodes were enlarged (figure 1). Positron emission tomography-CT showed that the nodule in the right lung and the enlarged lymph nodes were related, with high standardised uptake value (figure 2). A biopsy was taken of the pleural effusion, and the pathological diagnosis was lung adenocarcinoma of the right lower lobe. The tumour markers carcinoembryonic antigen and Sialyl Lewis X were elevated (111.8 ng/mL and 300 U/mL, respectively). The patient was diagnosed with T1bN3M1b stage IV lung adenocarcinoma with pleural seeding. *EGFR* exons 18, 19, 20 and 21 were sequenced (real-time PCR Cycleave and fragment analysis) using DNA from a section of the pleural effusion cell block. As shown in figure 3, a mutation was found in exon 21 (L861Q).

Erlotinib therapy (150 mg/day taken orally) was chosen as a first-line therapy. Within 6 months, the patient experienced a partial remission of the lung disease. The CT scan indicated that the nodule in the right lower lobe was smaller and the pleural effusion was decreased (figure 4). Because of a severe rash, we reduced the erlotinib dose to 100 mg/day. After 2 years of observation, a CT scan showed that the

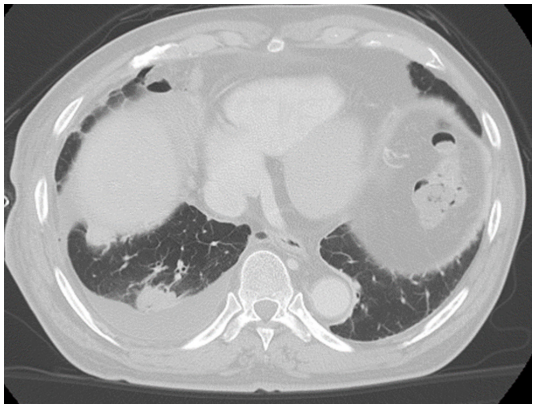

Figure 1 A CT scan before any treatment showed a nodule (2.8 cm×1.4 cm) in the right lower lobe and pleural effusion.

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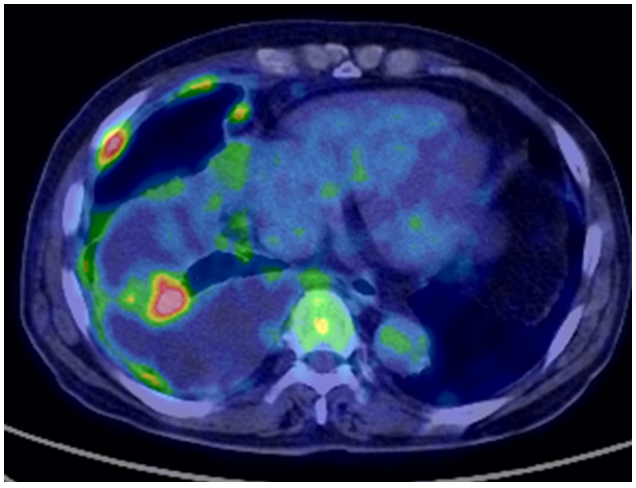

Figure 2 Positron emission tomography-CT before any treatment showed the nodule in the right lung, the enlarged lymph nodes and pleural seeding.

lesion in the right lower lobe had grown, and a new nodule could be seen in the right middle lobe (figure 5). We continued the erlotinib therapy because the patient had no symptoms. After 5 months, the CT scan showed the lesions had grown even larger (figure 6). At this time, we performed transbronchial lung biopsy on a new region. We detected an exon 20T790M mutation and an exon 21L858R mutation, but did not find an exon 21 L861Q mutation. The patient was started on osimertinib (80 mg/day). After 6 weeks, a CT scan showed a partial remission of the lung disease (figure 7).

OUTCOME AND FOLLOW-UP

Currently, the patient is doing well without any side effects and continues on osimertinib. As previously described, the CT

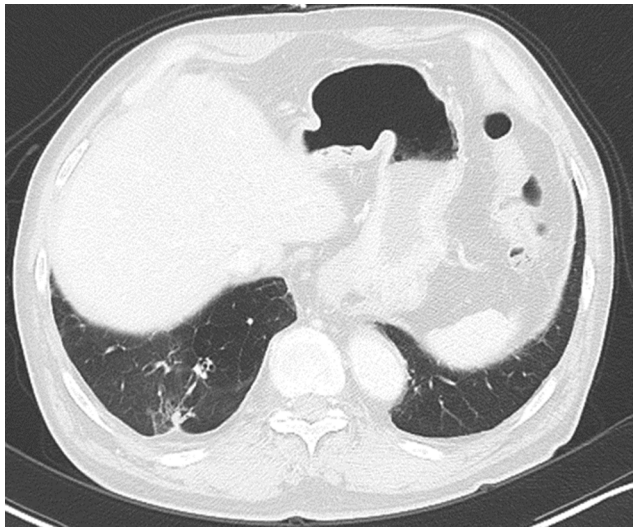

Figure 4 A CT scan after 6 months of erlotinib treatment showed that the nodule in the right lower lobe had shrunk and the pleural effusion had decreased.

scan showed the tumour of the patient shrinked. In addition, the tumour marker carcinoembryonic antigen (CEA) elevated 69.4 ng/mL before the osimertinib administration, and CEA 17.7 ng/mL after the administration of the osimertinib for 2 months.

DISCUSSION

Recent studies have suggested that G719X, S768I and L861Q constitute approximately 6% of all EGFR mutations.[8] The clinical effectiveness of the first-generation EGFR-TKI for tumours with these uncommon mutations is lower than for tumours

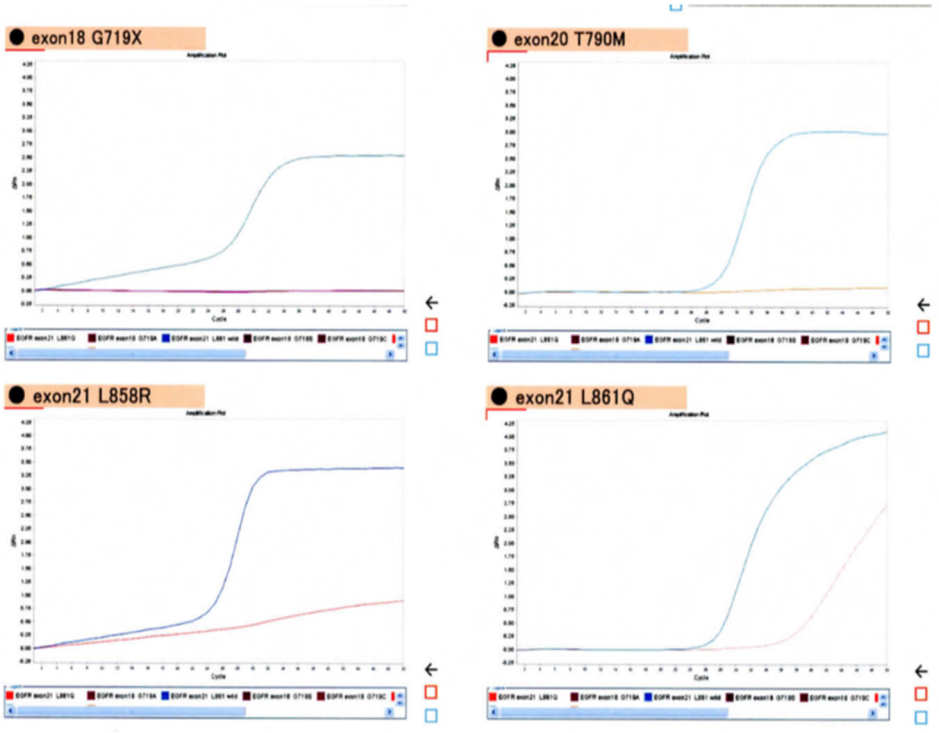

Figure 3 A cell block containing pleural effusion was taken before erlotinib treatment and analysed by real-time PCR Cycleave for EGFR mutations. It shows a signal strength that detected DNA density by a blue line, the fluorescence in a red line, we could judge the upward trend of the red line which accompany a blue line as positive.

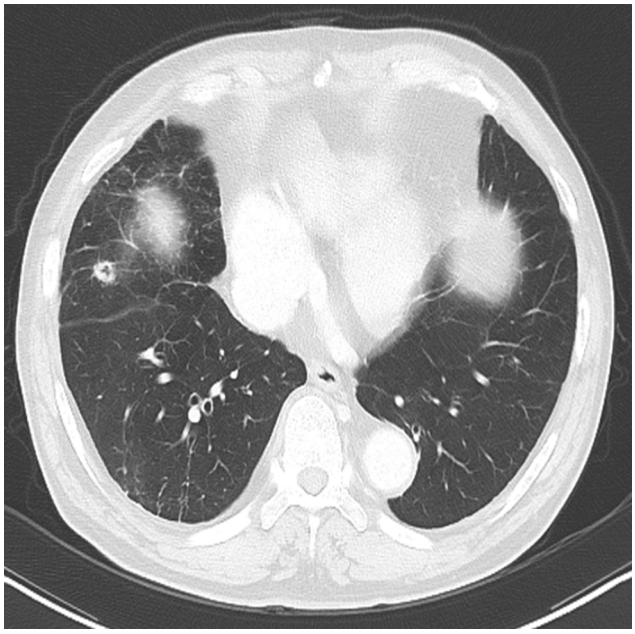

Figure 5 A CT scan after 2 years of erlotinib treatment showed a new nodule in the right middle lobe.

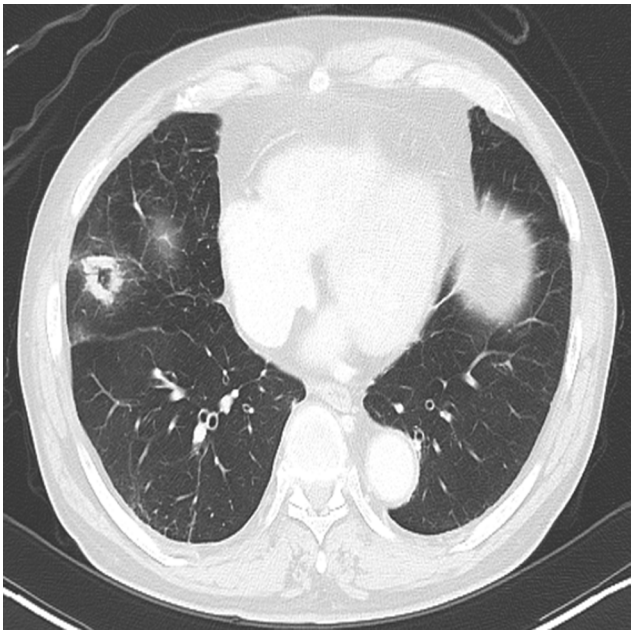

Figure 6 A CT scan after 2 years and 5 months of erlotinib treatment showed that the new lesion was much larger.

with common mutations, such as exon 19 deletions and exon 21L858R. Compared with patients with common mutations, patients with uncommon mutations had a significantly lower tumour response rate (41.6% vs 66.5%; p<0.001) and progression-free survival (PFS) (median, 7.7 vs 11.4 months; p<0.001).[6] The second-generation EGFR-TKI, afatinib, was found to be active in patients with the uncommon mutation L861Q.[9]

After EGFR-TKI treatment, NSCLC tumours with EGFR mutations regrow because of acquired resistance. Several resistance mechanisms have been proposed, including acquisition of a T790M mutation in EGFR exon 20, transformation to small cell lung cancer and the emergence of bypass signalling pathways such as MET, human epidermal growth factor receptor 2, insulin-like growth factor 1 receptor and AXL.[4 10 11]

The most frequent reason for failure of first-generation EGFR-TKI is thought to be acquisition of a T790M mutation.[3] Osimertinib is a third-generation EGFR-TKI. In patients with T790M mutations in a large phase I trial, the osimertinib response rate was 61% and PFS was 9.6 months.[5] Since osimertinib was approved in Japan in March 2016, our goal has been to detect T790M mutations in patients with acquired resistance to EGFR-TKI who could potentially benefit from osimertinib.

We diagnosed a patient with stage IV lung adenocarcinoma with the exon 21 mutation L861Q in 2013 and chose the first-line therapy, erlotinib. Although previous studies reported that the PFS of patients with uncommon mutations treated with first-generation EGFR-TKI was 7 months on average, our patient survived 2 years without progression. After the disease progressed, we took a biopsy of the patient's lung and detected the EGFR exon 20 mutation T790M and the exon 21 mutation L858R. This result suggested two possibilities. First, the patient might have started with the L861Q mutation before treatment and acquired the T790M mutation, leading to EGFR-TKI resistance. Alternatively, the patient's tumour may have been heterogeneous before treatment, containing a portion with the L858R mutation and a portion with the L861Q mutation. Because the patient was successfully treated with erlotinib for 2 years, we favour the latter possibility and hypothesise that the T790M mutation arose in the portion of the tumour with the L858R mutation.

Mutational heterogeneity is common in NSCLC. Hata *et al*[7] reported that three out of ten patients exhibited T790M heterogeneity between tissue from a primary tumour and metastases without cerebrospinal fluid. Furthermore, Chen *et al*[12] analysed EGFR mutations in primary lung tumours and metastases from 180 patients and found an overall discordance rate of 13.9%. Synchronous tumours had a discordance rate of 7.5% (3 of 40), whereas metachronous tumours had a discordance rate of 15.7% (22 of 140). A higher discordance rate (24.4% or 10 of 41) was observed when lung tissue from patients with multiple pulmonary nodules was compared with tissue from distant metastases.

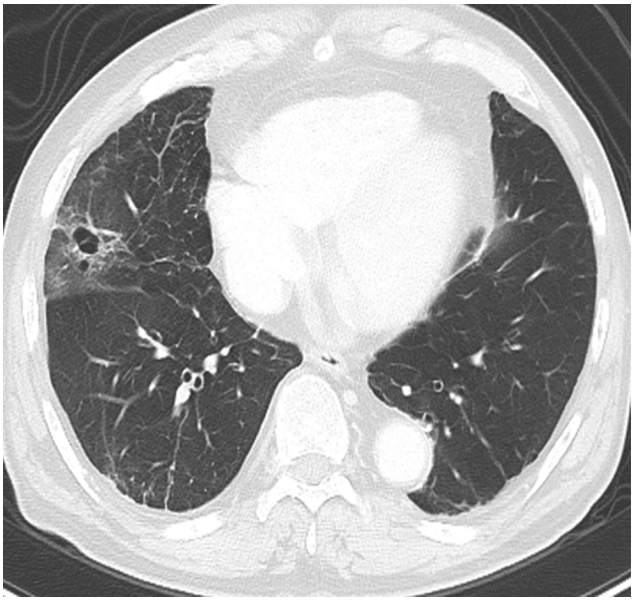

Figure 7 A CT scan after 6 weeks of osimertinib treatment showed that the lesion had shrunk.

Our case report shows that re-biopsy after acquiring resistance to EGFR-TKI can be effective both for patients with uncommon EGFR mutations and for those with common mutations because of the potential for tumour heterogeneity.[13] Exon 21 L861Q and L858R likely co-existed in our patient prior to initial therapy. The presence of uncommon and common EGFR mutations in the same tumour could provide an opportunity for the emergence of T790M-mediated EGFR-TKI resistance. The data from the re-biopsy were highly informative, and we were able to optimise our patient's treatment plan. Large studies to validate our result will be difficult because patients with NSCLC with uncommon mutations are a minority. However, when patients with NSCLC with uncommon EGFR mutations are identified, researchers should repeat the biopsy after EGFR-TKI treatment because EGFR mutation status could be heterogeneous.

Learning points

- The first-generarion epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is effective in some patients with EGFR uncommon mutations.
- In particular, we may expect the emergence of T790M, if the patient has the heterogeneity the EGFR uncommon mutation/ the EGFR common mutation.
- We should confirm EGFR mutation status of the patients with non-small cell lung cancer with the uncommon mutation before the second-line therapy.

Contributors HN gave this patient the treatment. YN and HN performed re-biopsy with bronchoscopy. JS and NM are the advising doctor of HN and YN. They checked this case report.

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Patient consent Obtained.

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