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CASE REPORT

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Successful treatment of triple EGFR mutation T785A/L861Q/H297_E298 with afatinib

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Abstract

Patients with non-small cell lung cancer (NSCLC) and uncommon epidermal growth factor receptor (EGFR) mutation are characterized by high heterogeneity, and globally considered to have a worse prognosis than patients with the two common mutations; exon 19 deletion, and exon 21 L858R. Nevertheless, some uncommon mutations do confer sensitivity to tyrosine kinase inhibitors (TKIs) which is comparable with common mutations. In particular, some compound EGFR mutations seem to be characterized by a favorable prognosis. Unfortunately, the rarity of complex EGFR mutations results in difficult clinical decision-making. Herein, to the best of our knowledge, we report the first case of an NSCLC patient with an EGFR triple mutation containing T785A/L861Q/H297_E298 who was successfully treated with afatinib.

KEYWORDS

compound EGFR mutations, kinase inhibitors, tyrosine, uncommon EGFR mutations

INTRODUCTION

Non-small cell lung cancer (NSCLC) patients with uncommon epidermal growth factor receptor (*EGFR*) mutations account for up to 10%–20% of patients with *EGFR* mutations, indicating that it is not uncommon to care for a patient with "uncommon" *EGFR* mutations. This group of patients are characterized by high heterogeneity. In general, patients with uncommon *EGFR* mutations are associated with a worse outcome when compared to those with common *EGFR* mutations and first-line chemotherapy results in a better overall survival (OS) in patients than those treated with tyrosine kinase inhibitors (TKIs). Nevertheless, some uncommon mutations confer sensitivity to TKIs comparable with common mutations for example the major uncommon G719X, L861Q, and S768I which show a favorable response to treatment with a second-generation TKI, namely afatinib. L861Q is also sensitive to osimertinib.[1] Interestingly, patients with compound mutations seem to have a better prognosis than patients with one uncommon *EGFR* mutation. This has been observed not only in patients with compound mutations consisting of a common and an uncommon mutation[2] but also in patients with rare compound mutations involving two uncommon mutations. All these cases have been reported to have a better prognosis.[1,3] On the other hand, clinical data regarding triple uncommon *EGFR* mutations are scarce, resulting in difficult clinical decision-making for this type of patient. Here, to the best of our knowledge, we report the first case of *EGFR* T785A/L861Q/H297_E298 mutation.

CASE REPORT

A 58-year-old man, a smoker of 60 pack-years, presented with dyspnea, chest pain and general fatigue. His medical history included a hepatitis C viral infection previously treated with antiviral therapy and a stage 4 Non-Hodgkin's lymphoma treated two years previously with the R-CHOP regimen. Computed tomography (CT) revealed a pulmonary

mass in the right lung with enlargement of bilateral mediastinal lymph nodes, an ipsilateral massive pleural effusion, and bilateral pleural nodules. Brain CT sections also showed metastases in the bilateral frontal lobes and the right parietal lobe. Biopsy specimens from the pleural nodes were obtained, and the patient was diagnosed as having lung adenocarcinoma. Next-generation sequencing (NGS) revealed the compound *EGFR* mutation T785A/L861Q/H297_E298 and also a MET exon 1 mutation, namely M51I (Figure 1). Due to the absence of clinical data concerning the mutation profile of the patient, chemotherapy with carboplatin and pemetrexed was commenced. The patient also received whole brain radiotherapy. After four courses of chemotherapy, he had clinical progression with an increase of dyspnea and fatigue. Together with these symptoms, the CT scan confirmed disease progression with an enlargement of the pulmonary mass in the right lung. CT also revealed the existence of lymphangitic carcinomatosis, and an increase in pleural involvement. Based on the disease progression, we treated the patient using afatinib with an oral dose of 40 mg daily as second-line therapy. There was a rapid improvement in the dyspnea and fatigue after a period of one month with this therapy. A CT scan obtained after two months of afatinib therapy showed a significant response with a marked reduction in the right lung pulmonary mass, lymphangitic carcinomatosis, pleural involvement, and also mediastinal lymph node enlargement (Figure 2). To date, the patient has been receiving afatinib at a dose of 40 mg daily for four months with a complete resolution of the symptoms.

DISCUSSION

Triple *EGFR* mutations are rarely reported and there is a lack of data necessary for clinical decision-making. Are triple uncommon *EGFR* mutations similar to other compound *EGFR* mutations? Unfortunately, the few cases reported in the literature are not able to supply an answer to this question. However, this is an issue that could concern several patients in the future. In fact, due to the improvement in NGS technology, the current data on *EGFR* mutations in NSCLC samples from the Genomic Data Commons Data Portal at the National Cancer Institute suggests that the frequency of uncommon mutations and also of compound mutations may be higher than what has previously been reported.[4] In case reports, both afatinib and osimertinib were found to be active against the rare triple uncommon mutation H833V/H835L/R670W,[5] while to our knowledge, no clinical data on the use of TKIs for the compound mutation of our patient are available. Our patient's results were sensitive to a second-generation EGFR TKI which agrees with

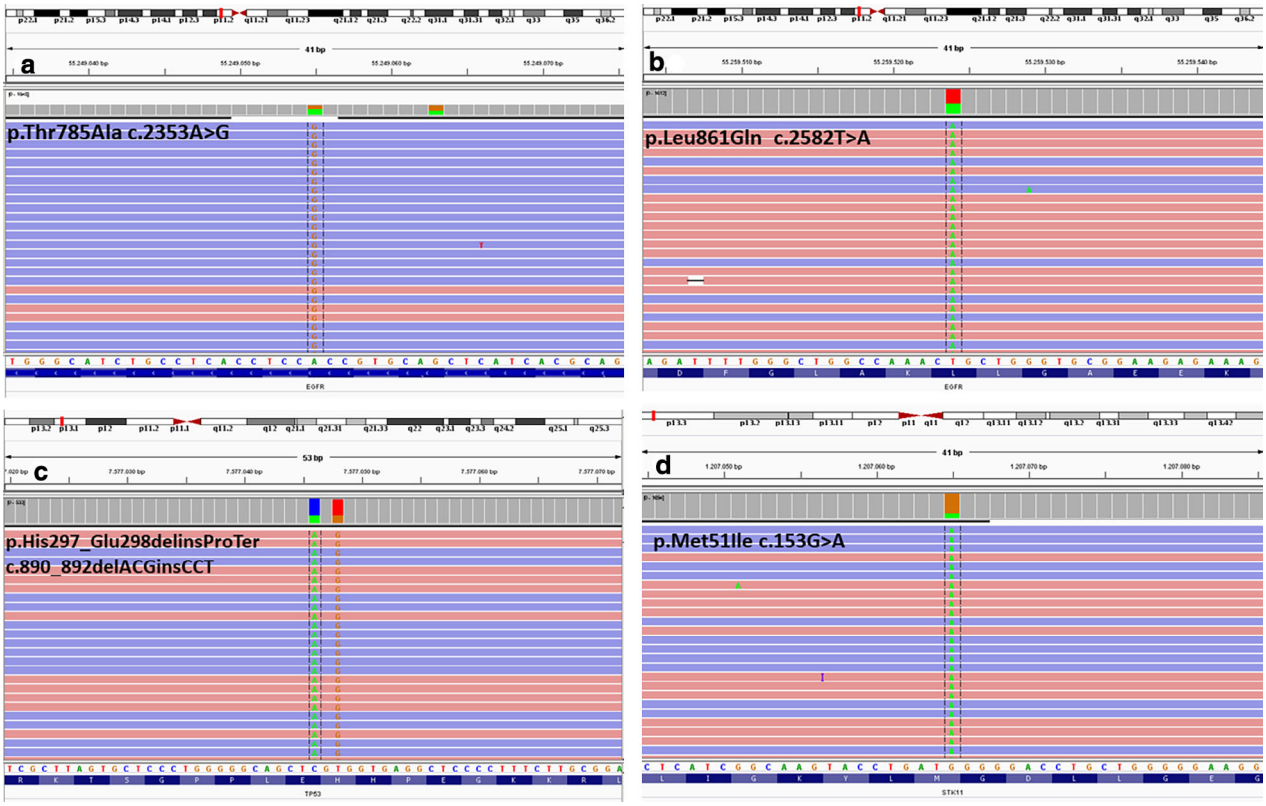

FIGURE 1 Lymphangitic carcinomatosis (a) which decreased after therapy with afatinib (b). Reduction of pleural involvement (c) after treatment with afatinib (d). Mediastinal lymph node enlargement (e) responsive to aftinib (f). Reduction of the right upper lobe pulmonary mass (g) after treatment with afatinib (h)

the data concerning compound mutations. In particular, we used afatinib due to its efficacy previously demonstrated in patients with L861Q mutation in a phase III clinical trial.[6] Moreover, afatinib has previously been reported to be effective in some double *EGFR* mutations containing L861Q.[7–9] There is a probability that the *EGFR* L861Q mutation also confers sensitivity to afatinib in compound *EGFR* mutations. As seen by observation of other cases, another characteristic shown in our patient and reported in other patients with compound mutations is the fact that they are more frequently smokers or former smokers than patients with common *EGFR* mutations. Nevertheless, the high heterogeneity of this group makes it difficult to elaborate hypotheses that are valid for all cases. Therefore, tools able to predict the sensitivity of the different TKIs to uncommon *EGFR* mutations may be very useful. In fact, some experiences have

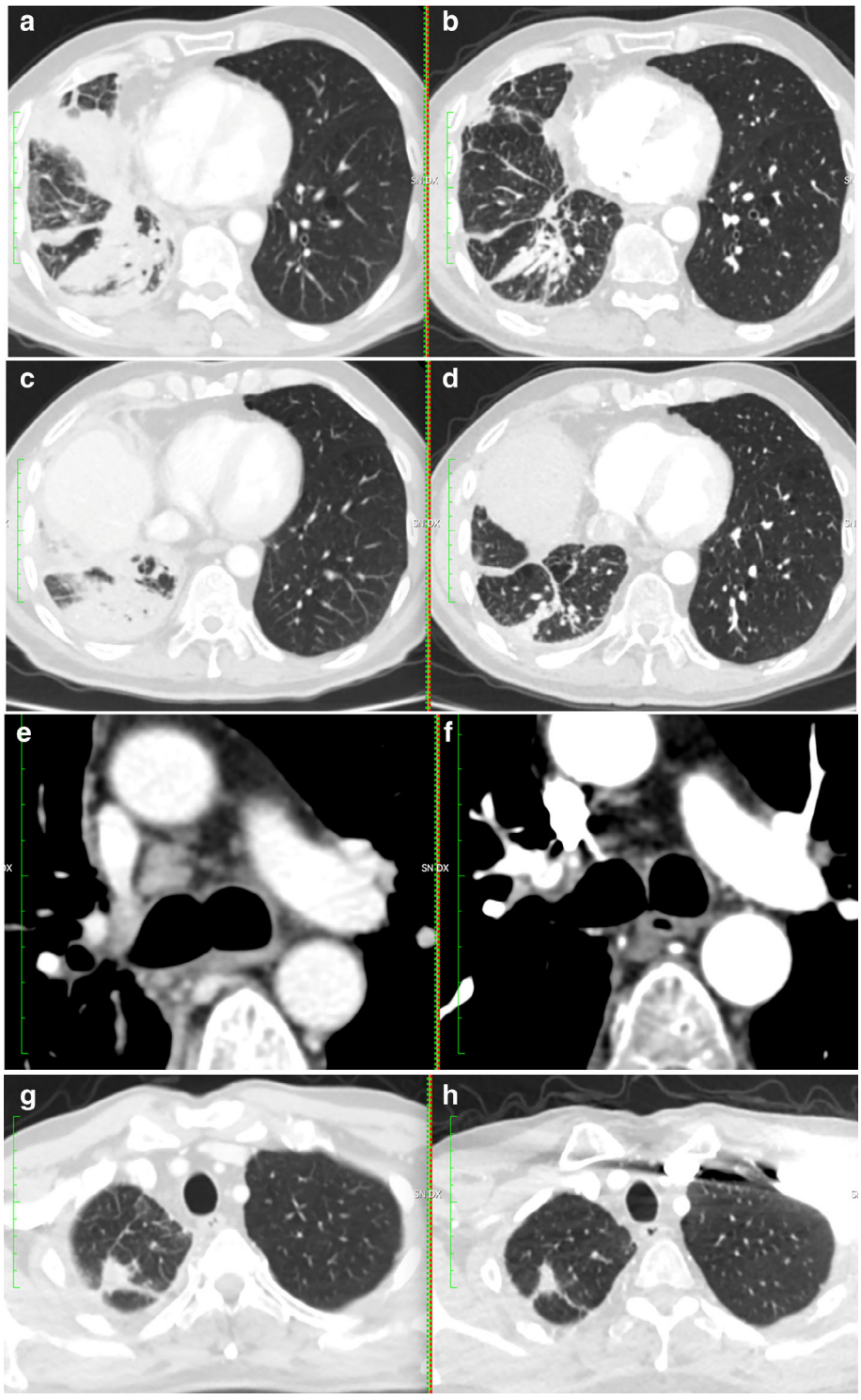

FIGURE 2 Next generation sequencing (NGS) images of *EGFR* mutation. (a) Exon 20 T785A, (b) exon 21 L861Q, and (c) exon 8 H297_E298. (d) NGS image of MET exon 1 mutation M51I

been described, including in silico approaches for the relative binding affinities of EGFR TKIs, in vitro assay based on measurement of cell viability, immunoblot analyses of EGFR phosphorylation, and also visual assay based on cells transfected with expression plasmids for yellow fluorescent protein-tagged fragments of the EGFR intracellular domain.[10] Due to the rarity of triple *EGFR* mutations, a prediction of TKI efficacy may be obtained from in vitro experiments and accumulated case reports.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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