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CASE REPORT

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Durable response to afatinib rechallenge in a long-term survivor of non-small cell lung cancer harboring *EGFR* L858R and L747V mutations

Mio Kanbe[1] | Noriaki Sunaga[1] | Kenichiro Hara[1] | Hiiru Sawada[1] | Ikuo Wakamatsu[1] | Kentaro Hara[1] | Sohei Muto[1] | Yuri Sawada[1] | Hiroaki Masubuchi[1] | Mari Sato[1] | Yosuke Miura[1] | Hiroaki Tsurumaki[1] | Masakiyo Yatomi[1] | Reiko Sakurai[2] | Yasuhiko Koga[1] | Yoichi Ohtaki[3] | Toshiteru Nagashima[3] | Naoko Okano[4] | Nobuteru Kubo[4] | Toshitaka Maeno[1] | Takeshi Hisada[5]

[1]Department of Respiratory Medicine, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

[2]Oncology Center, Gunma University Hospital, Maebashi, Gunma, Japan

[3]Department of General Surgical Science, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

[4]Department of Radiation Oncology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

[5]Gunma University Graduate School of Health Sciences, Maebashi, Gunma, Japan

Correspondence
Noriaki Sunaga, Department of Respiratory Medicine, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan.
Email: nsunaga@gunma-u.ac.jp

Abstract

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors are standard therapeutic agents for non-small cell lung cancer (NSCLC) patients with major *EGFR* mutations such as exon 19 deletions and a L858R mutation, whereas treatment strategies for cases with uncommon *EGFR* mutations remain to be fully established. Here, we report a long-term (≥20 years from initial diagnosis) NSCLC survivor carrying *EGFR* L858R and L747V mutations. The patient received gefitinib monotherapy, systemic chemotherapy/chemoimmunotherapy, and local consolidative therapies for oligometastatic lesions, and responded to afatinib rechallenge with a progression-free survival of 12 months. The current case suggests that afatinib is effective in NSCLC patients with *EGFR* L858R and L747V mutations and that a therapeutic approach combining appropriately timed systemic therapies with local consolidative therapies for oligometastatic lesions improves long-term survival.

KEYWORDS

afatinib, epidermal growth factor receptor, progression-free survival

INTRODUCTION

Epidermal growth factor receptor (*EGFR*) mutations are common driver mutations in non-small cell lung cancer (NSCLC). The major *EGFR* mutations are exon 19 deletions and a L858R mutation, whereas 10% of patients with *EGFR*-mutated NSCLCs have minor, "uncommon" *EGFR* mutations.[1] Recent advances in next-generation sequencing-based technologies have enabled the detection of a number of rare *EGFR* mutations, including L747X[2]; therapeutic strategies against NSCLC harboring single or compound uncommon *EGFR* mutations are under investigation. Here, we report a long-term (≥20 years from the initial diagnosis) NSCLC survivor carrying *EGFR* L858R and L747V mutations who responded to afatinib rechallenge with a 12-month progression-free survival (PFS).

CASE REPORT

A 32-year-old man who had never smoked was diagnosed with stage IIA (pT2N1M0) primary lung adenocarcinoma in the left S6 and underwent lobectomy in 2001. Two years later, recurrence manifested as multiple pulmonary

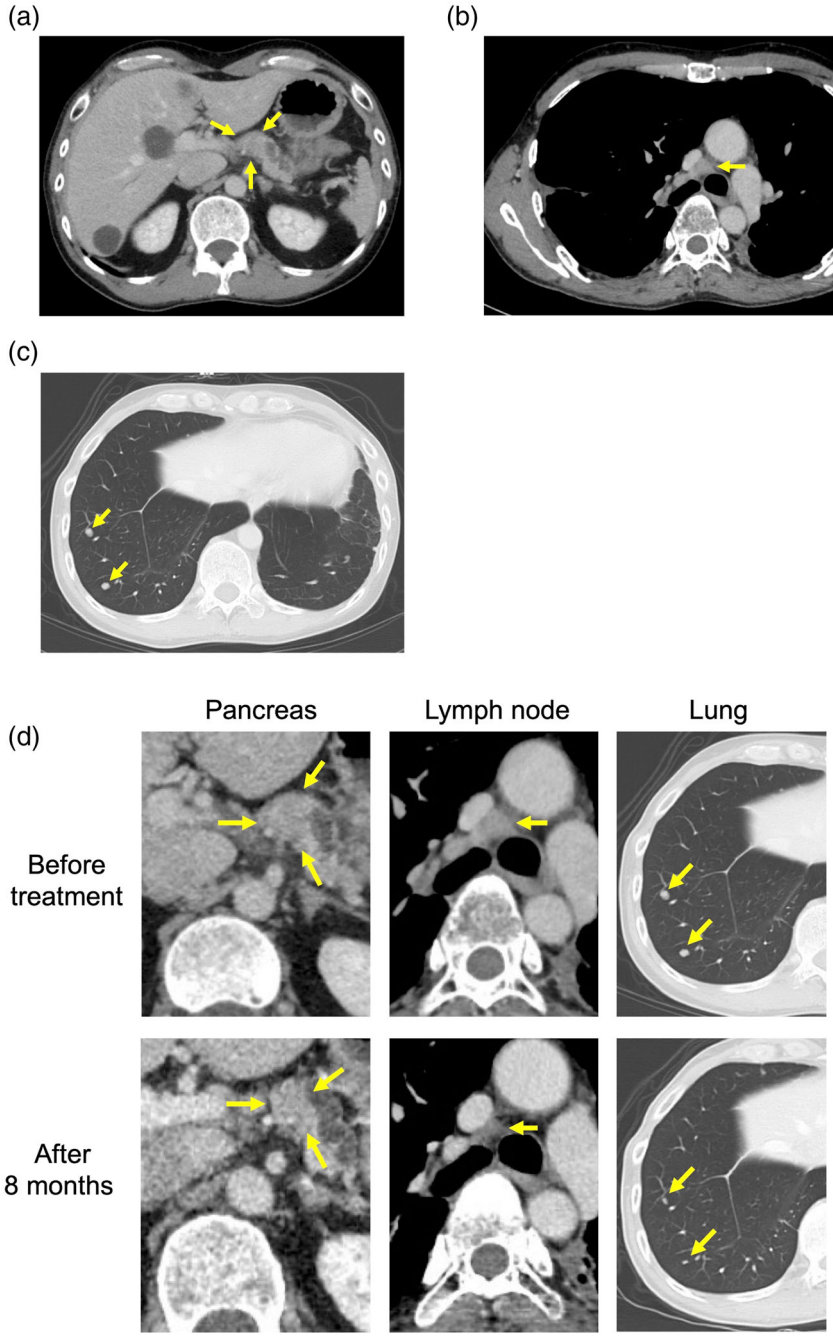

FIGURE 1 Metastatic lesions of the (a) pancreas, (b) mediastinal lymph node, and (c) right lower lobe of the lung before initiation of afatinib monotherapy. (d) Tumor shrinkage of the metastatic lesions of the pancreas, lymph nodes and lung before and after 8 months of afatinib treatment.

metastases. Gefitinib was initiated at 250 mg/day and yielded a complete response. After 7 years of gefitinib treatment, the patient developed a single pulmonary metastasis in the right S4 and underwent partial resection. The tumor was diagnosed as small cell lung cancer (SCLC) harboring the *EGFR* L858R mutation, indicating resistance to gefitinib due to SCLC transformation. Because of no other recurrent lesions, gefitinib was administered for a total of 9.1 years until the appearance of mediastinal lymph node metastases of SCLC. Subsequently, the patient received cisplatin plus etoposide with concurrent thoracic radiotherapy and achieved a partial response. In 2017, a pulmonary metastatic lesion appeared in the right S6, and the patient underwent segmentectomy. The tumor was an adenocarcinoma. After 8 months, the patient developed mediastinal lymph node metastases of SCLC, and cisplatin plus irinotecan chemotherapy resulted in a partial response. However, after repeated recurrences of regional lymph node metastases, the patient underwent stereotactic radiotherapy. In 2020, the patient showed multiple pulmonary and mediastinal lymph node metastases with SCLC. Atezolizumab plus carboplatin and etoposide was administered, and stable disease was achieved. The patient subsequently showed mediastinal lymph node metastases and received carboplatin plus albumin-bound paclitaxel chemotherapy, achieving a stable disease. Nevertheless, the patient developed metastatic lesions in the lung, mediastinal lymph nodes, and pancreas (Figure 1a–c). The FoundationOne CDx assay (Foundation

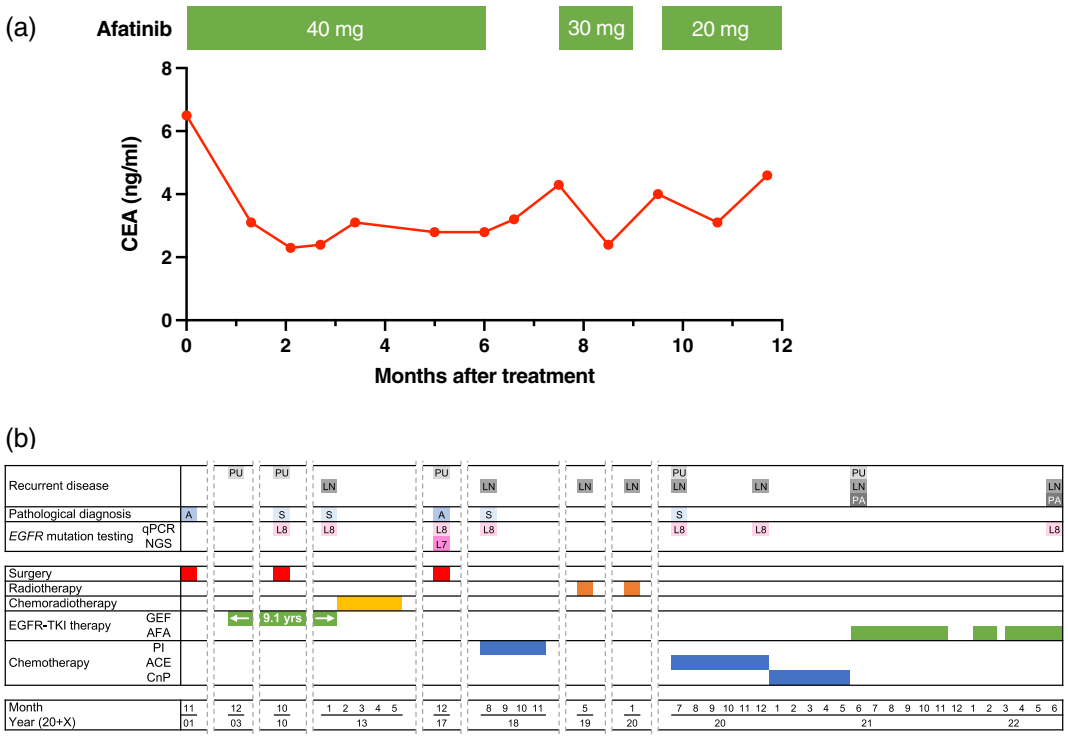

FIGURE 2 (a) Change in the serum carcinoembryonic antigen levels during treatment with afatinib. (b) Clinical course of the present case. Chemoradiotherapy: cisplatin plus etoposide with concurrent thoracic radiation. *EGFR* mutation testing was conducted with qPCR-based assays (the peptide nucleic acid-locked nucleic acid-PCR clamp assay from October 2010 to December 2017, the Cobas *EGFR* mutation test version 2 using tissue specimens in August 2018 and July 2020, the Cobas EGFR mutation test version 2 using plasma specimens in December 2020 and June 2022) and the NGS-based assay (FoundationOne CDx assay in December 2017), which revealed the presence of *EGFR* L858R (c.2573 T > G; variant allele frequency [VAF], 82.9%) and L747V (c.2239 T > G; VAF, 83.9%) compound mutations accompanied by *EGFR* amplification and *TP53* R196* (c.586C > T; VAF 75.4%) mutations. *EGFR* L858R mutations were confirmed in all samples that underwent genotyping. PU, pulmonary metastasis; LN, lymph node metastasis; PA, pancreatic metastasis; A, adenocarcinoma; S, small cell carcinoma; qPCR, quantitative polymerase chain reaction; NGS, next-generation sequencing; L8, L858R mutation; L7, L747V mutations; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; GEF, gefitinib; PI, cisplatin plus irinotecan; ACE, atezolizumab plus carboplatin plus etoposide; CnP, carboplatin plus nab-paclitaxel; AFA, afatinib.

Medicine, Inc.) was conducted on the surgical specimen obtained in 2017, revealing *EGFR* L858R and L747V mutations accompanied by *EGFR* amplification and *TP53* R196* mutations. Afatinib was initiated at 40 mg/day causing regression of the metastatic lesions (Figure 1d). However, the dose of afatinib was decreased to 20 mg/day due to intolerable skin toxicities (Figure 2a). Twelve months after afatinib administration, the patient showed pancreatic and right hilar lymph node metastases. At present (August 2022), the overall survival (OS) times from initial diagnosis and gefitinib administration are 20.8 and 18.8 years, respectively, and *EGFR* L858R mutations were consistently detected in all samples that underwent genotyping (Figure 2b).

The patient provided informed consent for the publication of this report.

DISCUSSION

L747X (L747P, L747S, and L747V) mutations are rare in NSCLC; only 2.2% of all uncommon mutations are L747X mutations.[3] Afatinib has shown better activity against NSCLCs carrying *EGFR* L747P/S mutations than gefitinib and erlotinib,[3–5] which is supported by preclinical studies showing higher sensitivities of afatinib to L747P- or L747S-mutant cells.[6,7] Regarding L747V mutations, a lung adenocarcinoma patient with *EGFR* L858R and L747V mutations achieved a 6-month PFS with erlotinib,[8] while another patient with lung adenocarcinoma harboring *EGFR* G719A and L747V mutations responded to afatinib with a 25-month PFS.[9] The clinical effectiveness of EGFR-tyrosine kinase inhibitors (TKIs) against *EGFR* L747X-mutated NSCLCs in previous reports is summarized in Table S1. Together with the findings in our case, afatinib appears to be clinically active against *EGFR* L747V-mutated NSCLC.

Our patient was administered gefitinib for 9.1 years, and the OS from gefitinib initiation was 18.8 years. Hirsch et al. analyzed long-term (>10 years) survivors of NSCLC treated with gefitinib, showing that the median duration of gefitinib treatment was 11.1 years and the 15-year survival rate from gefitinib initiation was 59%.[10] A previous study suggests that salvage surgery, which is defined as the resection of relapsed residual tumors within the thorax, after TKI treatment is safe and feasible and may contribute to prolonged OS time

by reducing the local tumor burden.[11] Furthermore, local consolidative therapies improve the OS in stage IV NSCLC with ≤3 synchronous metastases.[12] Thus, local consolidative therapy for oligometastatic lesions may be a valid approach to prolong the survival of patients with *EGFR*-mutated NSCLC in combination with EGFR-TKI therapies.

The transformation from NSCLC to SCLC is a mechanism of resistance to EGFR-TKIs.[13,14] Marcoux et al. investigated the clinical outcomes of *EGFR*-mutated lung adenocarcinomas transforming to SCLC, showing that the median OS since the time of SCLC transformation was 10.9 months,[15] whereas another report described long-term survival with an OS of 58 months from SCLC transformation.[16] In comparison with these reports, our patient survived for more than 142 months from the initial diagnosis of SCLC transformation, which may be partly attributed to repeated salvage surgeries and stereotactic radiotherapy along with systemic therapies.

In summary, the current case suggests that afatinib rechallenge is effective in NSCLC patients with *EGFR* L858R and L747V mutations and that a therapeutic approach that combines appropriately timed systemic therapies with local consolidative therapies for oligometastatic lesions improves long-term survival.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Noriaki Sunaga https://orcid.org/0000-0002-5966-4579
Hiroaki Tsurumaki https://orcid.org/0000-0003-0837-9329
Yoichi Ohtaki https://orcid.org/0000-0001-5485-3234
Toshitaka Maeno https://orcid.org/0000-0002-8428-1617

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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