CASE REPORT

EGFR-Mutated Lung Adenocarcinoma With Li–Fraumeni Syndrome: The Imperative for Germline Testing in Patients With a Family History, a Case Report

Hiroyuki Fujii, MD,[a,b] Yusuke Okuma, MD, PhD,[a,*] Makoto Hirata, MD, PhD,[c] Yuki Shinno, MD, PhD,[a] Tatsuya Yoshida, MD, PhD,[a] Yasushi Goto, MD, PhD,[a] Hidehito Horinouchi, MD, PhD,[a] Noboru Yamamoto, MD, PhD,[a] Yuichiro Ohe, MD, PhD[a]

[a]*Department of Thoracic Oncology, National Cancer Center Hospital, Chuo, Tokyo, Japan*
[b]*Department of Pulmonary Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo, Kyoto, Japan*
[c]*Department of Genetic Medicine and Services, National Cancer Center Hospital, Chuo, Tokyo, Japan*

ABSTRACT

Comprehensive genomic profiling (CGP) has progressed rapidly and plays an important role in advancing precision medicine in oncology. However, CGP provides opportunities for molecular-targeted therapy, but it also unveils incidental germline findings, posing challenges and opportunities in patient care. We present the case of a 32-year-old female patient, diagnosed with stage IVB lung adenocarcinoma harboring an *EGFR* p.L746_A750del, who was also subsequently diagnosed with Li–Fraumeni syndrome (LFS) through CGP testing. Remarkably, despite the presence of *EGFR* mutation, the response to EGFR-tyrosine kinase inhibitor was poor, whereas the response to cytotoxic anticancer drugs and immunotherapy was favorable. After the diagnosis of LFS, she underwent genetic counseling and has been screened for the development of a second cancer based on the Toronto protocol. This case highlights the importance of family history interviews and considering the practice of germline genomic testing for optimal management of lung cancer patients with a hereditary cancer syndrome such as LFS. Further research is warranted to delineate the impact of germline variants on treatment outcomes and secondary cancer prevention in lung cancer.

Keywords: Case report; Li–Fraumeni syndrome; EGFR mutation; Lung adenocarcinoma

Introduction

Comprehensive genomic profiling (CGP) has progressed at an exponential pace since the advent of next-generation sequencing (NGS), providing opportunities for molecular-targeted therapy. This has also led to the discovery of potentially incidental germline findings, which occur in approximately 1% to 2% of individuals who undergo CGP testing.[1] Germline findings require scrupulous care because they affect families. Nevertheless, they can help avoid serious, preventable harm or death from hereditary diseases. The information about the status of the gene responsible for the hereditary tumors can enable individuals or their blood relatives receive beneficial healthcare interventions such as early detection and improved prognosis through periodic surveillance, risk-reducing surgery, and prevention of secondary cancers.[2] Appropriate approaches for germline findings remain to be integrated as the standard of care in thoracic oncology and require an improved understanding of the interactions between

*Corresponding author.

Address for correspondence: Yusuke Okuma, MD, PhD, Department of Thoracic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo, Tokyo 104-0045, Japan. E-mail: yokuma@ncc.go.jp

Cite this article as: Fujii H, Okuma Y, Hirata M, et al. *EGFR*-mutated lung adenocarcinoma with Li-Fraumeni syndrome: the imperative for germline testing in patients with a family history, a case report. *JTO Clin Res Rep* 2025;6:100691.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100691

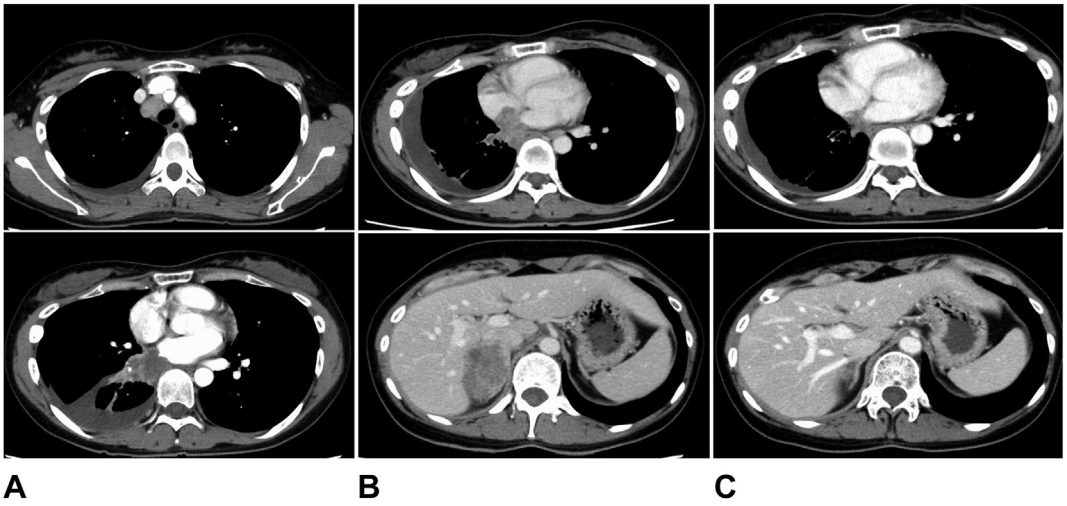

Figure 1. Timeline of tumor control *(A)* CT scan at diagnosis: The CT scan revealed a right lower lobe tumor, right pleural effusion, and mediastinal lymph node enlargement; *(B)* CT scan before combination therapy with the ABCP regimen: In addition to re-enlargement of the primary lesion, right adrenal metastasis was markedly increased; *(C)* CT scan after combination therapy with the ABCP regimen: The primary lesion and right adrenal metastases were shrinking. ABCP, atezolizumab, bevacizumab, carboplatin, and paclitaxel; CT, computed tomography.

pathogenic germline variants (PGVs) and lung cancer development.

Here, we report a young female patient with lung adenocarcinoma harboring a somatic *EGFR* mutation, who was diagnosed with Li-Fraumeni syndrome (LFS) by CGP testing.

Case Presentation

A 32-year-old female patient with a smoking history of 10 cigarettes per day for 10 years complained of dyspnea. She underwent enhanced computed tomography (CT), which revealed a right lower lobe tumor (Fig. 1*A*). Transbronchial biopsy and real-time polymerase chain reaction of tissue samples revealed that the lung tumor was an adenocarcinoma bearing *EGFR* mutation, p.L746_A750del. Positron emission tomography-CT revealed multiple bone metastases and the diagnosis was stage IVB (T4N3M1c).

Treatment with afatinib was initiated, however afatinib controlled the adenocarcinoma for only four months. Biopsy of the right supraclavicular fossa lymph node did not reveal the presence of *EGFR* p.T790M; combination therapy with cisplatin, pemetrexed, and bevacizumab was started as second-line treatment. Cytotoxic agents responded strongly and the tumor was controlled for more than three years. Thereafter, she continued third line of chemotherapy with a combination of tegafur, gimeracil, and oteracil; followed by fourth line docetaxel; and fifth line osimertinib. Osimertinib, used as the rechallenge EGFR-tyrosine kinase inhibitor (TKI), was effective for only four months and ended in progression of the disease. Figure 2 summarizes the courses of anticancer treatment.

A sixth line therapy with atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) was started approximately five years after her diagnosis. Further, the right adrenal metastatic lesion was re-biopsied and CGP was performed using the OncoGuide NCC Oncopanel System (NCC Oncopanel) (Sysmex, Kobe, Japan). The NCC Oncopanel, a matched-pair NGS-based test for both tumor and germline cancer-associated gene DNA, simultaneously provides tumor genomic alterations and germline findings.[3] NCC Oncopanel showed the following results: tumor mutational burden: 9.30 Muts/Mb; tumor genomic alterations: *EGFR* p.L746_A750del [variant allele frequency (VAF) 33.6%] and *ARID1A* p.Q386* (VAF 19.7%); germline genomic alteration: *TP53* p.R110L (VAF 44.4%). *TP53* p.R110L is a PGV, and she was genetically diagnosed with LFS.

A detailed family history review revealed multiple relatives with cancer (Fig. 3). The patient's eldest sister, mother, and maternal aunt had all died of early-onset cancer. Her mother was diagnosed with a brain tumor at 42 years of age. Her eldest sister was diagnosed with NSCLC, harboring an *EGFR* p.L746_A750del at 36 years of age, and her maternal aunt was also diagnosed with NSCLC, harboring an *EGFR* p.L858R mutation, at 56 years of age.

After diagnosis of LFS, magnetic resonance imaging rather than CT evaluation was planned to avoid radiation-induced secondary carcinogenesis. She is

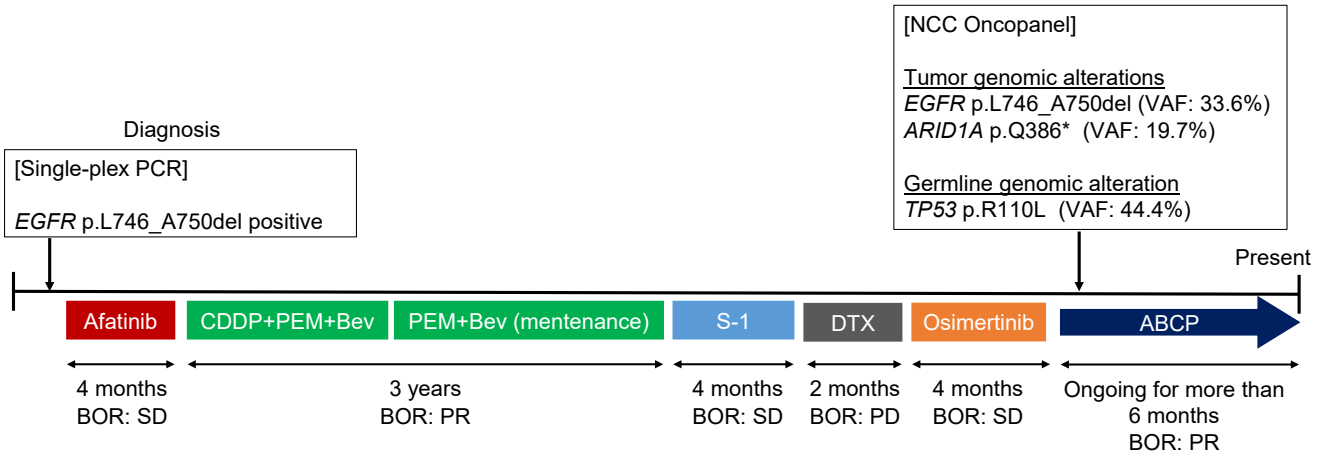

Figure 2. Timeline of patient's clinical course. BOR, best overall survival; CDDP, cisplatin; DTX, docetaxel; PEM, pemetrexed; PD, progressive disease; PR, partial response, SD, stable disease; VAF, variant allele frequency.

currently continuing combination therapy with ABCP, and her primary lesion and right adrenal metastases are markedly shrinking (Fig. 1*B* and *C*). Genetic counseling continues to be provided to her and her relatives for their psychosocial support and surveillance.

Discussion

LFS is an autosomal dominant syndrome characterized by PGVs of the *TP53*. *TP53* controls cell growth and division and protects cells against genome changes resulting from DNA damage by suppressing proliferation or activating apoptosis.[4] Early loss of heterozygosity of *TP53* with a gain of the mutant allele is characteristic of LFS, occurring earlier in these tumors compared to tumors with somatic *TP53* alterations.[5] Patients with LFS are known to be at increased risk of various cancers, including sarcoma, leukemia, brain tumors, adrenal cortical carcinoma, breast cancer, choroid plexus tumors, and lung cancer.[6] Complications in NSCLC, particularly in patients harboring *EGFR* mutations, are well documented.[7] In a European study, 17 of 22 patients (77%) with LFS and lung cancer had *EGFR* variants; of these, 15 patients (68%) had the most common exon 19 deletion, L858R.

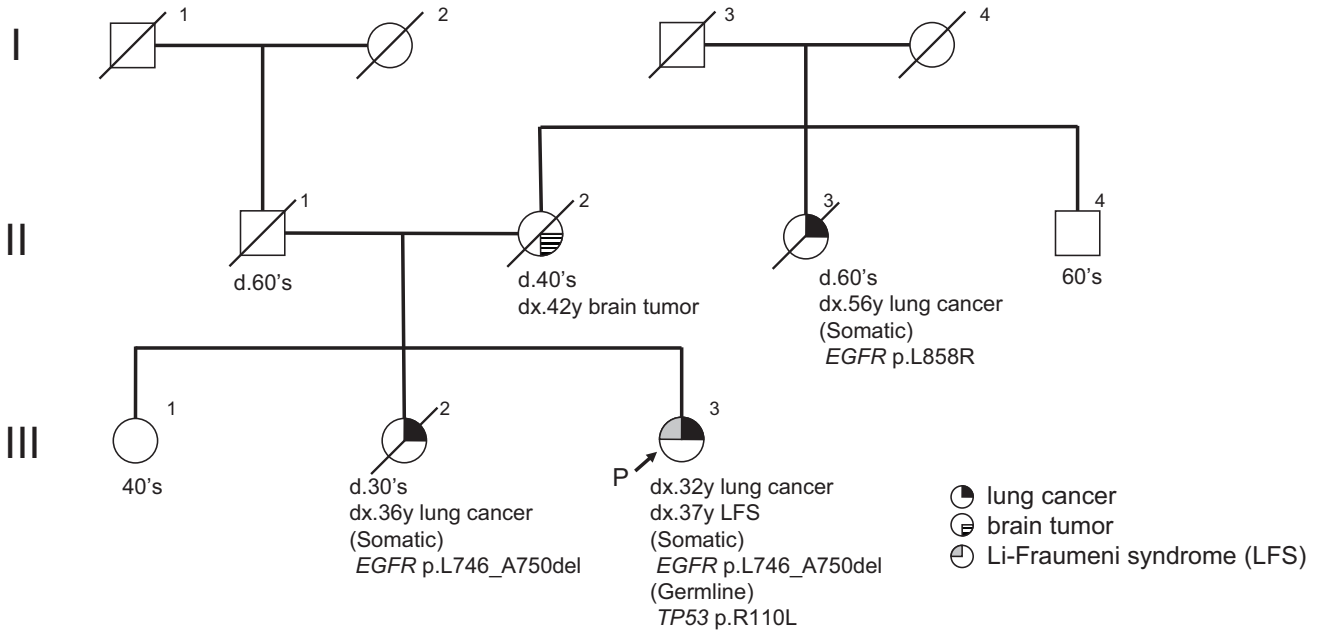

Figure 3. Family pedigree. A&W, alive and well; d, diet; E+, examination result positive.

Poorer response to EGFR-TKIs and shorter prognosis were observed when somatic *TP53* inactivation was found concomitantly with *EGFR* variants,[8] consistent with this case. However, a small study of 22 patients with LFS reported that some patients with germline *TP53* alterations may show a good response to EGFR-TKIs in contrast to patients with somatic *TP53* alterations.[7] This indicates a varied impact of somatic versus germline *TP53* alterations on EGFR-TKI sensitivity. *TP53* alterations in NSCLC correlate with the efficacy of immunotherapy and overall survival.[9] The patient is currently undergoing ABCP therapy and is expected to show a long-term response. Most previous reports have focused on somatic *TP53* variants rather than germline variants; thus, large-scale studies investigating the efficacy of EGFR-TKIs and immunotherapy in NSCLC developed based on LFS are desirable.

In a study evaluating 7788 patients with lung cancer for pathogenic or likely pathogenic germline variants, the proportion of patients with variants was 14.9%.[10] The most common variants were *BRCA2* (2.8%), *CHEK2* (2.1%), *ATM* (1.9%), *TP53* (1.3%), and *BRCA1* (1.3%).[10] If LFS is diagnosed, avoidance of radiation exposure and surveillance based on the Toronto protocol can prevent the development of a second cancer. The lesson to be drawn from this case is that even for common thoracic malignancies, although not LFS core tumors such as sarcoma or breast cancer, a thorough family history should be obtained, and genomic testing should be considered if necessary. It should also be noted that a majority of CGP tests do not include paired blood tests for germline findings. It is necessary to ascertain whether the CGP to be performed will test tumors exclusively or also include blood samples, and consideration should be given to implementing additional germline genomic testing if deemed necessary.

Currently, routine germline genomic testing for thoracic malignancies is not a standard in clinical practice. However, germline testing is considered the standard for patients with ovarian, pancreatic, breast, and prostate cancers.[11] In the future, universal germline testing of patients with lung cancer could be justified, if more evidence accumulates for PGVs that promote the development of thoracic malignancies as part of hereditary tumor syndromes, especially if the identified PGVs have implications for screening or management. For patients of familial *EGFR*-mutant lung cancer harboring germline *EGFR* T790M variant, investigation of CT-based screening for these high-risk individuals is beginning to be discussed. The natural history of patients with lung cancer harboring PGVs needs to be understood for future cancer prevention, precise counseling, cancer management, and improving the quality of life.

Conclusion

We describe a patient with NSCLC harboring *EGFR* mutation as a phenotype of LFS. Because the detection of germline variants is beneficial for appropriate treatment strategies and future secondary cancer prevention, further research on these aspects is needed.

Informed Consent

The authors are responsible for all aspects of the work to ensure that questions regarding the accuracy or integrity of any part of the work are appropriately investigated and resolved. For this case report, the concerned patient was fully informed, and written consent for submission and publication was obtained.

CRediT Authorship Contribution Statement

Hiroyuki Fujii: Conceptualization, Investigation, Data curation, Visualization, Writing - original draft

Yusuke Okuma: Conceptualization, Investigation, Data curation, Writing - review and editing

Makoto Hirata: Writing - review & editing

Yuki Shinno: Writing - review and editing

Tatsuya Yoshida: Writing - review and editing

Yasushi Goto: Writing - review and editing

Hidehito Horinouchi: Writing – review & editing

Noboru Yamamoto: Writing - review and editing

Yuichiro Ohe: Writing - review and editing

(Shinno, Yoshida, Goto, Horinouchi, Yamamoto, and Ohe have contributed equally)

Disclosure

Dr. Okuma reports grants from AbbVie, personal fees from AstraZeneca and Ono Pharmaceuticals, Nippon Boehringer Ingelheim, grants and personal fees from Chugai, personal fees from Eli Lilly, Eisai, Taiho Pharmaceutical, and Takeda. Dr. Yoshida reports grants and personal fees from Amgen, grants and personal fees from AstraZeneca, grants from Takeda, grants from Daiichi-Sankyo, grants, and personal fees from Ono Pharma Co. Ltd., grants and personal fees from Merck Sharp & Dohme, grants from Abbvie G.K., grants and personal fees from Novartis, grants, and personal fees from Chugai Pharma Co. Ltd., grants and personal fees from Bristol Myers Squibb, personal fees from Taiho Pharma Co. Ltd., Eli Lilly, Roche, and ArcherDX, outside the submitted work. Dr. Goto reports grants from AstraZeneca K.K., grants, and personal fees from Pfizer, grants from Abbvie G.K., grants and personal fees from Eli Lilly,

grants, and personal fees from Bristol Myers Squibb, grants and personal fees from Ono Pharma Co. Ltd., grants and personal fees from Novartis, grants from Kyorin, grants and personal fees from Daiichi-Sankyo, grants from Preferred Network, personal fees from Chugai Pharma Co. Ltd., Taiho Pharma Co. Ltd., Boehringer Ingelheim, Merck Sharp & Dohme, Merck, Thermo Fischer, AstraZeneca, Guardant Health Inc., and Illumina, outside the submitted work. Dr. Horinouchi reports grants and personal fees from Merck Sharp & Dohme, grants from Abbvie G.K., grants and personal fees from AstraZeneca, grants and personal fees from Bristol Myers Squibb, grants and personal fees from Ono Pharma Co. Ltd., grants from Merck Biopharma, grants from Daiichi-Sankyo, grants from Janssen, grants from Genomic Health, grants and personal fees from Chugai Pharma Co. Ltd., grants and personal fees from Roche, grants and personal fees from Novartis, personal fees from Eli Lilly, and Kyowa-Kirin, outside the submitted work. Dr. Yamamoto reports grants and personal fees from Chugai, grants from Taiho, grants and personal fees from Eisai, grants and personal fees from Eli Lilly, grants from Quintiles, grants from Astellas, grants and personal fees from Bristol Myers Squibb, grants from Novartis, grants from Daiichi-Sankyo, grants and personal fees from Pfizer, grants and personal fees from Boehringer Ingelheim, grants from Kyowa-Hakko Kirin, grants from Bayer, grants and personal fees from Ono Pharma Co. Ltd., grants, and personal fees from Takeda, grants from Janssen Pharma, grants from Merck Sharp & Dohme, grants from Merck, personal fees from Sysmex, grants from GSK, grants from Sumitomo Dainippon, grants from Chiome Bioscience Inc., grants, and personal fees from Otsuka, grants from Carna Biosciences, grants from Genmab, grants from Shionogi, personal fees from AstraZeneca and Cimic, outside the submitted work. Dr. Ohe reports grants and personal fees from AstraZeneca, grants, and personal fees from Chugai, grants and personal fees from Eli Lilly, grants and personal fees from Ono Pharma Co. Ltd., grants and personal fees from Bristol Myers Squibb, grants and personal fees from Kyorin, grants from Dainippon-Sumitomo, grants and personal fees from Pfizer, grants and personal fees from Taiho, grants from Novartis, grants from Takeda, grants from Kissei, grants from Daiichi-Sankyo, grants from Janssen, grants from LOXO, personal fees from Boehringer Ingelheim, Bayer, Merck Sharp & Dohme, Nippon Kayaku, Kyowa Hakko Kirin, Celltrion, Amgen, and AnHeart Therapeutics Inc., outside the submitted work. The remaining authors declare no conflict of interest. All authors have completed the ICMJE uniform disclosure form.

Acknowledgments

The authors thank Editage (www.editage.com) for English language editing. The authors report that no funding was received for the work featured in this article. All authors (1) made substantial contributions to the study concept or the data analysis or interpretation; (2) drafted the manuscript or revised it critically for important intellectual content; (3) approved the final version of the manuscript to be published; and (4) agreed to be accountable for all aspects of the work.

References

1. Amendola LM, Dorschner MO, Robertson PD, et al. Actionable exomic incidental findings in 6503 participants: challenges of variant classification. *Genome Res*. 2015;25:305–315.
2. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23:1381–1390.
3. Sunami K, Ichikawa H, Kubo T, et al. Feasibility and utility of a panel testing for 114 cancer-associated genes in a clinical setting: a hospital-based study. *Cancer Sci*. 2019;110:1480–1490.
4. Vousden KH, Prives C. Blinded by the Light: the growing complexity of p53. *Cell*. 2009;137:413–431.
5. Light N, Layeghifard M, Attery A, et al. Germline TP53 mutations undergo copy number gain years prior to tumor diagnosis. *Nat Commun*. 2023;14:77.
6. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer*. 2016;122:3673–3681.
7. Mezquita L, Jove M, Nadal E, et al. High prevalence of somatic oncogenic driver alterations in patients with NSCLC and Li-Fraumeni syndrome. *J Thorac Oncol*. 2020;15:1232–1239.
8. Vokes NI, Chambers E, Nguyen T, et al. Concurrent TP53 mutations facilitate resistance evolution in EGFR-mutant lung adenocarcinoma. *J Thorac Oncol*. 2022;17:779–792.
9. Assoun S, Theou-Anton N, Nguenang M, et al. Association of TP53 mutations with response and longer survival under immune checkpoint inhibitors in advanced non-small-cell lung cancer. *Lung Cancer*. 2019;132:65–71.
10. Sorscher S, LoPiccolo J, Chen E, et al. Landscape of pathogenic germline variants in patients with lung cancer. *J Clin Oncol*. 2022;40:388570.
11. Esplin ED, Nielsen SM, Bristow SL, et al. Universal germline genetic testing for hereditary cancer syndromes in patients with solid tumor cancer. *JCO Precis Oncol*. 2022;6:e2100516.