

A Primary Lung and Breast Cancer Patient with Germline *EGFR* R776H Mutation: A Case Report and Literature Review

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Abstract: For advanced non-small cell lung cancer (NSCLC) patients with common epidermal growth factor receptor (*EGFR*) mutations (exon 19 deletions or the exon 21 L858R mutation), tyrosine kinase inhibitors (TKIs) are the standard therapies. However, *EGFR* germline mutations are extremely rare in lung cancer, and the effective therapy is unclear. This study reports a patient with primary breast and lung cancer carried rare germline *EGFR* R776H and somatic L861Q mutation, who benefit from *EGFR* TKIs. Her family cancer history review demonstrated that her three out of four sisters with lung cancer were positive for *EGFR* R776H. Interestingly, only her healthy sister had type O blood, different from other sisters with type B blood. Our study provides a meaningful insight into the potential treatment option for patients with germline *EGFR* R776H and somatic L861Q mutation and highlights the importance of next-generation sequencing (NGS) in discovering rare genetic alterations to guide the prevention of genetic disease.

Keywords: *EGFR* R776H, germline mutation, non-small cell lung cancer, Gefitinib, Osimertinib

Introduction

Lung cancer is the most frequently diagnosed cancer and also the major cause of cancer-related deaths worldwide.¹ In non-small cell lung cancer (NSCLC) patients, the most frequent epidermal growth factor receptor (EGFR) mutations are point mutation L858R within exon 21 and short in-frame deletions within exon 19, which are the most common oncogenic driver mutations and hypersensitive to EGFR tyrosine kinase inhibitors (TKIs).² Other less prevalent but clinically relevant EGFR mutations that predict a resistant response to EGFR-TKIs include G719A/S/C, S768I, T790M and L861Q. Multiple studies have revealed the involvement of inherited susceptibility in the development of cancers. Moreover, family history of lung cancer still had a significantly increased risk in never-smoker probands.³ *EGFR* germline mutations are rare and associated with genetic susceptibility to lung cancer, including the mutations T790M and R776H in exon 20 and V843I in exon 21.⁴

With the development of genetic testing techniques, rare EGFR germline alterations are increasingly observed. Here, we reported a patient with primary breast and lung cancer carried rare germline *EGFR* R776H and somatic L861Q mutation, who benefit from EGFR-TKIs.

Case Presentation

A 45-year-old Chinese female non-smoker was diagnosed with synchronous stage I (pT1cN0M0) primary breast cancer, which was surgically removed, and stage IVA (cT4N0M1a) primary lung adenocarcinoma (LUAD) in October 2015 (Figure 1A). Immunohistochemistry (IHC) staining of the resected breast tumor tissue was positive for estrogen receptor (ER, 50%), progesterone receptor (PR, 70%) and human epidermal growth factor 2 (HER2) and negative for Cytokeratin

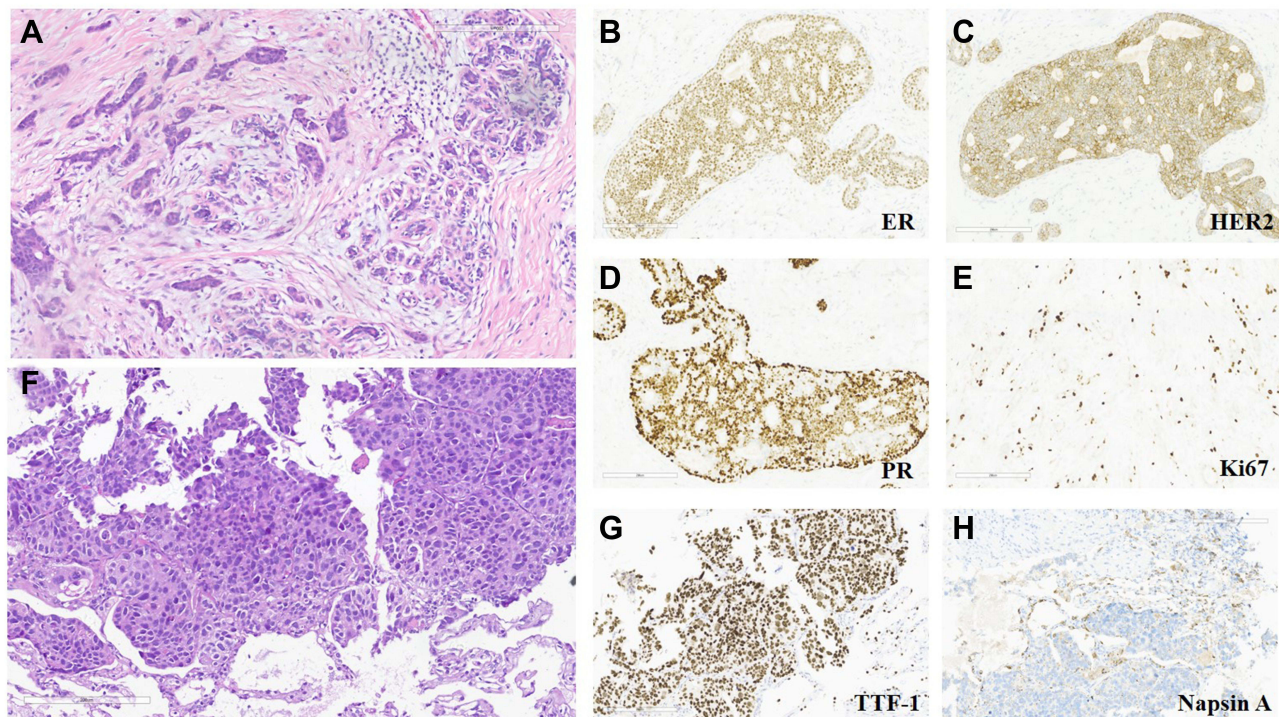


Figure 1 Representative clinical images during the treatment course. **(A)** Disease time line showed the various treatment received by the patient and her clinical response. **(B)** Chest-CT scans showed the disease progression under treatment. **Abbreviations:** BC, breast cancer; LUAD, lung adenocarcinoma.

5/6 (CK 5/6), P53, Topoisomerase I (TOPO I) and EGFR. Ki67 labeling in the tumor cells was 15% (Figure 2A–E). IHC analysis of a right lung tumor biopsy showed positive staining for LUAD markers, TTF-1 and Napsin A (Figure 2F–H), which confirming the primary LUAD. In November 2015, the patient received tamoxifen, a hormone therapy, to treat breast cancer. In December 2015, two cycles of chemotherapy with pemetrexed (0.8 g on d3) and cisplatin (50 mg on d1, 40 mg on d2,3) were administered for the treatment of LUAD (Figure 1B). Due to a positive result of sanger sequencing for exon 21 mutation (p.L861Q) and a rare *EGFR* exon 20 mutation (p.R776H), the patient was subsequently given

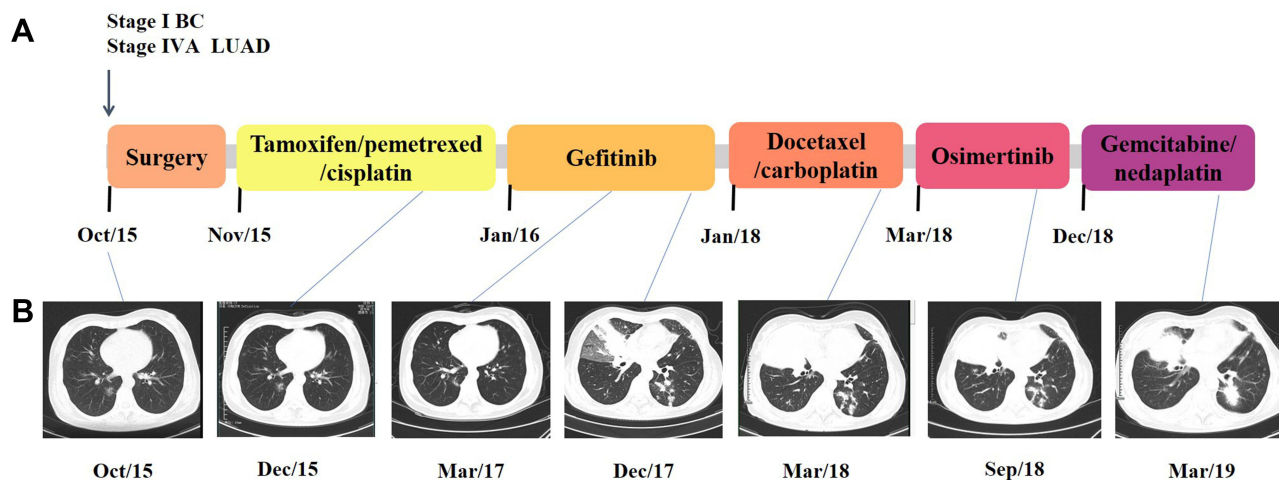


Figure 2 Hematoxylin & eosin (HE) and immunohistochemical (IHC) staining for the breast tumor tissue and the right lung tumor biopsy. **(A)** HE staining (200×) of the primary breast cancer. **(B–E)** IHC examinations (200×) of the breast tumor tissue was positive for estrogen receptor (ER, 50%), progesterone receptor (PR, 70%) and human epidermal growth factor 2 (HER2). The ki67 index was 15%. **(F)** HE staining (200×) of the primary lung adenocarcinoma. **(G and H)** IHC staining (200×) of the right lung tumor biopsy showed positive staining for TTF-1 and Napsin A.

Gefitinib (250 mg once daily), the first-generation EGFR TKI, in January 2016. The patient exhibited a stable disease (SD) (Figure 1B) and continued to be treated with Gefitinib until December 2017. At that time, the patient developed progressive disease (PD) with an enlarged primary lung tumor (Figure 1B). Therefore, the patient was switched to docetaxel (120 mg on d1) and carboplatin (0.55 g on d2) in January 2018. Two months later, the lung lesion increased again indicating PD (Figure 1B).

To identify a more efficient therapeutic strategy, freshly collected blood sample was subjected to targeted next-generation sequencing (NGS) of 139 cancer-related genes (Nanjing Geneseeq Technology Inc., Nanjing, China). Genomic profiling observed a rare *EGFR* R776H germline mutation (49.1%), *EGFR* L861Q (1.2%), *NF1* E836X (2.6%) and *TP53* P177T (2.3%). Investigation on her family history showed that her two older sisters died of lung cancer at the age of 53 years and 40 years, respectively. Her younger sister was diagnosed with lung cancer in October 2017 at the age of 44. Genetic testing revealed another three carriers of *EGFR* R776H aside from the proband, two elder sisters and her younger sister with lung cancer without her daughter (Figure 3). Additionally, her healthy younger sister, who was not an *EGFR* R776H carrier, had type O blood, which was different other sisters with type B blood.

The patient then received osimertinib (80 mg once daily) in March 2018. Six months post treatment, CT scans revealed no marked enlargement of the lesion indicating an SD (Figure 1B). Whereas, after 9 months of Osimertinib treatment, the patient refused to take it. In December 2018, the patient suffered from headache and CT scans revealed the lung lesions increased with pleural effusion, thus indicating PD (Figure 1B). The follow-up genomic testing with 139 cancer-relevant genes indicated *EGFR* L861Q (3.2%), *NF1* E836X (6.7%) and *TP53* P177T (5.3%). In January 2019, the patient received gemcitabine (1.4 g on d1,8) and nedaplatin (100 mg on d2). Unfortunately, the patient succumbed to a fourth-grade myelosuppression, then the chemotherapy was discontinued and she died in April 2019.

Discussion

Lung cancer is a major cause of death from cancer in the world. Genetic alterations are risk factors for lung cancer development, especially familial lung cancer. Germline *EGFR* mutations are rare but may contribute to oncogenesis,⁵ such as the mutations p.T790M and p.R776H in exon 20 and p.V843I in exon 21.⁴ Our study described a case of a female LUAD patient, who was a nonsmoker, with a germline *EGFR* R776H. The occurrence of germline *EGFR* R776H mutation is uncommon, and literature review of patients with an *EGFR*-R776H germline mutation identified four cases (Table 1). Including our family case (the proband and her three sisters with lung cancer), the mean age at diagnosis was

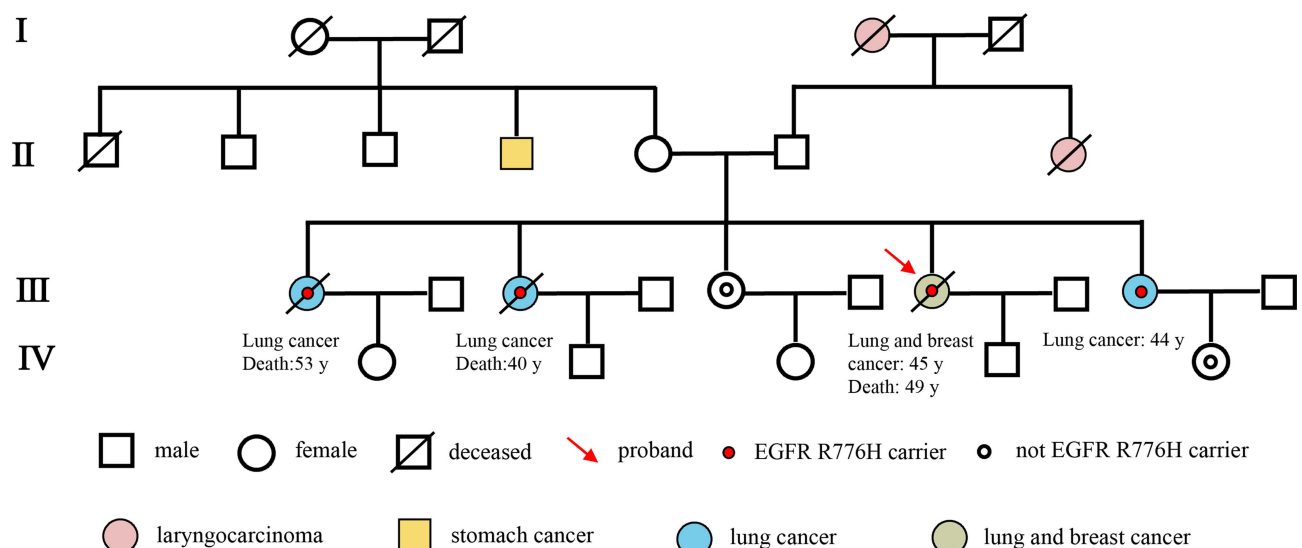


Figure 3 Pedigree of the proband's family. Squares and circles denote males and females, respectively. Roman numerals indicate generations. The proband was marked with an arrow. A small red circle indicates which family members were tested and found to carry *EGFR* R776H. A small hollow circle indicates which family members were tested and found not to carry *EGFR* R776H. The numbers after cancer sites indicate the age at diagnosis. The age of death is marked if known.

Table 1 Literature Review of Lung Cancer Patients with Germline *EGFR* R776H Mutations

Family	First Author (Year)	Ethnicity	Gender	Age at Diagnosis	Smoking	Somatic <i>EGFR</i> Mutation (s)	Personal History	Treatment/Line	Survival
Family 1	Genteno (2011) ⁵	Northern Spain	M	47	Yes	L858R	Undifferentiated ADC at stage IIIA	Surgery	OS: 1 yr
Family 2	van Noesel (2013) ¹¹	Caucasian	F	57	No	G719A	SCC	Chemotherapy & local radiotherapy/1st	OS: 17 mos
			F	36	No	G719S	SCC at stage II/IIIA	Surgery followed by erlotinib adjuvant treatment	RFS >1 yr
Family 3	Kai Su (2018) ¹⁴	Eastern Asian	F	52	No	No	TC; ADC at stage T1a or Tis	Surgery	-
Family 4	Tianxing Guo (2021) ¹²	Eastern Asian	F	42	No	G719A	ADC at stage IA	Surgery	RFS >11 mos
			M	17	No	No	Multiple nodules in both lung	-	-
Family 5	Justin Lin Sovich (2022) ¹⁵	Caucasian	F	50	No	L861R	ADC	Osimertinib	RFS >6 mos

Abbreviations: F, female; M, male; ADC, adenocarcinoma; SCC, squamous cell carcinoma; TC, thyroid carcinoma; OS, overall survival; RFS, relapse-free survival; “-”, not available.

44 years (range 17–57), and two males (18%) and nine females (82%) were identified. Two out of seven patients had a personal history of another malignancy, including breast and thyroid cancers. In addition, six patients, including our proband, harbored additional somatic *EGFR* variations, such as G719A/S, L858R and L861Q, which is usually oncogenic. It was also observed in patients with germline *EGFR* T790M,⁶ indicating a proliferative advantage in the tumors.⁷ The role of germline *EGFR* R776H in tumor progression has not yet been elucidated. The *EGFR* R776H mutation is located in exon 20, which encodes the third most important kinase domain, and the mutation class encompasses in-frame insertions and indels following or within the regulatory C-helix amino acids that activates *EGFR* in the absence of the activating EGF ligand.⁸ It has been reported that these variants were selectively inhibited by second-generation TKIs, sometimes even in cases of acquired resistance to osimertinib.⁹ The R776H mutation activates *EGFR* in a dimerization-dependent manner by adopting the acceptor position in the asymmetric dimer and increased phosphorylation of monomeric *EGFR* in cotransfection assays using cells and activates *EGFR* by relieving autoinhibitory interactions with the α C-helix in computational approaches.¹⁰

In our literature research of case reports who had germline *EGFR* R776H mutation (Table 1), we found one patient with a germline G776H mutation and a somatic G719S received surgery followed by erlotinib adjuvant treatment and achieved an RFS of more than 1 year.¹¹ To the best of our knowledge, other studies also reported that cases with somatic R776H with other oncogenic *EGFR* mutations, such as L858R and L861Q, received *EGFR* TKIs and achieved a clinical benefit.¹² In our case, the patient carried germline *EGFR* R776H and somatic L861Q mutations, who received gefitinib and achieved SD with a PFS of 23 months. Since the patient was resistant to first-generation TKI, osimertinib was administered and received an SD. Recent study also reported that osimertinib could be of benefit and may potentially be an effective treatment strategy to improve survival outcomes in patients with *EGFR* R776H.¹³

More interestingly, we also found the proband's sisters with lung cancer all had type B blood, but only the healthy sister had type O blood. However, the mechanistic details of the relationship between blood type and germline mutations are not understood. Moreover, this study indicates a need for genetic testing for people with familial cancer history.

Conclusion

In summary, we reported the case of a rare *EGFR* R776H germline mutated patient with confirmed family history developing breast and advanced LUAD who received chemotherapy, followed by TKI-treatment and achieved clinical benefit. This report highlights the importance of comprehensive genomic profiling in discovering rare gene mutations and provides a valuable clue for treatment-decision-making in patients with *EGFR* germline R776H and somatic L861Q mutations. More effective therapeutic strategies for these patients need to be further studied in the future.

Data Sharing Statement

All datasets generated for this study are included in the manuscript.

Ethics Approval and Consent for Publication

This research was approved by the Ethics Committee of The Second Hospital of Dalian Medical University. Written informed consent to publish the clinical details and images were obtained from the patient.

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Author Contributions

All authors contributed to data analysis and drafting or revising of the manuscript. All authors agreed on the journal to which the article is submitted, provided final approval of the manuscript version to be published, and agreed to be accountable for all aspects of the study.

Disclosure

Evenki Pan and Peng Yang are employed by Nanjing Geneseeq Technology Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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