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Case Report

Identification of *EGFR* R776H germline mutations in a patient with multifocal lung adenocarcinoma: A case report and literature review

Tianli Wang [1], Qin Zheng [1], Cong Deng [1], Xiang Li, Jia Huang, Jun Fan, Bo Huang, Jiwei Zhang, Xiaona Chang [**], Xiu Nie [*]

Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, Hubei, China

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ABSTRACT

The advancement of molecular pathology techniques has led to the discovery of rare *EGFR* mutations for targeted therapy in lung cancer. Additionally, a substantial body of evidence indicates a connection between the development of lung cancer and genetic variations in the EGFR gene. Here, we present a case report of a patient with multifocal lung adenocarcinoma who possessed a rare germline mutation, *EGFR* R776H. An investigation into the family history of the patient exposed the notable incidence of lung adenocarcinoma, indicating a plausible genetic vulnerability to the ailment. To be specific, the patient's older brother and sister both suffered from lung cancer, which underlines the hereditary predisposition. Furthermore, it should be noted that the patient's daughter has inherited the germline mutation and also presented with multiple lung ground-glass nodules, emphasizing the clinical importance of this genetic variation. Following the lobectomy, the patient received treatment with almonertinib, a third-generation *EGFR* tyrosine kinase inhibitor (TKI), and at the latest follow-up, the patient has achieved partial remission. This case highlights the significance of taking into account germline possibilities when multiple lesions carry the same mutation. It stresses the importance of acquiring a comprehensive family history and performing genetic testing on leukocytes. Moreover, for the infrequent *EGFR* R776H mutation, third generation EGFR-TKIs may be a viable option.

1. Introduction

Lung cancer is a prevalent malignancy and the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) represents the most common histological subtype [1]. *Epidermal growth factor receptor* (*EGFR*) mutations are important events in carcinogenesis. Classic *EGFR* mutations, namely exon 19 deletions and exon 21 $L^{858}R$ mutations, account for 85 % of *EGFR* mutations in NSCLC, and have been found to confer sensitivity to *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) [2]. Researchs on *EGFR* in lung cancer primarily focused on somatic mutations, and targeted therapies based on these mutations have been implemented in clinical practice. However, there is limited research on germline mutations of *EGFR* in familial lung cancer, highlighting the need for

* Corresponding author. Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei, China.

** Corresponding author. Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei, China.

E-mail addresses: pathologycxn@163.com (X. Chang), niexiuyishi@126.com (X. Nie).

[1] Tianli Wang, Qin Zheng, and Cong Deng contributed equally to this work.

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further investigation in this area. Approximately 8 % of lung cancer cases are associated with a genetic predisposition to the disease. The occurrence of lung cancer in multiple individuals within the same family is commonly referred to as familial lung cancer (FLC) [3]. The majority of FLC cases are attributed to germline mutations, which can involve alterations in chromosome number such as triploidy and aneuploidy, as well as changes in gene dosage caused by duplications or deletions spanning varying sizes, ranging from a few base pairs to megabases [4].

Here, we present the case of a patient who presented with multiple pulmonary nodules on positron emission tomography computed tomography (PET-CT) and proved multifocal lung adenocarcinoma (ADC) after surgery. Second-generation gene sequencing (NGS) and peripheral blood verification revealed the presence of a rare germline mutation of *EGFR* R776H, in addition to common targets such as *EGFR* L861Q/G719S.

2. Case presentation

A 59-year-old man with a smoking history of over 30 years was found to have multiple nodules in both lungs on physical examination in November 2018. After two years, the patient came to our hospital for further diagnosis and treatment. A CT scan in July 2021 identified a shadow of a nodule measuring approximately 1.5cm × 1.5cm in the upper lobe of the right lung, along with multiple ground glass nodules in both lungs. PET-CT imaging revealed two mixed opacities in the right lung, one measuring approximately 1.8cm × 1.7cm with a standardised uptake value (SUV) of 4.3, and another measuring approximately 2.2cm × 1.8cm with a SUV of 1.1. Additionally, a mixed ground glass nodule in the upper lobe of the left lung was identified, measuring 2.9cm × 2.0cm with a SUV of 1.2 (Fig. 1). Subsequently, thoracoscopic right upper and middle lobectomy plus lymph node resection was performed in our hospital. Postoperative pathology revealed multifocal invasive adenocarcinoma in the upper and middle lobe of the right lung (three lesions, lesion 1: 2cm × 1.5cm; lesion 2: 1.9cm × 1.4cm; lesion 3: 0.9cm × 0.5cm) (Table 1 and Fig. 2). Genomic profiling of the tumour tissue using NGS revealed the mutations present in the three lesions as shown in Table 1; confirmation of the *EGFR* R776H germline mutation was obtained through blood sampling (Fig. 3).

The patient then received almonertinib for targeted therapy in October 2021. CT scans in April 2023 revealed a reduction in the upper left lung nodule. As of this writing, the patient has not shown tumour progression.

Investigation on his family history showed that one of his older brother and one of sister died of lung cancer. Moreover, their offspring were also confirmed to have multiple lung nodules by CT (Fig. 3). Through Sanger sequencing of the patient's son and daughter, we found that his daughter carried the *EGFR* R776H mutation, while his son did not (Fig. 4).

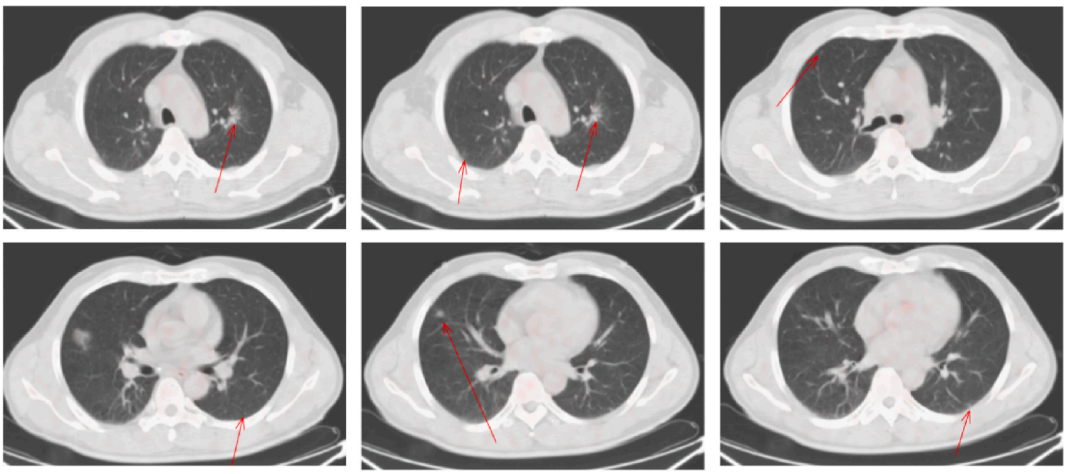

Fig. 1. PET CT shows multiple pulmonary nodules.

Table 1
Mutations in three lesions.

lesion	size	mutation				
lesion 1	2.0cm × 1.5cm	*EGFR* G719S[a]	*EGFR* R776H[b]	TP53 G266E[a]	TP53 V272M[a]	CTNNB1 S33A[b]
lesion 2	1.9cm × 1.4cm	*EGFR* L861Q[a]	*EGFR* R776H[b]	/	/	/
lesion 3	0.9cm × 0.5cm	*EGFR* L861Q[a]	*EGFR* R776H[b]	/	/	/

[a] Mutations of clinical significance.
[b] Mutations of no clinical significance temporarily.

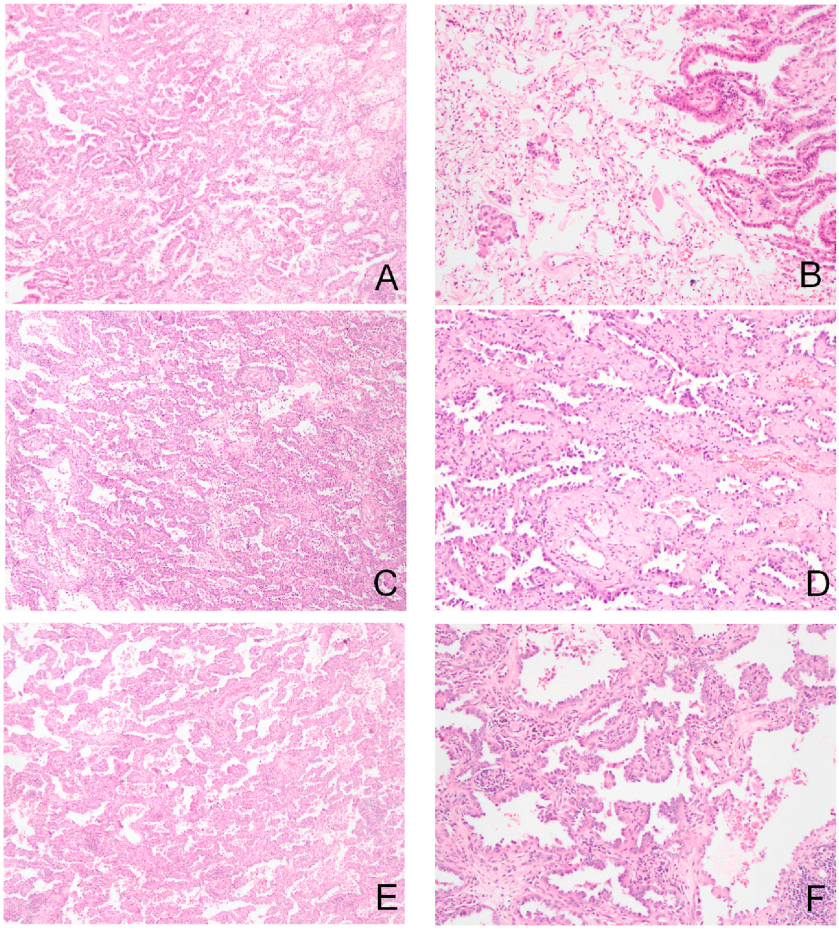

Fig. 2. Pathological characteristics of three lesions. (A) and (B) show that lesion 1 was mainly in the form of acinar and papillary growth and accompany with tumour spread through air spaces. (C) and (D) show lesion 2 predominantly grew in acinar pattern, and (E) and (F) show lesion 3 grew in papillary pattern.

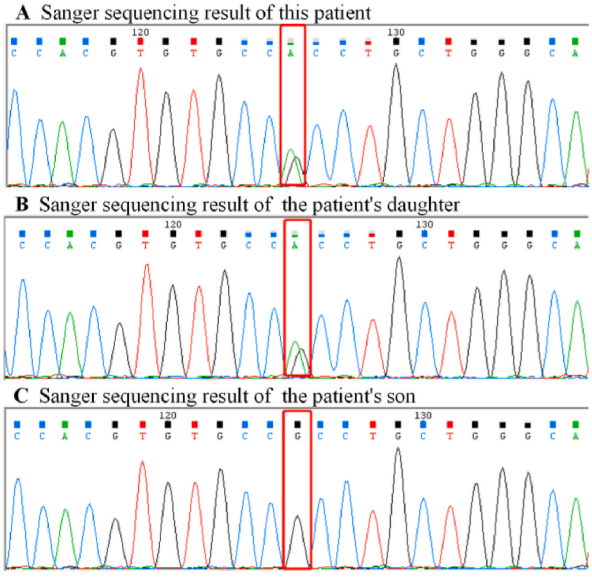

Fig. 3. Sanger sequencing results show that this patient and his daughter carry EGFR R776H mutation (A and B), while his son did not (C).

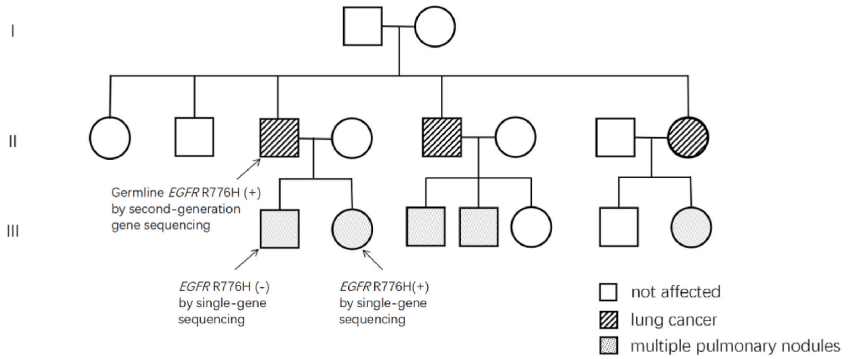

Fig. 4. Pedigree of the patient's family.

Table 2
Literature review of non-small cell carcinoma patients with *EGFR* R776H mutations.

Patient	Author	Gender	Age	Germline or somatic mutations	*EGFR* commutation mutation	Personal history	Family history	Treatment	Survival
1	Van Noesel [7]	F	57	Germline	G719A	SCC	Yes	Chemotherapy and radiotherapy	OS:18mos
2	Van Noesel [7]	F	36	Germline	G719S	SCC	Yes	chemotherapy and radiotherapy + lobectomy + erlotinib	PFS > 12mos
3	He,S.Y [11]	F	59	Somatic	G724S	ADC at stage IVB	No	afatinib	PFS:17mos
4	Guo,T [8]	M	48	Somatic	L861Q	ADC at stage IVB	No	afatinib	PFS > 12mos
5	Guo,T [8]	F	42	Germline	G719A	ADC at stage IA	Yes	surgical resection	PFS > 3mos
6	Sovich, J.L [9]	F	50	Germline	L861R	ADC	yes	Osimertinib	PFS > 6 mos
7	Li,D [10].	F	45	Germline	L861Q	ADC at stage IVB	Yes	Osimertinib	PFS:9mos

Abbreviations: F: female; M: male; ADC: adenocarcinoma; SCC: squamous cell carcinoma; PFS: progression-free survival.

3. Discussion

EGFR is located on chromosome 7's short arm (7p11.2) and plays a crucial role in regulating cell proliferation, differentiation and apoptosis [5]. The three *EGFR* mutations involved in this case (L861Q, G719S and R776H) are considered *EGFR* non-classic mutations, of which L861Q and G719S have been verified to be sensitive to afatinib in clinical trials [6]. However, the sensitivity of NSCLC with R776H mutation to *EGFR*-TKI remains undetermined. There have been case reports of benefit from afatinib or osimertinib in NSCLC patients with *EGFR* R776H mutations [7–11]. Almonertinib, as a third-generation *EGFR*-TKI, has been approved by the China National Medical Products Administration for the treatment of some *EGFR*-mutant NSCLC, and showed better overall efficacy than first-generation *EGFR* TKIs [12]. This is the first documented case of a patient with multifocal lung adenocarcinoma carrying the germline *EGFR* R776H mutation, accompanied by distinct somatic mutations (G719S and L861Q) in different tumour lesions. Treatment with almonertinib proved to be effective, emphasizing the intricate interplay between germline and somatic *EGFR* alterations in lung cancer. Due to the limited nature of this single case report, it is difficult to ascertain whether the efficacy of almonertinib in this patient resulted from the rare somatic mutations (L861Q/G719S) or the germline mutation (R776H) in *EGFR*. Further cell-based studies and mechanistic investigations are required for a comprehensive understanding. Nevertheless, this clinical case offers valuable insights for potential treatment approaches in similar patients and lays the foundation for future mechanistic research.

Similarly, we have also observed that patients with the germline *EGFR* R776H mutation appear to have a familial predisposition to NSCLC [7–10] (Table 2). In our case, this patient, his brother and his sister both had lung ADC. His son and his daughter had ground glass nodules on CT.

In addition, case reports have described that patients with *EGFR* R776H mutation appear to be associated with multiple lung nodules (with or without confirmed non-small cell lung cancer) [8,13]. In our case report, this patient was pathologically confirmed as multifocal lung adenocarcinoma, and his daughter had multiple lung nodules on CT. Both of them had *EGFR* R776H mutation, suggesting that *EGFR* R776H mutation may confer susceptibility to multiple lung nodules. Unfortunately, the relationship between the R776H mutation and multiple lung nodules cannot be definitively established due to the limited number of reported cases.

4. Conclusion

In this case report, we present a 59-year-old man with multifocal lung adenocarcinoma who had a notable family history of lung cancer and harboured the rare *EGFR* R776H germline mutation, along with distinct somatic mutations (G719S and L861Q) in different tumour lesions. Notably, the patient exhibited a favourable response to treatment with almonertinib. This report highlights the importance of considering germline mutations in patients with multiple lesions, and suggests the potential efficacy of targeted therapies for the similar cases. Given the limited nature of this case, further research is warranted to validate these findings and provide valuable insights for personalised treatment strategies and germline mutation screening in lung adenocarcinoma patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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