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CASE REPORT

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Inherited rare epidermal growth factor receptor mutation and somatic mutations in patients with non-small cell lung cancer: a case report

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Abstract

Background Recent advances in molecular oncology have increasingly illuminated the role of germline *EGFR* mutations in non-small cell lung cancer (NSCLC). This case report presents the presence of a unique familial occurrence of *EGFR* mutations in patients with NSCLC.

Case description A mother and son, both never-smokers of Caucasian ethnicity, were diagnosed with advanced metastatic lung adenocarcinoma. In one patient, tumor molecular analysis by next generation sequencing (NGS) identified two *EGFR* mutations: the activating mutation c.2573T > G; p.Leu858Arg (p.L858R) in exon 21 of the *EGFR* gene, and the somatic non-pathogenic mutation c.2612 C > A; p.Ala871Glu (p.A871E) in exon 21 of the *EGFR* gene. The second patient also harbored the same two *EGFR* mutations. The patient underwent genetic testing which revealed the germline origin of the A871E mutation. Whether the presence of this mutations was associated with increased predisposition to cancer has yet to be determined. Our case report highlights the need for further exploration of the role of germline mutations, including the A871E mutation, in tumorigenesis and its implications for treatment response and inheritance patterns.

Conclusions The investigation and comprehension of the significance of each individual *EGFR* mutation hold the promise for potential in cancer prevention or early diagnosis within family cohorts and understanding the mechanisms of tumorigenesis in sporadic cases.

Keywords Case report, EGFR mutation, Non-small cell lung cancer, Osimertinib

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Background

Recent advances in molecular oncology have increasingly illuminated the role of genetic factors in lung cancer pathogenesis. One such discovery pertains to the pathogenic variants in the epidermal growth factor receptor (*EGFR*) gene. While acquired somatic point mutations, such as the *EGFR* T790M, have been identified as resistance markers to certain EGFR inhibitors in patients with non-small cell lung cancer (NSCLC), their occurrence in patients without prior exposure to tyrosine kinase inhibitors (TKIs) may suggest a germline predisposition [1]. Such findings underscore the importance of genetic counseling and further investigation into these variants, as recommended by the National Comprehensive Cancer Network (NCCN) guidelines. Furthermore, specific demographics, such as never-smokers, women, and individuals of Asian descent, are more commonly associated with activating *EGFR* mutations [1].

Case presentation

This case report presents a unique familial occurrence of *EGFR* mutations in patients with NSCLC. A mother and son, both never-smokers of Caucasian ethnicity, were diagnosed with advanced metastatic lung adenocarcinoma at ages 57 and 43, respectively. The mother was diagnosed with a large mass in the right upper lung lobe, mediastinal lymph node enlargement, pleura involvement, and multiple metastatic lung lesions. Molecular analysis of the primary tumor site by next generation sequencing (NGS) identified two *EGFR* mutations: the activating mutation c.2573T > G; p.Leu858Arg (p.L858R) in exon 21 of the *EGFR* gene, which predicts sensitivity to EGFR TKIs, and the somatic non-pathogenic mutation c.2612 C > A; p.Ala871Glu (p.A871E) in exon 21 of the *EGFR* gene, of unclear significance (VUS). Classification of the EGFR A871E as a VUS was performed based on the American College of Medical Genetics and Genomics (ACMG) guidelines [2]. Specifically, the following criteria were applied to reach this classification: PP3-MOD, PM1-SUP and PM2-SUP. The patient received several lines of therapy, including EGFR TKIs, chemotherapy, and immunotherapy, over almost 6 years. Specifically, she underwent two lines of chemotherapy followed by nivolumab monotherapy. Following this course of treatment, she experienced disease progression characterized by the emergence of brain metastases. Osimertinib was then introduced as the fourth line of treatment. With this regimen, she achieved stable disease for 6 months prior to her passing. No drug-related adverse events were reported, nor drug reduction or discontinuation (Fig. 1).

The son also presented with a stage IV adenocarcinoma of the lung. Molecular analysis of the primary tumor site by NGS revealed the same two *EGFR* mutations as the mother. Given his young age and family history, the patient received genetic counseling and testing which revealed the germline nature of the A871E mutation, likely inherited from the mother. For germline status investigation, NGS testing was performed on whole blood (coverage depth > 500x), similarly to the aforementioned tumor samples. He initiated treatment with osimertinib, which was well tolerated, and demonstrated a notable partial response after 3 months, which persisted for 15 months, leading to an approximate treatment duration of 18 months. No dose reduction or dose interruption was reported. Subsequent to this, he experienced disease progression, with bone metastases. No re-biopsy or liquid molecular testing was conducted post-disease progression. He subsequently received chemotherapy combined with immunotherapy, without any therapeutic benefit. Rapid disease progression ensued, and he passed away 2 months later (Fig. 1).

For all described samples, targeted NGS was performed after DNA isolation. Library preparation was performed with the Ion AmpliSeq Library kit 2.0, using Thermo Fisher Oncomine Dx derived amplicons. Sequencing was performed on an Ion Torrent PGM platform and data analysis was performed using Torrent Suite (5.12) and Ion Reporter (5.2 to 5.14, different versions for each sample described in the paper) software. For all tests described, including formalin-fixed paraffin-embedded (FFPE) tissue sample for the mother and plasma and whole blood for the son, the same NGS panel was used,

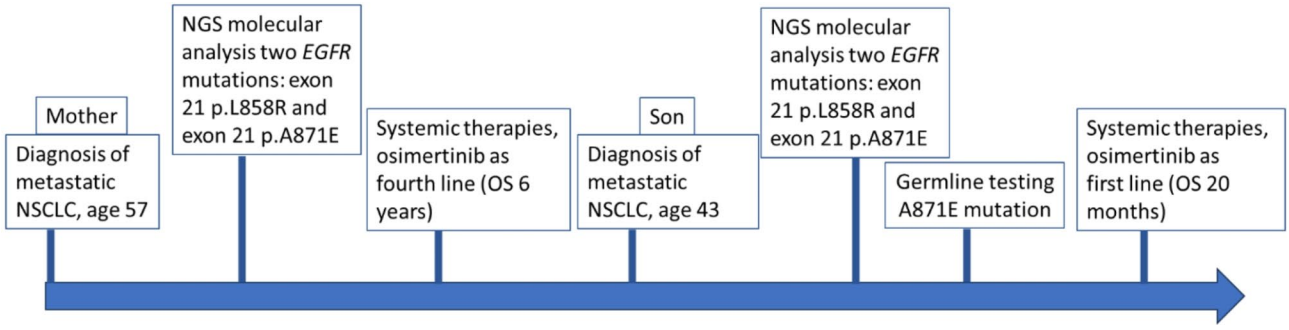

Fig. 1 Timeline

which targeted hotspots in cancer-related genes, and in particular exon 21 of the EGFR gene were the two described variants were located.

Initial tumor testing of the mother was performed on FFPE; neoplastic cells were >50% and NGS coverage depth was >1000x. Initial tumor testing of the son was performed on plasma; circulating tumor DNA (ctDNA) fraction was unknown while coverage depth was >3500x. In both tumor testing (performed on FFPE for the mother and plasma for the son), allelic frequency was a bit higher for the A871E variant, in comparison to the L858R variant. However, these findings need to be addressed with caution since clear conclusions cannot by drawn from variant allelic frequency from a single test, especially when this testing is performed on FFPE tumor tissue, particularly in a single test.

For germline status investigation, NGS testing was performed on whole blood (coverage depth > 500x), similarly to the other samples.

Discussion and conclusions

In our study, we describe a mother and son with metastatic lung adenocarcinoma who both harbored the activating exon 21 (p.L858R) *EGFR* mutation and a germline EGFR (A871E) mutation. Our case report highlights the need for further exploration of the role of germline mutations, including the A871E mutation, in tumorigenesis and its implications for treatment response and inheritance patterns.

Germline testing in patients with NSCLC has clinically important implications for future patients, particularly regarding familial risk assessment and early detection in case of increased predisposition to NSCLC. By the time of patients' death, no other member of the family underwent germline testing, since no known variant pathogenicity had been reported. While information about other relatives diagnosed with lung cancer and their germline findings would be of interest, no additional information can be retrieved on the patients' family history. However, when a pathogenic germline variant, known to be associated with increased predisposition to NSCLC is identified, cascade testing of the relatives can facilitate the assessment of their risk. Individuals at high risk can then benefit from enhanced surveillance strategies or participation in clinical trials, depending on the risk of cancer. Whether the risk of developing NSCLC increases with other risk factors, including smoking, has yet to be defined. No significant difference regarding smoking history between patients with and without pathogenic variants has been previously shown [3]. In addition, the presence of pathogenic variants in diverse populations and respective risks also needs further evaluation. The compilation of published cases may provide further insights into the role of these variants in individual carriers. To date, no recommendations have been established regarding lung cancer screening in patients with germline variants in diverse genes.

The pivotal discovery of somatic, activating *EGFR* mutations in a subset of NSCLC cases, which are associated with significant responsiveness to EGFR TKIs, heralded a new era in targeted therapies [4, 5]. These mutations are located in exons 18 to 21 of the *EGFR* gene, which encompass a significant portion of the tyrosine kinase-binding domain within the EGFR protein [6]. *EGFR* mutations are commonly detected in NSCLC patients who are women, never-smokers, and have been diagnosed with adenocarcinoma, and of Asian ethnicity [7]. In lung adenocarcinomas, numerous *EGFR* mutations have been identified. More than 85% of these mutations are sensitizing, specifically exon 19 deletions and the L858R substitution in exon 21, which show favorable responses to EGFR TKIs [8, 9]. The remaining 15% of *EGFR* mutations, classified as rare or uncommon, have received comparatively less investigation. Among these mutations, G719X in exon 18, L861Q in exon 21, and insertions in exon 20 (ex20ins) each constitute approximately 2% of all *EGFR* mutations. While G719X and L861Q mutations have been shown to be sensitive to EGFR TKIs, albeit with a diminished treatment response compared to common mutations, the S768I substitution and ex20ins have been linked to resistance against EGFR TKIs [10].

In a study conducted by Wu e*t al*., a comprehensive analysis was performed on a large series of 1,261 lung cancer cases, including 627 cases with *EGFR* mutations [11]. The primary objective of the study was to assess the response to erlotinib or gefitinib based on the specific type of *EGFR* mutation. The results of the study confirmed that patients with typical *EGFR* mutations derived the greatest benefit from EGFR TKI treatment in terms of overall response rate (ORR) (74%), progression-free survival (PFS) (8.5 months), and overall survival (OS) (19.6 months) [11]. However, the differences in outcome were less pronounced when considering the less frequent G719 and L861 mutations. These mutations exhibited lower ORRs (53.3% and 60.0%, respectively), shorter PFS (8.1 and 6.0 months), and comparable OS (16.4 and 15.2 months) compared to the typical mutations. In contrast, rare, uncommon mutations, such as V769M and A871E, showed poor response to EGFR TKIs with a clinical trend similar to that observed in the *EGFR* wild-type population. The ORR for these mutations was only 20%, and patients experienced shorter PFS (1.6 months) and OS (11.1 months) [11]. In another study, which aimed to investigate the prevalence and clinical significance of in cis compound *EGFR* mutations in Chinese patients with advanced NSCLC and evaluate the efficacy of EGFR TKIs in this population, patients with *in cis* compound

mutations involving L858R and mutations at positions 870 to 873 (such as H870R, A871E, or G873E) tended to have an unfavorable response to first-generation EGFR TKIs. These patients experienced shorter PFS compared to patients with single L858R mutations [12]. In our presented case report, both the mother and son exhibited the A871E mutation in addition to the L858R mutation, yet the son demonstrated a remarkable response to the EGFR TKI osimertinib while the mother demonstrated a survival period of almost 6 years despite metastatic disease. Our findings are consistent with the study of Kuiper et al.., which reported a similar case in a Dutch cohort featuring a double sensitizing exon 21 L858R mutation and A871E mutation. In that case, a partial response to EGFR TKI was observed, along with a median PFS of 18 months [13]. While studies show that the majority of lung adenocarcinomas associated with germline pathogenic mutations do not harbor a second *EGFR* somatic activating mutation, that was not the case for the two patients of our study [14]. These discrepancies emphasize the need for additional clinical data to further understand the nature and implications of the A871E mutation in relation to TKI responsiveness.

Limitations of the study include the lack of in vitro validation of the role of the A871E EGFR mutation along with the limited information on the cascade testing of the relatives. Since EGFR germline mutations are rare, the main strength of our case report is the description of two first-degree relatives with two mutations in EGFR, a germline and a common activating one, thus enhancing our knowledge on EGFR germline mutations and triggering further research on their clinical significance. The possibility of mosaicism could be considered given the occurrence of the same mutation in both mother and son. However, since the allelic frequency of the A871E variant on whole blood, obtained during the investigation of germline status was 50%, mosaicism did not seem likely. Finally, the lack of the dynamic results of genes of re-biopsy after progression is a significant limitation. However, repeated tumor molecular testing, including re-biopsy and/or tumor or ctDNA NGS is not reimbursed in Greece, although significantly costly. Therefore, the patients of the study did not opt for re-biopsy and assessment of tumor molecular profiling.

Our case report highlights the need for further exploration of the role of A871E mutation in tumorigenesis and its implications for treatment response and inheritance patterns. Thorough investigation and comprehension of the significance of each individual *EGFR* mutation, including the role of *EGFR* germline mutations, hold potential in both preventing the disease within family cohorts and understanding the mechanisms of tumorigenesis in sporadic cases. Unanswered questions surrounding the impact of A871E mutation on mutation accumulation, oncogenesis, and the need for genetic germline testing warrant further investigation. Addressing these queries will enhance our knowledge and guide clinical management in the context of *EGFR* mutations.

Abbreviations

EGFR	Epidermal growth factor receptor
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
TKIs	Tyrosine kinase inhibitors

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NA.

Author contributions

Contributions ZS: Conceptualization, writing - review & editing, supervision, project administration EF: Writing - review & editingAA: Resources NK: Investigation, writing original draft. All authors have approved the manuscript.

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Data availability

The variant has been uploaded at ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/submitters/509565 The raw data reported in the current study are available in the FIGSHARE repository, at https://figshare.com/articles/dataset/BAM_files/25645548.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Informed consent for publication was obtained from the next of kin of the deceased patients.

Competing interest

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