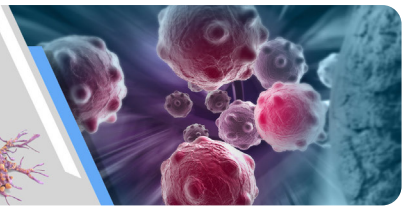
fortune Journals

Case Repot

JOURNAL OF CANCER SCIENCE AND CLINICAL THERAPEUTICS

ISSN: 2637-5079



Homozygous *EGFR* Gain-of-Mutation in a Patient Presenting with Metachronous Non-Small Cell Lung Adenocarcinoma and Invasive Ductal Breast Carcinoma

Hanifeh Mirtavoos-Mahyari[1], Ramin Ajami[2,3], Mahbuba Chowdhury[4], Saiji Nageshwaran[2], Farbod Bahreini[5,6], Hassan Vahidnezhad[7,8], Sathiji Kathiresu Nageshwaran[9*]

Abstract

The epidermal growth factor receptor (EGFR) exon-19 deletion is the most common EGFR mutation occur-ring in more than 40% of lung cancer patients. Exon-19 deletion is frequently detected in adenocarcinomas but is rare in the germline. Additionally, the occurrence of homozygous and heterozygous mutations in met-achronic cancers is uncommon. We present a 53-year-old female non-smoker diagnosed with two primary cancers; invasive ductal carcinoma and lung adenocarcinoma. A family history of breast and lung cancer was present in her sister and father, respectively. To determine the most appropriate treatment, EGFR gene sequencing was performed from the patient's lung tissue sample and a peripheral blood sample was taken to identify the presence of EGFR mutation in the patient's germ line. Loss-of-heterozygosity was discovered between the blood and tissue samples, with the extremely rare occurrence of a homozygous EGFR exon-19 deletion within the tumour sample.

Keywords: Adenocarcinoma of lung; Ductal carcinoma; Breast Neoplasms; ErbB receptors; Germ cells.

Introduction

Epidermal growth factor receptor (EGFR) is a member of the ErbB family of receptor tyrosine kinas-es. Exon-19 deletions are the most common mutations in *EGFR*, which contribute to oncogenesis. Mutations in the EGFR coding gene are frequently reported in lung cancers and are correlated with sensitivity to inhibition of EGFR tyrosine kinase (erlotinib and gefitinib) [1,2]. Additionally, exon-19 deletion of *EGFR* in non-small cell lung cancer patients is linked to an unusual pattern of metastasis [3]. It is well established that these mutations are heterozygous in the primary tumour site and identification of a disease-causing mutation with the homozygous form is rare [4]. The occurrence of synchronous lung and breast cancers is infrequent, with even fewer studies reporting simultaneous lung and breast primary tumours [5,6]. Data about gene mutations that would cause one to two synchronous primary cancers is scarce [7]. We report the presence of a germline *EGFR* mutation in a 53-year-old female non-smoker with a positive family history of breast and lung cancer. Based on our case and the literature reviewed, we recommend testing germline *EGFR* in patients presenting with two synchronous tumours.

Case Presentation, Methods, and Results

53-year-old post-menopausal female presented with progressive dyspnea and back pain. She reported no alcohol intake, tobacco, or oral contraceptive

Affiliation:

[1]Lung Transplantation Research Center (LTRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Leaders in Oncology Care, Oncology Department, HCA, UK

[3]Department of Oncology, Guys and ST Thomas' NHS Trust London, UK

[4]Department of Gynaecological Oncology, Southend University Hospital, Southend on Sea, UK

[5]Department of Biochemistry, Faculty of Biological Sciences, Tarbiat Modares University, Tehran, Iran

[6]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

[7]Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

[8]Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA, USA

[9]Department of Neurology, Mount Sinai Hospital, New York City, NY, USA

***Corresponding author:**
Sathiji Kathiresu Nageshwaran, Department of Neurology, Mount Sinai Hospital, New York City, NY, USA

Citation: Hanifeh Mirtavoos-Mahyari, Ramin Ajami, Mahbuba Chowdhury, Saiji Nageshwaran, Farbod Bahreini, Hassan Vahidnezhad, Sathiji Kathiresu Nageshwaran. Homozygous *EGFR* Gain-of-Mutation in a Patient Presenting with Metachronous Non-Small Cell Lung Adenocarcinoma and Invasive Ductal Breast Carcinoma. Journal of Cancer Science and Clinical Therapeutics. 8 (2024): 143-146.

Received: June 14, 2024
Accepted: June 20, 2024
Published: July 03, 2024

Mirtavoos-Mahyari H, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079235

pill use. Figure 1A illustrates the patient's pedigree. The pro-band (patient IV.1) was the oldest of four children. The patient's sister and father died from breast and lung cancer at the age of 34 and 55, respectively.

On examination, the patient was cachectic, tachypneic (24 respirations/min) with an oxygen saturation 96% in ambient room air. There was a soft, non-tender, freely mobile mass in the upper outer quadrant of her right breast. No nipple or areolar discharge was detected. Supraclavicular and axillary lymph nodes were impalpable. An irregular hypoechoic soft tissue density mass measuring 2.5 × 3.5 × 3 cm was noted in the right breast on the mammographic exam. A whole-body bone scan showed numerous bone metastasis. Histopathology of the biopsied right upper lobe mass (Figure 1C and 1D) showed features compatible with primary pulmonary lung adenocarcinoma (TTF-1 and Napsin A). Fine-needle aspiration of the right breast mass (figure 1E) showed invasive ductal carcinoma (grade II). Thus, a diagnosis of synchronous dual primary cancers of the lung and breast were made. Based on clinical manifestations and the positive family history of cancer, a hereditary form of cancer was considered. DNA extracted from the patients peripheral blood underwent Sanger sequencing and revealed a heterozygous in-frame mutation in exon-19 of *EGFR*: NM_005228.5: c.2237_2251del15, p.Glu746_Thr751delinsAla (Figure 1B).

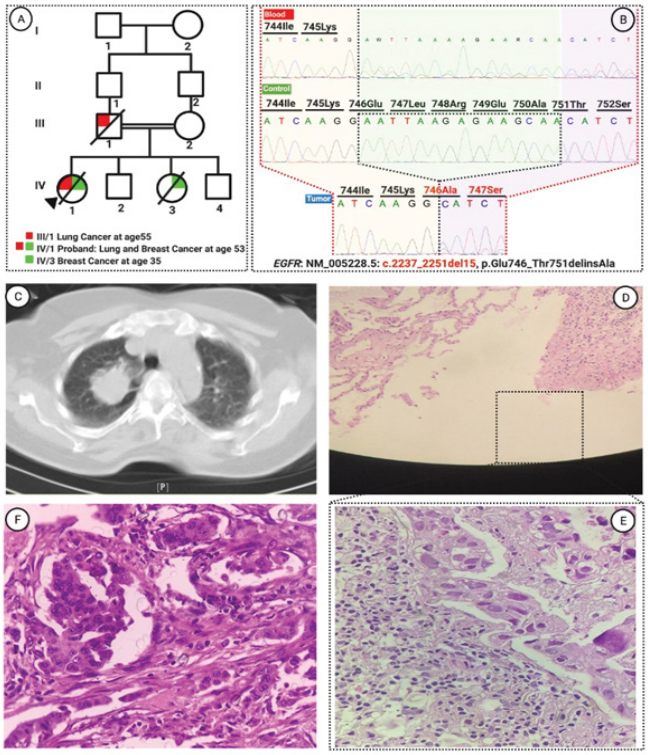


Figure 1: A: Family pedigree: Proband IV/I diagnosed with breast and lung cancer: died at the age of 53, IV/3 sister died from breast Ca at the age of 35. Father III/I: Died from Lung cancer at the age of 55.

B: Sequence and chromatogram of the peripheral blood patient genome, wild-type genome, and tumour genome in the patient. Double curves manifest the result of Sanger's sequencing for two genes.

The top lane shows a heterozygous deletion within the peripheral blood sample. The bottom lane highlights the homozygous EGFR mutation within the tumour.

C: Spiral CT scan of thorax without IV contrast: Right apical mass with pleural tag measuring approximately 41 mm, tiny nodular infiltrations surrounding the mass, a lytic rib lesion with necrosis, lytic lesions in the sternum and possibly within the vertebrae.

D & E: Primary pulmonary lung adenocarcinoma H&E: Cores of neoplastic tissue composed of atypical cells with vesicular nuclei

F: Invasive ductal carcinoma of breast H&E.

The mentioned exon of the *EGFR* gene was wild-type in the proband's mother and brother (cases III.2 and IV.2); case IV.4 was unavailable for a blood test. The detected mutation in the proband is present in the normal database of genetic variants in Gnomad (https://gnomad.broadinstitute.org) and Ensemble (https://www.ensembl.org) in heterozygous and homozygous forms. Sequencing of lung tissue revealed the same *EGFR* mutation, but in a homozygous state. It is plausible that the existence of a hereditary form of cancer is due to germline heterozygous *EGFR* mutation with ex-tensive phenotypic heterogeneity in the family. The management of adenocarcinoma of the lung in this patient included palliative chemotherapy with 150 mg per day of erlotinib. After nine months of treatment, she developed metastases to the brain, and palliative whole brain radiotherapy was the given. The patients unfortunately died 13 months after first being diagnosed with her primary cancer. Progression-free survival was nine months.

Discussion

EGFR mutations not only promote lung adenocarcinoma but also are linked to the sensitivity to erlotinib and gefitinib. These mutations, when occurring in the kinase domain of EGFR, affect the molecular structure of this receptor, lead to abnormal activation of EGFR, and influence the downstream kinases, and cause anti-apoptotic and/or proliferation signaling [8]. *EGFR* exon-19 deletion, specifically, is reported to be responsible for the sensitivity of lung cancer to gefitinib [9]. It is demonstrated that exon-19 deletion (both germline and somatic mutations) elevates the autophosphorylation of EGFR, activates AKT and STAT pathways, and consequently promotes cell survival. *In-silico* analysis revealed that exon-19 deletion can shift the inactive form of EGFR to its active form [10]. This mutation can be detected in a homozygous or heterozygous manner [11,12]. Despite the ongoing research on this field, underlying two different cancers with different source of mutations is not frequently observed. Similarly, Moran et. al. and Hu et al. have reported simultaneous occurrence of EGFR-mutant lung cancer and

Citation: Hanifeh Mirtavoos-Mahyari, Ramin Ajami, Mahbuba Chowdhury, Saiji Nageshwaran, Farbod Bahreini, Hassan Vahidnezhad, Sathiji Kathiresu Nageshwaran. Homozygous *EGFR* Gain-of-Mutation in a Patient Presenting with Metachronous Non-Small Cell Lung Adenocarcinoma and Invasive Ductal Breast Carcinoma. Journal of Cancer Science and Clinical Therapeutics. 8 (2024): 143-146.

Mirtavoos-Mahyari H, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079235

breast cancer [5,6]. Additionally, Lu et al. have reported the coexistence of both germline and somatic mutations in patients with lung cancer [13]. Herein, we reported a 53-year-old female who was diagnosed with dual primary cancers of lung and breast at the same time. Due to the family history of cancer, a hereditary form of cancer was considered. A heterozygous mutation in exon-19 of *EGFR* (NM_005228.5: c.2237_2251del15, p.Glu746_Thr751delinsAla) of blood sample-extracted DNA was identified in the patient. On the other hand, lung carcinoma tissue sequencing detected the same mutation was detected but in a homozygous state. Additionally, as studies have demonstrated that mutations in the EGFR gene are associated with the incidence of breast cancer, we contemplate that the mentioned mutation caused not only NSCLC adenocarcinoma but also breast cancer simultaneously [14]. Accordingly, we suggest that all the patients diagnosed with NSCLC adenocarcinoma that harbor *EGFR* mutation, should be tested for breast cancer. Further, we suggest other studies to evaluate the effect of this mutation on the incidence of breast cancer *in-vitro*.

Ethics Declaration

The study design was approved by the ethics committee of Shahid Beheshti University of Medical Sciences. The Ethics committee approval number is IR.SBMU.NRITLD.REC.1399.187. Written informed consent was obtained from the patient.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Hanifeh Mirtavoos-Mahyari defined the study protocol, contributed to the laboratory work, analyzed the data, and drafted the manuscript. Farbod Bahreini analyzed the data, provided the final revision of the manuscript alongside Sathiji Nageshwaran and Ramin Ajami who were in charge of the submission process. Hassan Vahidnezhad analyzed the data and drafted the manuscript. All the authors have given the final approval of the version to be published and they take responsibility for appropriate portions of the content.

Conflicts of Interest

The authors declare no potential conflict of interest.

Funding

The authors did not receive financial support for any part of this article.

Acknowledgments

We would like to acknowledge the support of Shahid Beheshti University of Medical Sciences.

References

1. Sigismund S, Avanzato D, Lanzetti L. Emerging functions of the EGFR in cancer. Mol Oncol 12 (2018): 3-20.
2. Centeno I, Blay P, Santamaría I, et al. Germ-line mutations in epidermal growth factor receptor (EGFR) are rare but may contribute to oncogenesis: a novel germ-line mutation in EGFR detected in a patient with lung adenocarcinoma. BMC cancer 11 (2011): 1-8.
3. Sekine A, Kato T, Hagiwara E, et al. Metastatic brain tumours from non-small cell lung cancer with EGFR mutations: distinguishing influence of exon 19 deletion on radiographic features. Lung cancer 77 (2012): 64-69.
4. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. New England Journal of Medicine 350 (2004): 2129-2139.
5. Moran T, Quiroga V, Cirauqui B, et al. A single-center retrospective study of patients with double primary cancers: breast cancer and EGFR-mutant non-small cell lung cancer. Oncology research and treatment 42 (2019): 107-114.
6. Hu Z, Zou X, Qin S, et al. Hormone receptor expression correlates with EGFR gene mutation in lung cancer in patients with simultaneous primary breast cancer. Translational Lung Cancer Research 9 (2020): 325.
7. Larouche V, Akirov A, Thain E, et al. Co-occurrence of breast cancer and neuroendocrine tumours: New genetic insights beyond Multiple Endocrine Neoplasia syndromes. Endocrinol Diabetes Metab 2 (2019): e00092.
8. Zhu J-q, Zhong W-z, Zhang G-c, et al. Better survival with EGFR exon 19 than exon 21 mutations in gefitinib-treated non-small cell lung cancer patients is due to differential inhibition of downstream signals. Cancer letters 265 (2008): 307-317.
9. Banno E, Togashi Y, Kobayashi Y, et al. Afatinib is especially effective against non-small cell lung cancer carrying an EGFR exon 19 deletion. Anticancer research 35 (2015): 2005-2008.
10. Tamirat MZ, Koivu M, Elenius K, et al. Structural characterization of EGFR exon 19 deletion mutation using molecular dynamics simulation. PLoS One 14 (2019): e0222814.
11. Nakano H, Soda H, Nakamura Y, et al. Different epidermal growth factor receptor gene mutations in a patient with 2 synchronous lung cancers. Clin Lung Cancer 8 (2007): 562-564.
12. Schaller A, Beau-Faller M, Mennecier B, et al. Lung

Mirtavoos-Mahyari H, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079235

Adenocarcinoma with Pulmonary Miliary Metastases and Complex Somatic Heterozygous EGFR Mutation. Case Rep Oncol 7 (2014): 769-773.

13. Lu S, Yu Y, Li Z, et al. EGFR and ERBB2 germline mutations in Chinese lung cancer patients and their roles in genetic susceptibility to cancer. Journal of Thoracic Oncology 14 (2019): 732-736.

14. Teng YH-F, Tan W-J, Thike A-A, et al. Mutations in the epidermal growth factor receptor (EGFR) gene in triple negative breast cancer: possible implications for targeted therapy. Breast Cancer Research 13 (2011): 1-9.

Citation: Hanifeh Mirtavoos-Mahyari, Ramin Ajami, Mahbuba Chowdhury, Saiji Nageshwaran, Farbod Bahreini, Hassan Vahidnezhad, Sathiji Kathiresu Nageshwaran. Homozygous *EGFR* Gain-of-Mutation in a Patient Presenting with Metachronous Non-Small Cell Lung Adenocarcinoma and Invasive Ductal Breast Carcinoma. Journal of Cancer Science and Clinical Therapeutics. 8 (2024): 143-146.