Case Report

EGFR-mutated lung cancer as a secondary neoplasm in a patient with Li-Fraumeni syndrome: case report

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Background: Li-Fraumeni syndrome (LFS) is a rare hereditary disorder caused by mutations in the tumor protein p53 (*TP53*). It causes a predisposition for the development of multiple malignancies, primarily including breast cancers, sarcomas, and central nervous system tumors. There are a few cases reported in the literature of patients with LFS presenting with an epidermal growth factor receptor (EGFR) mutated lung cancer. Still, it has been suggested that there may be an association between the *TP53* pathogenic variant and lung cancer with EGFR mutation in somatic cells.

Case Description: A 47-year-old non-smoker woman with LFS with a history of multiple tumors, including bilateral breast cancer, pecoma, and sarcoma. In one of her computed tomography, a lesion in the lingula of the lung was detected. It was biopsied, which diagnosed lung adenocarcinoma, and genetic studies detected an EGFR exon 19 deletion. She was treated with a left inferior lobectomy, followed by pemetrexed and cisplatin.

Conclusions: The association between *TP53* and lung cancer with EGFR mutation has been suggested in case reports. Studies in lung cancer cell lines have shown a link between TP53 mutation and EGFR overexpression. Nonetheless, as more cases are reported, further research is needed to comprehend the interrelation between these two pathologies and the risk posed by LFS to the emergence of EGFR-mutated lung cancer.

Keywords: Li-Fraumeni syndrome (LFS); lung cancer; epidermal growth factor receptor mutation (EGFR mutation); case report

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Introduction

In 1969, while working at the National Cancer Institute, Dr. Frederick Li and Dr. Joseph Fraumeni described four families with numerous early-onset malignancies in young adults and children (1). In 1990, a multi-institutional research team headed by Drs. Stephen Friend and David Malkin discovered inherited germline mutations of tumor protein p53 (*TP53*) as the primary cause of Li-Fraumeni syndrome (LFS) (2).

LFS is a rare inherited disorder caused by mutations in the *TP53*. It is an autosomal dominant disease that causes a predisposition for the development of multiple malignancies, primarily including breast cancers, sarcomas, central nervous system tumors, adrenocortical carcinomas, and osteosarcomas (3). It has been suggested that there may be a link between the *TP53* mutation and lung cancer with epidermal growth factor receptor (EGFR) mutation. However, despite advancing knowledge about LFS, we still lack literature concerning the association between EGFR lung cancers and *TP53* pathways (4,5). Here, we present a case of a woman with EGFR lung adenocarcinoma in an LFS patient with multiple previous malignancies in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-23-206/rc).

Case presentation

A 47-year-old non-smoker woman with a confirmed diagnosis of LFS by a hereditary genetic panel that identified a variant of the *TP53* gene c.771_782+13del in a heterozygous state. She has a significant family history that revealed a high occurrence of neoplasms at a young age. Her mother was diagnosed with leukemia at age 36 years, her maternal grandmother with breast cancer at age 47 years, and other relatives on her mother's side were also affected: her female cousin with sarcoma in her adolescence and breast cancer at 26 years, her uncle with sarcoma at 60 years, and her male cousin with sarcoma at age 51 years. With her personal and family history, the patient meets the classical clinical criteria of LFS. Nevertheless, the patient had no family history of lung cancer.

Her extensive pathological background began in when she was 28 years, with human epidermal growth factor 2 positive ($HER2^+$) bilateral breast cancer treated with bilateral mastectomy, and AC chemotherapy (doxorubicin, hydrochloride and cyclophosphamide). Herceptin adjuvant (HERA) protocol was available at our hospital, but she refused this treatment. At the age of 38 years, a perivascular epithelioid cell tumor (pecoma) in her liver was detected, for which she underwent a partial hepatectomy in January 2014. Five months later, two more malignancies were detected: a grade three pleomorphic spindle cell sarcoma in her right thigh and a grade three infiltrating ductal carcinoma (IDC) in the right breast. She was treated with resection of the sarcoma with adjuvant radiotherapy and mastectomy of the right breast, TCH regimen (docetaxel, carboplatin, and trastuzumab) for 1 year and tamoxifen for 5 years. The involvement of radiotherapy for the sarcoma was decided through a multidisciplinary team due to its size, depth, and grade.

At the age of 44 years, she presented three recurrent pleomorphic sarcoma lesions of the right thigh that were subsequently resected. A full body computed tomography scan performed as a follow-up surveillance of the sarcomas detected a 1.4 cm nodule in the lung's lingula when she was 46 years. She was not undergoing Toronto protocol screening due to lack of resources in the institution. The patient denied the presence of any symptomology. There were no evident abnormalities in the physical examination. A biopsy was performed, which led to the diagnosis of lung adenocarcinoma (*Figure 1*). Further genetic testing detected a deletion of EGFR exon 19. She was treated with a left inferior lobectomy, followed by pemetrexed and cisplatin. Mutation analysis in peripheral lymphocytes was also performed, and EGFR mutations were not detected. The patient had a good response to treatment and is currently

Highlight box

Key findings

- Another example of the coexistence of epidermal growth factor receptor (EGFR)-mutation lung cancer in a patient with Li-Fraumeni syndrome (LFS).

What is known and what is new?

- LFS is a rare inherited disorder caused by mutations in tumor protein p53 (TP53).
- A new case report of a patient with LFS and EGFR-mutated lung cancer.

What is the implication, and what should change now?

- Physicians should be aware that patients with LFS may present with EGFR-mutated lung cancer.
- Research should be carried out in search of the possible association between these two mutations and thus eventually evaluate the risk posed by LFS for the development of EGFR-mutated lung cancer.

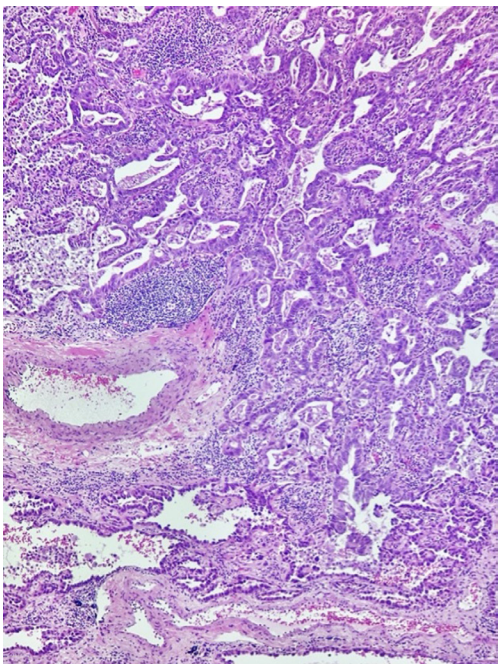

Figure 1 Infiltrating adenocarcinoma with lepidic and acinar pattern (hematoxylin and eosin stain, ×10). Source: Pathology Service of National Oncologic Institute, Panama.

free of relapse 2 years after treatment.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying image. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We report a case of a non-smoker woman with LFS detected with an EGFR-mutated lung cancer. There are currently very few cases reported in the literature (*Table 1*) that involve this condition together, and even fewer cases of patients with such an extensive background of previous tumors.

The *TP53* gene is located on chromosome 17p13.1. In the absence or malfunction of the standard *TP53* protein, cells with defective deoxyribonucleic acid (DNA) do not go through repair or apoptosis, which leads to a predisposition to malignant cell formation (6). EGFR is a transmembrane protein that, upon ligand binding, increases intracellular activity through tyrosine kinase activity that through phosphorylation activates pathways related to phospholipase C-y, mitogen-activated protein kinase (MAPK) and the ras GTPase-activating protein (GAP) that promote cell proliferation.

Wild-type p53 (*TP53*) binds to the EGFR promoter region, increasing its activity. Similarly, the tumor-associated mutant transcription factor p53 also binds to the EGFR promoter but at a different site than wild-type p53, resulting in dysregulation of this receptor and increased cell proliferation and mutational load that may contribute to carcinogenesis (6). Also, lung cancer cell line studies have suggested that lung cancer cells with *TP53* mutations overexpress EGFR, leading to tumor formation (5).

The *TP53* gene has different variations, including NM_000546.6, due to alternative promoters and splicing. It is located on the negative strand of chromosome chr17 and covers 19,070 base pairs, including introns, at position 7668421 (14). The messenger ribonucleic acid (mRNA) resulting from transcription and splicing has 2,512 bases, with only 1,182 translated into a protein. Alternative isoforms can arise from exon 7 of 11 position 99 of 110 to intron 7 of 10 position 13 of 343 (splicing, splicing, intronic, coding), where identical transcript variants have alternative translation start codons (15).

Loss of function is a disease mechanism that affects this gene, and there are 540 reported ClinVar null pathogenic variants in ten different exons, with 56 variants in exon 7. The genome aggregation database (gnomAD) observed/expected score for these variants is 0.449. The coding chain is on the reverse chain, and exon skipping can lead to altered reading frames. ClinGen has assigned the Null classification as a loss-of-function mechanism for ten exons, including exon 6. The skipped exon is a crucial region for the protein's function and has several pathogenic missense variants (16).

In the case presented, EGFR mutation was only identified in malignant cells in the lung since peripheral blood tests were also performed, and this mutation was not found. This opens a hypothesis that *TP53* mutations in LFS may contribute to developing somatic EGFR mutations, which results in EGFR-mutant lung cancer. According to an international project led by the Clinical Lung Cancer Genome Project, tumoral somatic *TP53* mutations and EGFR mutations co-occurrence have been found in 34% of lung adenocarcinomas (17).

Most of the reported cases of patients who have lung

Table 1 Some mutation profile of EGFR-mutated lung adenocarcinomas in patients with LFS reported in the literature until 2022

Age, years	Smoking status	Medical history	Germline TP53 variant	EGFR mutation	Reference
55	Non-smoker	None	H179Y	Exon 19 and 20 deletion	(4)
57	Non-smoker	Breast cancer	R273H	L858R	(4)
28	Unknown	None	Exon 7 deletion	Exon 19 deletion	(6)
46	Non-smoker	Breast cancer, shwannoma	G245S	L858R	(7)
41	Unknown	Osteosarcoma, thyroid benign tumor, uterine benign tumor, bone metastasis	R333Vfs*12	L747-S752 del	(8)
29	Non-smoker	Malignant phyllodes tumor, breast cancer	R248W	Exon 20 insertion	(9)
39	Non-smoker	Breast cancer	T E285K (c.853G>A)	EGFR-KDD	(10)
30	Non-smoker	Breast cancer	p.R273H	Deletion in exon 19	(11)
24	Non-smoker	Breast cancer, histiocytoma	Deletion at codon 153	L858R	(12)
40	Non-smoker	None	c.542G>A (p.Arg181His)	Exon 19 deletion	(13)
47	Non-smoker	Breast cancer, sarcoma, pecoma	c.771_782+13del	Exon 19 deletion	Our case

TP53, tumor protein p53; EGFR, epidermal growth factor receptor; LFS, Li-Fraumeni syndrome.

cancer with EGFR mutation and mutated *TP53* LFS have been women, many without smoking history (4). Our case supports this tendency, as shown in the reported cases shown in *Table 1*. But this is yet to be supported by studies that include a representative sample of all individuals with LFS.

Lopes *et al.* published the largest cohort of lung cancer patients with the TP53 R337H mutation (28 patients), representing 16% of the 175 cases with tumors diagnosed in the Brazilian Li-Fraumeni Syndrome Study (BLISS) database, among these cases 14 were presented EGFR alterations located in the exon 19. In this research, lung adenocarcinoma was the first neoplasm diagnosed in 78.6% of the cases, reinforcing the hypothesis of potential interactions between the TP53 R337H variant and the ERBB family for the carcinogenesis of lung adenocarcinoma. Thus, proposing that lung cancer may be the first manifestation of LFS in non-smoking women over 50 years of age (18). This pattern was described by Barbosa *et al.* where in their case series 4 of 9 patients presented lung cancer as the first neoplasm diagnosed. In these tumors, 89% frequency of EGFR activating mutations was identified (19). Results published by Mezquita *et al.* in patients with non-small cell lung cancer (NSCLC) and pathogenic germline TP53 variant where molecular screening was performed in 21 tumors, somatic oncogenic alterations were detected in 90% of the tumors (19/21), with 18 cases of somatic mutation of the EGFR gene (20). In a single-institution case series, of 91 patients in the LFS cohort, 6.6% (6 patients) were diagnosed with lung cancer. All diagnosed cases were stage I–III adenocarcinomas, 80% of the patients had never smoked, 60% were women, and the mean age at diagnosis was 48 years. A significant proportion of these patients had other cancer diagnoses, and none had received previous thoracic irradiation treatment. Genetic analysis revealed that 40% of the patients had common EGFR mutations (21).

Currently, EGFR tyrosine kinase inhibitors (TKIs) are considered the first line of treatment for patients with NSCLC with EGFR mutations; they have demonstrated high efficacy and tolerability. There are three generations of EGFR-TKIs, but the preferred choice for patients with advanced or metastatic NSCLC is osimertinib, a potent third-generation irreversible inhibitor (22). In the case of our patient, she was not treated with Osimertinib due to unavailability in our institution, and a surgical approach was opted for.

This patient was treated with radiotherapy for her sarcoma. Even though use of radiation is typically avoided in patients with LFS, some studies have shown that the frequency of radiotherapy-related malignancies is lower than reported in the literature. Hendrickson conducted a study evaluating forty patients with LFS who received radiotherapy with curative intent where 4 (10%) developed malignancies following radiotherapy. Still, none can be

stipulated to be associated with radiotherapy because they have the same histology as the primary tumor, suggesting a local recurrence. The authors comment that radiotherapy can be considered part of the treatment after a multidisciplinary discussion and when clinically indicated (23). Another retrospective study by Le *et al.* identified 51 patients diagnosed with breast cancer and LFS, 27 of these patients received adjuvant radiotherapy in the curative setting, of all patients 1 (6%) developed thyroid cancer and 1 (6%) developed sarcoma in the radiation field. Despite the potential risk of inducing sarcomas and other secondary cancers, the benefits of radiotherapy in reducing the risk of recurrence and improving overall survival outweighs the risk (24).

This case is another example of LFS with EGFR-mutated lung cancer. Further research should be carried out in search of the possible association between these two pathologies and, thus, evaluate the risk posed by LFS for the development of EGFR-mutated lung cancer.

Conclusions

This specific type of lung cancer has been understudied in the LFS spectrum. The complex interconnection between LFS and EGFR-mutant lung cancer represents an area that has received insufficient exploration in current research endeavors. The lack of in-depth investigation into this particular subtype amidst the broader spectrum of LFS and emphasizes the imperative need for forthcoming studies.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-23-206/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-23-206/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying image. A copy of the written consent is available for review by the editorial office of this journal.

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