Case Report

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A case series of non-small cell lung cancer patients with *EGFR* or *HER2* exon 20 insertion in Li Fraumeni syndrome

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Abstract

Introduction: Germline pathogenic mutations in *TP53* gene are associated with a cancer predisposition syndrome known as Li Fraumeni syndrome. Albeit infrequently, non-small cell lung cancer, especially as oncogene-addicted disease, may be diagnosed in young patients with Li Fraumeni syndrome.

Case description: We report three cases of patients affected by Li Fraumeni syndrome who developed non-small cell lung cancer with *EGFR* or *HER2* exon 20 insertions. The first patient suffered from liposarcoma and, then, brain metastases from *HER2*-mutated non-small cell lung cancer: after stereotactic radiotherapy, he benefited from enrollment in a clinical trial with a *HER2*-targeted therapy. The second young patient was a female with personal history of rhabdomyosarcoma, diagnosed with brain metastases from *EGFR*-mutated non-small cell lung cancer: enrollment in a clinical trial led to a temporary clinical benefit. The last case was a female diagnosed with breast carcinoma, ovarian granulosa cell tumor and advanced *EGFR*-mutated non-small cell lung cancer at a young age.

Conclusions: Young patients affected by oncogene-addicted non-small cell lung cancer and with a positive familial cancer history should be referred for an accurate genetic counselling to look for Li Fraumeni syndrome. The underlying molecular connection between *TP53* and HER family receptor tyrosine kinases remains unclear, but an extensive molecular characterization of tumors from patients with Li Fraumeni syndrome should always be performed, to offer patients a personalized therapeutic approach.

Keywords

Non-small cell lung cancer, Li Fraumeni syndrome, HER2, EGFR

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Introduction

Li Fraumeni syndrome (LFS) is a rare autosomal dominant genetic condition, predisposing individuals to a wide range of cancer types. Approximately 70% of LFS cases are caused by germline mutations in tumor suppressor gene *TP53*, involved in regulation of cell cycle, DNA repair and apoptosis.[1]

About 2-7% of individuals with LFS received a diagnosis of non-small cell lung cancer (NSCLC) and common epidermal growth factor receptor (*EGFR*) mutations are frequently found in LFS-related NSCLC.[2] Here, we report three rare cases of patients with LFS developing NSCLC with an *EGFR* or human epidermal growth factor receptor 2 (*HER2*) exon 20 insertion (ex20ins).

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Case 1

A 20-year-old patient, who never smoked, underwent surgery for a myxofibrosarcoma-like pleomorphic liposarcoma of the left thigh, followed by adjuvant anthracyclines-based chemotherapy.

At 25 years old, a chest computed tomography (CT) scan showed a left pulmonary nodule and the patient underwent radical surgery. The pathological diagnosis was lung adenocarcinoma, stage IIIB (pT3N2), according to TNM staging VIII edition. The next generation sequencing (NGS) analysis on tissue sample revealed an ex20ins in *HER2* gene, c.2325_2326delinsAGTGT p.(Gly776delinsValCys). After surgery, adjuvant platinum-based chemotherapy was administered.

Nineteen months after surgery, for the appearance of a metastasis in the right superior cortico-frontal area, stereotactic radiotherapy was administered. Then, because of lung and lymph nodal disease progression, the patient was enrolled in a clinical trial to receive a *HER2*-targeted therapy. To date, he has completed four cycles and radiological assessment showed stable disease.

In his family history, his father died from cholangiocarcinoma at 62, while his paternal aunt developed breast cancer at the age of 75. Due to the suspicion of LFS, the NGS analysis, performed on peripheral blood, highlighted the heterozygous tandem duplication of exon 2 to exon 9 in the *TP53* gene, c.(-29+1_-28-1)_(933+1_934-1)dup p.(Ile332Glnfs*18); this novel frameshift variant was classified as pathogenic.

Case 2

An 18-year-old female patient, who never smoked, experienced episodes of aphasia and confusion. A brain magnetic resonance imaging (MRI) showed multiple and bilateral intracranial metastases and an ^{18}F-fluorodeoxgyglucose positron emission tomography (^{18}F-FDG PET)/CT revealed the presence of focal uptake in the left upper lung lobe. She underwent brain metastasectomy with histological diagnosis of lung mucinous adenocarcinoma.

Molecular analyses showed a somatic in frame ex20ins of *EGFR* gene, c.2310_2311insGGGTGT p.(Asp770_Asn771insGlyCys). Whole brain radiotherapy was carried out, and the patient was enrolled in a clinical trial with a novel *EGFR* ex20ins targeted inhibitor. Despite a partial response in brain metastases and lung lesion, after four months from treatment start the patient experienced disease progression and discontinued experimental treatment.

When the patient was two years old, she received a diagnosis of rhabdomyosarcoma of the right calf, which was surgically removed. Her father died from acute leukemia at 39 years old and her paternal grandfather died from lung cancer at 70 years old. Germline NGS analysis was performed revealing a heterozygous pathogenic variant of *TP53* gene, c.430C>T p.(Gln144*). This variant, identified in another LFS patient, is extremely rare and reported as pathogenic in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/).

Case 3

A 23-year-old female, who never smoked, underwent neoadjuvant chemotherapy and left mastectomy for infiltrating ductal breast cancer, followed by adjuvant chemotherapy and radiotherapy. After three years, the patient was subjected to surgical excision of a granulosa cell tumor of the left ovary. When she was 29 years old, a CT scan revealed a left pulmonary nodule, hilar lymph node, pleural thickenings, and a right ovarian mass. Pleural biopsies during thoracoscopy revealed metastases from lung adenocarcinoma and molecular analyses showed the presence of c.2308_2309insGCAGCGTGG p.(Val769_Asp700insGlySerVal) mutation in exon 20 of the *EGFR* gene.

The patient received first-line chemotherapy with carboplatin and pemetrexed. After one year of treatment for lung disease progression, she was candidate for mobocertinib. While on treatment, the patient underwent a right mastectomy for a ductal breast carcinoma in situ. A stereotactic radiotherapy on left fronto-basal metastases, site of oligo-progression, was performed after nine months. The patient continued mobocertinib for a total of 15 months until the progression of the disease. After one cycle of amivantamab, clinical conditions worsened rapidly, and she died.

Her family history reported a son died from anaplastic medulloblastoma at 10 years old and paternal grandmother died due to ovarian cancer. A heterozygous pathogenic germline variant of the *TP53* gene, c.711G>A p.(Met237Ile), was found on peripheral blood, together with variants of uncertain significance in *ATM* and *BARD1* genes.

Discussion

In this manuscript, we reported three distinct cases of NSCLC patients affected by LFS, with an *EGFR* or *HER2* ex20ins, treated at two Italian Oncology Centers (Table 1, Figure 1).

Lung cancer is not among the most frequent tumors in LFS. For reasons unknown, the majority (70-80%) of LFS-associated NSCLC harbor common *EGFR* activating mutations (exon 19 deletion or p.L858R exon 21 mutation).[2]

Regarding uncommon *EGFR* or *HER2* mutations, a few interesting cases are described in literature (Table 2). Serra et al.[3] described the case of a young patient with LFS, who was diagnosed with two primary NSCLCs: one with a

Table 1. Characteristics of NSCLC patients affected by Li Fraumeni Syndrome.

Case	Sex	Smoking history	Family cancer history		Previous cancer history	*TP53* variant	Other germline mutations	Age at NSCLC diagnosis	Histology	Stage at diagnosis	Somatic molecular alterations	PD-L1	Treatment
			1st-degree relative	2nd-degree relative									
1	M	Never smoker	Cholangiocarcinoma (father, 62 years)	Breast cancer (paternal aunt, 75 years)	Liposarcoma	*c.(-29+1_-28-1)_(933+1_934-1)dup p.(Ile332Glnfs*18)*	None	24 years	Acinar-cribriform adenocarcinoma	IIIB	HER2, exon 20 insertion p.(Gly776delinsValCys)	<1%	Cisplatin +Vinorelbin (adjuvant treatment), Trastuzumab deruxtecan
2	F	Never smoker	Acute leukemia (father, 39 years)	Lung cancer (paternal grandfather, 70 years)	Rhabdomyosarcoma	*c.430C>T p.(Gln144*)*	None	18 years	Mucinous adenocarcinoma	IVB	EGFR, exon 20 insertion p.(Asp770_Asn771insGly)	<1%	BAY 2927088
3	F	Never smoker	Anaplastic medulloblastoma (son, 10 years)	Ovarian cancer (paternal grandmother, 70 years)	Breast cancer, ovarian granulosa cell tumor	*c.711G>A p.(Met237Ile)*	ATM c.1236-13_1236-12insA p.? and BARD1 c.1714C>T p.(Leu572Phe)	29 years	Adenocarcinoma	IVB	EGFR, exon 20 insertion p.(Val769_Asp700insGlySerVal)	5%	Carboplatin +Pemetrexed, Mobocertinib, Amivantamab

Abbreviations: M, male; F, female. Pathological stage according to TNM staging VIII edition.

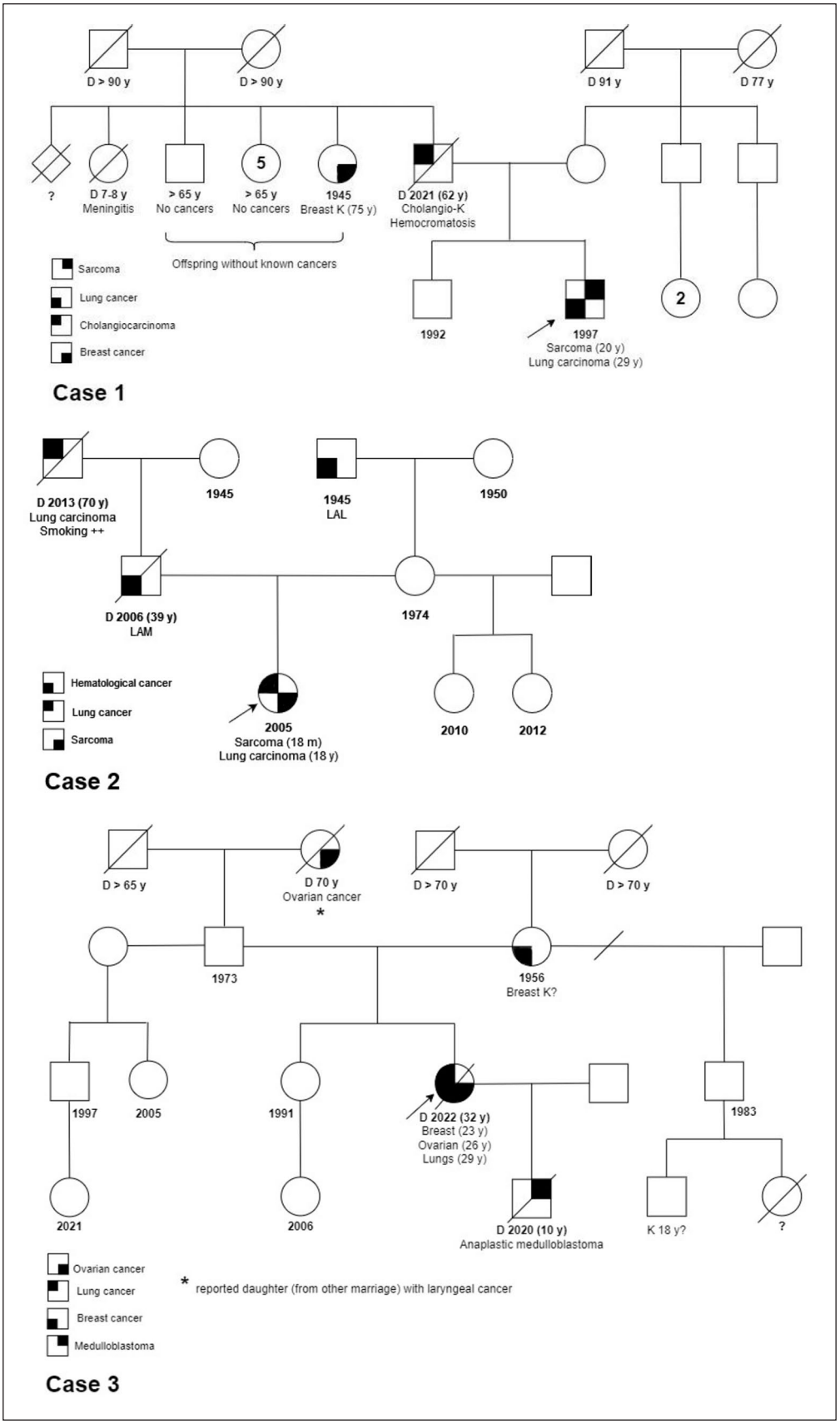

Figure 1. Family pedigree of reported cases. NSCLC patients undergoing genetic testing for Li Fraumeni syndrome are indicated by black arrows. Abbreviations: D, died; K, cancer; LAL, acute lymphoblastic leukemia; LAM, acute myeloid leukemia; y, years.

Table 2. NSCLC cases with EGFR exon 20 insertion or HER2 mutation reported in literature in the context of Li Fraumeni Syndrome.

Reference	Sex	Smoking history	Previous cancer history	*TP53* variant	Age at lung cancer diagnosis	Histologic type	Stage at diagnosis	Somatic molecular alterations	Treatment
Serra et al. 2013[3]	F	Never smoker	Breast malignant phyllodes tumor (29 years); bilateral in situ ductal breast carcinoma (29 years)	*p.(Arg248Trp)*	33 years	Adenocarcinoma	IVA	EGFR exon 20 insertion p.(Ala767_S768insSerValAsp) left lung tumor and mutation HER2 p.(Val659Glu) right lobe tumor	Cisplatin+Docetaxel (adjuvant), Cisplatin+pemetrexed, Lapatinib+trastuzumab
Mezquita et al. 2020[2]	M	Never smoker	Nonmelanoma skin cancer	*p.(Arg196*)*	48 years	Adenocarcinoma	I-II (two different lung tumor)	EGFR exon 20 insertion	Not reported
Marks et al. 2023[4]	F	Not reported	Hormone receptor–positive/ HER2-negative bilateral breast cancer (51 years)	*p.(Gly245Ser)*	54 years	Adenocarcinoma	IVA	EGFR exon 19 deletion right lobe tumor and EGFR exon 20 insertion (p.P772_H773 duplication) left lobe tumor	Osimertinib, surgery
Lopes et al. 2023[5]	M	Never smoker	Not reported	*p.(Arg337His)*	41 years	Adenocarcinoma	IVA	EGFR exon 20 insertion p.(Asp770-Asn771insTyr)	Carboplatin +pemetrexed, Docetaxel, Paclitaxel, experimental drug (not specified)
Lopes et al. 2023[5]	F	Never smoker	Not reported	*p.(Arg337His)*	Not reported	Adenocarcinoma	Not reported	EGFR exon 20 insertion	Not reported
Lopes et al. 2023[5]	M	Never smoker	Not reported	*p.(Arg337His)*	33 years	Adenocarcinoma	IIIA	HER2 exon 20 insertion	Cisplatin+ pemetrexed (adjuvant), Carboplatin+ paclitaxel +bevacizumab, Trastuzumab +pertuzumab+docetaxel, TDM1

Abbreviations: M, male; F, female. Pathological stage according to TNM staging VIII edition.

HER2 activating mutation p.(Val695Glu), while the other with an *EGFR* ex20ins. Another patient with LFS, reported by Marks et al.,[4] was diagnosed with two synchronous lung tumors, characterized by two distinct *EGFR* mutations (exon 19 deletion and ex20ins). Moreover, Lopes et al.[5] presented a cohort of 20 NSCLC patients with *TP53* p.(Arg337His) mutation, including two cases with *EGFR* ex20ins and one case with *HER2* ex20ins.

Metastatic NSCLC patients with LFS should be treated as patients without genetic syndrome, because of the good efficacy of a target therapy. Given the high incidence of oncogene-addicted NSCLC in LFS patients, some authors hypothesized a connection between *TP53* and HER family receptor tyrosine kinases to promote lung carcinogenesis,[2] but underlying molecular mechanisms are mostly unknown.

Conclusions

Young patients affected by oncogene-addicted NSCLC and with a positive familial cancer history should be referred for an accurate genetic counselling to look for LFS. Given the reported cases of NSCLC with *EGFR* or *HER2* ex20ins, an extensive molecular characterization should be always carried out and enrollment in clinical trial always offered to LFS patients.

Author Contributions

Guarantor of integrity of the entire study: E.C., M.T.; Study conception and design: E.C., P.Bo., P.Bi., M.T.; Data acquisition and curation: V.C., E.C., P.Bo., V.P., F.M.C., R.M., M.T.; Writing – Original Draft Preparation, V.C., E.C., P.Bo., V.P., F.M.C., R.M., E.A., A.P., D.G., M.T.; Writing – review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

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Consent

All the patients provided consent for the publication of the clinical case.

References

1. Malkin D. Li-Fraumeni syndrome. *Genes Cancer*. 2011 Apr;2(4):475–84. doi: 10.1177/1947601911413466
2. Mezquita L, Jové M, Nadal E, et al. High prevalence of somatic oncogenic driver alterations in patients with NSCLC and Li-Fraumeni syndrome. *J Thoracic Oncol*. 2020 Jul;15(7):1232–1239. doi: 10.1016/j.jtho.2020.03.005.
3. Serra V, Vivancos A, Puente XS, et al. Clinical response to a lapatinib-based therapy for a Li-Fraumeni Syndrome patient with a novel HER2V659E mutation. *Cancer Discov*. 2013 Nov;3(11):123–44. doi: 10.1158/2159-8290.CD-13-0132. Epub 2013 Aug 15.
4. Marks JA and Liu S V. NSCLC with synchronous EGFR mutations in Li Fraumeni syndrome: A case report. *JTO Clin Res Rep*. 2023 Apr 30;4(6):100521. doi: 10.1016/j.jtocrr.2023.100521
5. Lopes CDH, Antonacio FF, Moraes PMG, et al. The clinical and molecular profile of lung cancer patients harboring the TP53 R337H germline variant in a Brazilian cancer center: The possible mechanism of carcinogenesis. *Int J Mol Sci* 2023 Oct 10;24(20):15035. doi: 10.3390/ijms242015035.