CASE REPORT
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Preservation of fertility in a young woman with Li-Fraumeni syndrome: a case report

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ABSTRACT

Li-Fraumeni syndrome (LFS) is the term given to the mutation of the TP53 gene associated with the development of neoplasms, often at an early age. The following case report describes a 26-year-old female patient diagnosed with invasive breast carcinoma of no special type, with confirmation of a pathogenic mutation in the TP53 gene (R337H variant), consistent with LFS. In view of the oncologic diagnosis and the patient's reproductive desire, and considering the need for cancer treatment with potentially gonadotoxic drugs, oocyte cryopreservation was performed using a random-start ovarian stimulation protocol, combining hormonal agents and aromatase inhibitors to ensure safe hormonal control in the oncologic context. The patient underwent neoadjuvant chemotherapy followed by bilateral adenomastectomy, with subsequent multidisciplinary follow-up. This case underscores the importance of integrated management involving oncology, genetics, and reproductive medicine in young patients with hereditary cancer, highlighting the need for universal access to fertility preservation strategies, particularly within public health systems.

KEYWORDS: Li-Fraumeni syndrome; breast neoplasms; fertility preservation.

INTRODUCTION

Li-Fraumeni syndrome (LFS) is a rare genetic condition characterized by a mutation in the TP53 gene, located on chromosome 17p13.1. This gene has a tumor suppressor function, and its inactivation permits the survival and proliferation of cells with damaged deoxyribonucleic acid (DNA), contributing to the development of various types of cancer[1]. Individuals with LFS have a markedly increased risk of developing multiple malignancies throughout childhood and young adulthood. Estimates indicate that 73% to 100% of carriers develop at least one malignant neoplasm by 70 years of age[2]. Breast cancer is the most common malignancy among women with LFS, particularly in the premenopausal period, and approximately 85% of affected women are expected to develop breast cancer by 60 years of age[2]. Many of these patients have not yet had children, and oncologic treatments may permanently impair reproductive function. Accordingly, timely counseling on fertility preservation options before initiating cancer therapy is essential to safeguard the possibility of future childbearing[3]. This case report underscores the importance of addressing fertility preservation in patients who are candidates for cancer treatment, while also describing the presentation and management of an uncommon genetic syndrome.

This case report received approval from the responsible hospital, as well as informed consent from the patient for the collection of data from her medical record. The study was submitted to and approved by the Research Ethics Committee through the *Plataforma Brasil* system, under the identification number CAAE 87081125.6.0000.5436.

CASE REPORT

T.M.A., a 26-year-old woman, sought medical evaluation after detecting a nodule in her right breast during self-examination in July 2024. On clinical palpation, a nodule was identified in the superolateral quadrant of the right breast, measuring approximately 1 cm in diameter, with irregular margins and firm consistency. No palpable nodules were detected in the contralateral breast, and no axillary lymphadenopathy was observed. Nipple expression revealed no discharge.

The patient was nulliparous, experienced menarche at 12 years of age and reported regular menstrual cycles. She used combined oral contraceptives for five years and, over the past year, transitioned to an etonogestrel subdermal implant. She undergoes annual gynecological follow-up, with the most recent consultation occurring 10 months prior, during which no relevant findings were noted on clinical examination.

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Regarding personal history, the patient denies smoking, alcohol use, and other comorbidities. With respect to family history, there is no report of breast cancer in first-degree relatives, although multiple cases of cancer are present within the family (Table 1).

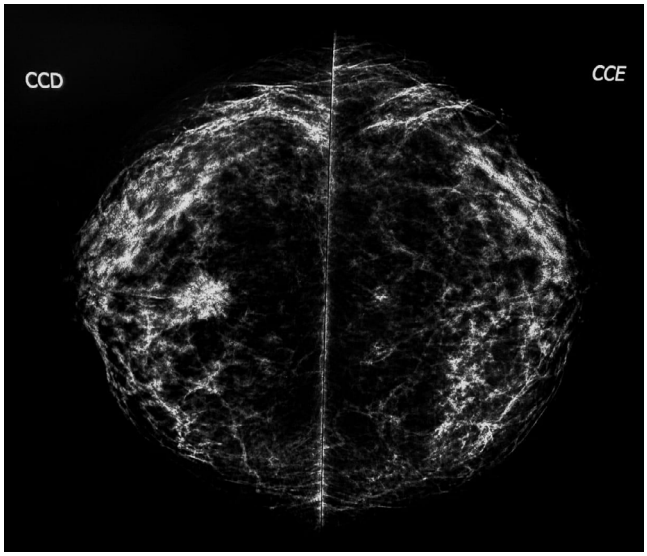
Based on the clinical findings, a breast ultrasound was requested for further characterization of the lesion. The examination, performed on September 24, 2024, revealed a hypoechoic, irregular, spiculated nodule in the right breast, oriented parallel to the skin and without posterior acoustic shadowing. The lesion measured 2.2 x 1.9 x 2.3 cm and was located at the junction of the upper quadrants, at the 12 o'clock position of the right breast, 0.3 cm from the skin and 3 cm from the areola-nipple complex. Doppler flow was present. The examination was classified as breast imaging reporting and data system (BI-RADS) category 4, indicating a moderate suspicion of malignancy.

Given the level of suspicion, the patient was referred for mammography and percutaneous ultrasound-guided biopsy. The mammogram (September 24, 2024) demonstrated unremarkable skin and subcutaneous tissue; predominantly fibroglandular breast composition; and an irregular nodule with microcalcifications at the junction of the upper quadrants of the right breast, measuring 2.2 cm. Axillary lymph nodes showed normal morphology bilaterally (Figure 1). The ultrasound was classified as BI-RADS 4, reinforcing the diagnostic suspicion.

A core biopsy was performed (September 27, 2024), and the histopathological report, issued ten days later, confirmed a diagnosis of moderately differentiated invasive carcinoma of no special type (NST) (tubular formation: 2; nuclear grade: 3; mitotic index: 2), associated with solid ductal carcinoma *in situ* (DCIS), nuclear grade 2. No perineural invasion or lymphovascular permeation was identified.

Immunohistochemical analysis demonstrated a luminal B phenotype, with estrogen receptors positive in 90% of tumor cells, progesterone receptors negative, a Ki-67 cell proliferation index of 35%, and human epidermal growth factor receptor 2 (HER2, also referred to as CERB B2) negative.

Upon diagnosis, the patient received counseling regarding therapeutic options and was referred for specialized oncologic evaluation. In addition, due to her family history of neoplasms, she was referred for genetic counseling. A multigene hereditary cancer panel revealed a heterozygous variant in the tumor protein p53 (TP53) gene, classified as pathogenic, and a heterozygous variant in the Nth like DNA glycosylase 1 (NTHL1) gene, classified as a variant of uncertain significance. The TP53 variant c.1010G>A;p.(Arg337His or R337H), identified in heterozygosity, results in an amino acid substitution in the encoded protein. According to the criteria of the American College of Medical Genomics (ACMG), this variant is considered pathogenic and is associated with LFS.



Source: Personal archive.

Figure 1. Craniocaudal mammographic view showing a fibroglandular nodule and microcalcifications in the right breast.

Table 1. Family history of neoplasms.

Degree of kinship	Maternal or paternal relatives	Cancer site/type	Age at diagnosis (years)	Current age or age at death (years)
Great-grandmother	Maternal	Uterus/no information	50	50 (deceased)
Great-aunt	Maternal	Bones/no information	18	18 (deceased)
Great-uncle	Maternal	Central nervous system/no information	50	50 (deceased)
Great-aunt	Maternal	Breast/no information	75	78 (deceased)
Uncle	Maternal	Blood/leukemia	50	50 (living)
Great-grandmother	Paternal	Stomach and pancreas/no information	84	84 (deceased)
Great-aunt	Paternal	Intestine/no information	72	72 (deceased)
Great-aunt	Paternal	Breast/no information	40	80 (living)
Second-degree cousin	Paternal	Central nervous system/no information	45	45 (deceased)
Grandmother	Paternal	Skin/carcinoma	50	77 (living)

Source: Personal archive.

The proposed treatment plan consisted of neoadjuvant chemotherapy followed by definitive surgery with bilateral mastectomy. The chemotherapy protocol includes 16 cycles: 4 cycles of anthracyclines (doxorubicin + cyclophosphamide – "red chemotherapy"), followed by 12 cycles of taxanes ("white chemotherapy").

Considering the patient's age and future reproductive intentions, an evaluation with an assisted reproduction specialist was recommended to discuss fertility preservation strategies. Given the oncologic urgency, the ovarian stimulation protocol was initiated using a random-start approach, which allows treatment to begin immediately, irrespective of the menstrual cycle phase.

For ovarian stimulation, corifollitropin-alpha, a sustained-release follicle-stimulating hormone (FSH) analogue, was administered. Concomitantly, an aromatase inhibitor was used to control serum estrogen levels and prevent excessive elevation — an essential consideration in the oncologic setting. Clomiphene citrate was added as an adjuvant to enhance the follicular response. Ovulation was triggered with triptorelin acetate, a gonadotropin-releasing hormone (GnRH) analogue that mimics the physiological luteinizing hormone (LH) surge. The procedure resulted in the retrieval of 24 oocytes, which were cryopreserved. Preimplantation genetic screening is planned to exclude embryos carrying the mutation associated with LFS.

On May 2, 2025, a bilateral adenomastectomy with expander placement was performed. Histopathological examination demonstrated clear surgical margins and no axillary involvement among the four lymph nodes evaluated.

DISCUSSION

In Brazil, breast cancer is the second most common neoplasm among women, surpassed only by non-melanoma skin cancer[4]. Although the disease is more prevalent from 50 years of age onward, the Brazilian Society of Mastology (*Sociedade Brasileira de Mastologia* – SBM) has reported a progressive increase in its incidence among women younger than 35 years[5].

Although the most common cause of breast cancer in young women is not hereditary, the occurrence of the disease outside the typical age range warrants investigation to rule out possible genetic mutations. According to the Chompret criteria, which guide the indication for genetic testing for TP53 gene mutations, the patient described in this case meets the criteria for testing, as she was diagnosed with breast neoplasia before 31 years of age[6].

After completion of the genetic panel, a pathogenic TP53 mutation was identified, specifically the c.1010G>A, p.(Arg337His or R337H) variant, which, when associated with early-onset breast neoplasia, is diagnostic of LFS[2]. The first association of the R337H variant with LFS in Latin America was described by Achatz et al., who demonstrated that this mutation was present in 50% of the Brazilian families included in their study that met the clinical criteria for the syndrome. This mutation results in the substitution of arginine by histidine (GCG to CAC) at codon 337 and is more prevalent in the South and Southeast regions of Brazil[7].

The proposed treatment plan in this case involves neoadjuvant chemotherapy followed by bilateral mastectomy, given the high rate of contralateral breast cancer. Petry et al. reported the development of a second malignancy in 41% of patients with LFS, with contralateral breast cancer being the most frequent, which supports the therapeutic decision. In the same study, a higher risk of radiotherapy-induced malignancy was observed in patients with LFS when compared with the control group composed of individuals with breast cancer without the genetic syndrome. Therefore, radiotherapy should be avoided in these patients[2].

Fertility preservation is a major concern among young women with reproductive intentions, particularly those who will undergo gonadotoxic therapies in the context of cancer treatment. The effects of chemotherapeutic agents on ovarian reserve are heterogeneous and influenced by individual patient characteristics, as well as by the type and dose of the drugs administered. Evidence indicates that the reduction in reproductive potential results primarily from damage to pre-ovulatory ovarian follicles. Women over 41 years of age exhibit a markedly increased risk of permanent ovarian failure. Among chemotherapeutic agents, cyclophosphamide stands out as a highly gonadotoxic drug and is widely used in adjuvant regimens[8].

In a cohort study conducted in Sweden[9], women diagnosed with cancer and exposed to treatments potentially harmful to ovarian function were evaluated. Participants were divided into two groups: those who underwent fertility preservation techniques and a control group that did not adopt such interventions. The results demonstrated that women who chose fertility preservation had a live birth rate more than twice that of the control group after diagnosis. Although the cryopreservation process requires ovarian stimulation with multiple hormones, the data presented in the study did not show any association between this intervention and worsening oncologic prognosis or tumor progression in women who underwent the procedure[9]. Thus, referral of cancer patients to specialized services is warranted.

Fertility preservation, although an effective strategy for women of reproductive age diagnosed with breast cancer, remains difficult to access, primarily due to its high cost. Therefore, it is essential to facilitate and expedite access to *in vitro* fertilization, whether through the Brazilian Unified Health System (*Sistema Único de Saúde* – SUS) or subsidized programs, as time is a decisive factor in fertility prognosis in situations such as this.

CONCLUSIONS

This case highlights the importance of early genetic diagnosis and coordinated management among oncology, genetics, and assisted reproduction in young patients with hereditary breast cancer. Identification of the TP53 gene mutation enabled the development of an individualized treatment plan and the implementation

of effective fertility preservation strategies. It also underscores the need for public policies that ensure equitable access to these services through SUS, given the urgency and complexity inherent to such cases.

AUTHORS' CONTRIBUTION

JMC: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, wWriting – review & editing. FCK: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. GPC: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. MGSC: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review and editing. FAK: Conceptualization, Data curation, Investigation, Project administration, Supervision, Validation, Writing – review and editing.

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