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Relato de Caso

Li-Fraumeni syndrome: case report

Síndrome de Li-Fraumeni: relato de caso

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ABSTRACT

Introduction: Li-Fraumeni syndrome is a rare, autosomal dominant disease, first described in the 1960s. Characterized by mutations in the p53 tumour protein gene, making the carrier more prone to developing neoplasms. It most often affects young women and the most prevalent neoplasms are breast cancer (most frequent), adrenocortical carcinoma (prevalent in children under 5), Central Nervous System (CNS) tumors, soft tissue sarcomas, osteosarcomas and leukemias. It has well-established diagnostic criteria in the medical literature and its diagnosis is confirmed by genetic mapping. **Objective:** To describe the case of a patient with Li-Fraumeni syndrome. **Case Report:** This is a case of a 33-year-old woman, diagnosed with bilateral breast carcinoma during an infertility investigation, who underwent bilateral mastectomy and adjuvant chemotherapy followed by hormone therapy. After two years, the patient had to give birth early due to a recent diagnosis of colorectal carcinoma. She was referred to a referral center for further investigation, where she was also diagnosed with lung carcinoma and melanoma in situ skin cancer. Genetic mapping was carried out and a diagnosis of Li-Fraumeni syndrome was made. **Conclusion:** Li-Fraumeni syndrome is a rare clinical and molecular condition that needs to be disseminated among health professionals for better management.

Keywords: Li-Fraumeni Syndrome; Breast Neoplasms; Medical Oncology.

RESUMO

Introdução: A síndrome de Li-Fraumeni é uma doença rara, autossômica dominante, descrita pela primeira vez na década de 60. Caracterizada por mutações no gene da proteína tumoral p53, fazendo com que seu portador apresente uma maior pré-disposição ao desenvolvimento de neoplasias. Acomete mais frequentemente mulheres jovens e as neoplasias mais prevalentes são o câncer de mama (mais frequente), carcinoma adrenocortical (prevalente em crianças com menos de 5 anos), tumores do sistema nervoso central (SNC), sarcomas de tecidos moles, osteossarcomas e leucemias. Possui critérios diagnósticos bem estabelecidos na literatura médica e tem seu diagnóstico confirmado por mapeamento genético. **Objetivo:** Descrever o caso de uma paciente diagnosticada com síndrome de Li-Fraumeni. **Relato de Caso:** Trata-se de um caso de uma mulher de 33 anos, diagnosticada com carcinoma mamário bilateral durante investigação de infertilidade, sendo realizada mastectomia bilateral e quimioterapia adjuvante, seguida de hormonioterapia. Após dois anos, a paciente precisou antecipar o parto devido ao recém diagnóstico de carcinoma colorretal. Encaminhada para centro de referência para investigação complementar, em que também recebeu diagnóstico de carcinoma pulmonar e câncer de pele melanoma in situ. Realizado mapeamento genético decretando diagnóstico de síndrome de Li-Fraumeni. **Conclusão:** A síndrome de Li-Fraumeni é uma condição clínica e molecular rara que precisa ser difundida entre os profissionais de saúde para seu melhor manejo.

Palavras-chave: Síndrome de Li-Fraumeni; Neoplasias da Mama; Oncologia Clínica.

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INTRODUCTION

Li-Fraumeni syndrome (LFS) is a rare, autosomal dominant disorder, first described in 1969 by Frederick Pei Li and Joseph F. Fraumeni Jr., associated with mutations in the TP53 tumor protein gene.[1,2] This is located on the short arm of chromosome 17p13, and is responsible for coding the synthesis of a nuclear phosphoprotein present at basal levels in all normal cells, which slows down the progression of the cell cycle and allows more time to repair DNA.[3-5]

However, when DNA repair is not efficient, TP53 can stimulate genetically unstable cell death with a predisposition to malignant transformation.[3,4] Thus, when there is a defective copy of this gene, they become prone to the development of malignancy, as the cells are unable to use the functional TP53 protein to repair the damage generated to the DNA or initiate the process of cell apoptosis.[3,4]

Patients with Li-Fraumeni syndrome can develop the classic form with a diagnosis of sarcoma before the age of 45, more than one 1° or 2° degree relative with any cancer before the age of 45 or a diagnosis of sarcoma at any age (syndrome disease model article).[3,4] The most prevalent neoplasms in Li-Fraumeni syndrome are breast cancer (most frequent), adrenocortical carcinoma, Central Nervous System (CNS) tumors, soft tissue sarcomas, osteosarcomas and leukemias.[6-10]

It affects the younger age group and is more prevalent in females. The chance of developing malignant tumors is twenty-five times higher than in the general population. At least 30% of patients with the syndrome develop a type of cancer before the age of 30 and 57% risk developing a second neoplasm within 30 years of the diagnosis of the first. It is estimated that the lifetime risk of developing a neoplasm in women is 90%, while in men the risk is approximately 73%. It is estimated that patients with LFS have a higher incidence of breast cancer.[3-5]

Therefore, the aim of this study is to report the case of a 33-year-old patient who was diagnosed in 2018 with Li-Fraumeni syndrome while undergoing treatment for breast cancer.

CASE REPORT

A 33-year-old female patient with no comorbidities presented in 2014, during investigation for infertility, with diagnosis of invasive indeterminate ductal carcinoma in the right breast and invasive non-special breast carcinoma in the left breast. The proposed treatment was neoadjuvant chemotherapy associated with bilateral mastectomy followed by hormone therapy.

In 2017, two years after taking tamoxifen, hormone therapy was suspended with the aim of planning conception. At the end of 2018, before restarting cancer treatment, a second pregnancy was discovered and delivery had to be brought forward for resection of newly diagnosed colon cancer.

One year later, the patient was referred to a referral center for further investigation. Proton emission tomography showed a pulmonary nodule which was diagnosed by histopathology as invasive adenocarcinoma of the lung with an acinar pattern. Lobectomy and adjuvant chemotherapy were performed to treat the neoplasm. In the same year, the patient was also diagnosed with a skin neoplasm, which was also confirmed by histopathology as a cutaneous melanoma in situ and treated by resection. Due to the clinical history, genetic mapping was carried.

A genetic test for expanded hereditary cancer was carried out on March 14, 2019, where the pathogenic variant c.742C>T was found in heterozygosity in the TP53 gene, associated with Li-Fraumeni syndrome, of autosomal dominant inheritance. The test also identified a variante of undetermined clinical significance in the MSH3 gene, associated with Familial Adenomatous Polyposis attenuated to MSH3, of autosomal recessive inheritance.

On September 26, 2019, the patient's onco-basic panel identified a clinically relevant mutation in the EGFR gene. Identified the mutation c.2239_2248delinsC; p.Leu747_Ala750delinsPro (Deletion of exon 19), in the EGFR gene, with an allelic fraction of 23%. No mutations were identified in hotspot regions in the KRAS, NRAS and BRAF genes.

Due to the patient's clinical history (Chompret criteria) combined with the results found in the genetic tests, the patient was diagnosed with Li-Fraumeni syndrome.

In 2022, after self-examination, the patient noticed a nodule in the region of the breast prosthesis, requiring a new resection in 2023 after neoadjuvant chemotherapy. She underwent intensity-modulated radiotherapy (IMRT) and has been undergoing chemotherapy and hormone therapy to date.

DISCUSSION

LFS is a rare and challenging pathology. The mutation in the p53 gene has a worldwide incidence of 1 in every 5-20 thousand people. However, Brazilian epidemiological data shows a higher incidence of the syndrome in the South and Southeast regions, occurring in 1 out of every 300 people.[3,4] Although the Brazilian incidence is higher than the world incidence, only one Brazilian case has been described in the last five years.[4]

The TP53 protein, located on chromosome 17p13, protects the body from genetically unstable cells with predisposition to malignant transformation, as the programmed cell apoptosis mechanism becomes ineffective. The mutant p53 allele only needs one event to affect the tumor suppressor gene activity, which is responsible for regulating the cell cycle. The most

frequent mutation is the substitution of nucleotide, resulting in a "missense" alteration (amino acid change), although a "non-sense" alteration (premature stop codon) can occur.[3,4]

The mutation in the p53 gene related to nucleotide substitution implies cell proliferation, apoptosis and genomic stability of the cell. Thus, the gene's function in identifying cells with damaged DNA becomes impaired, leaving the individual susceptible to the appearance of malignant cells, generating a clinical phenotype susceptible to multiple primary neoplasms such as breast, ovarian, soft tissue sarcomas, osteosarcomas, leukemia, lymphomas, colorectal, melanoma and lung.[6-10]

In patients with LFS, females have higher incidence of breast tumors, with 25% being diagnosed before the age of 30 and 89% before the age of 50.[11-13] There is multifocal development of primary neoplasms in the same organ or bilaterally, as shown in this study, in which the patient was diagnosed with invasive ductal carcinoma indeterminate in the right breast and invasive non-special breast carcinoma in the left breast, both before the age of 40.[11] In addition to the bilateral breast carcinoma, the histopathological study confirmed other neoplasms such as lung, skin and intestinal neoplasms.[3,4]

The Chompret criteria are used to diagnose Li-Fraumeni syndrome: patient with the presence of a tumor belonging to the SLF spectrum (premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma) before the age of 46 and at least one first or second degree relative with the presence of a tumor belonging to the SLF spectrum (except relatives with breast cancer in breast cancer patients) before age of 56 or with multiple tumors; patient with multiple tumors (except breast cancer), with two or more of the tumors belonging to the LFS spectrum and the first tumor occurring before age of 46; patient diagnosed with adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of the anaplastic embryonal subtype, regardless of family history; patient diagnosed with breast cancer before the age of 31.[14-16]

In the case reported here, there are no 1st or 2nd degree relatives diagnosed with cancer under the age of 45, which does not demonstrate the well-established heredity of LFS. Although these criteria were not met by the patient, the clinical history of multiple primary neoplasms at an early age raised the diagnostic hypothesis of the syndrome, and the diagnosis was confirmed in a genetic study of the patient, while her relatives chose not to undergo genetic sequencing.[14-16]

Once the diagnosis of LFS has been established, a follow-up routine is needed for primary prevention (changes in lifestyle habits such as the use of sunscreen and physical activity); secondary prevention (unusual screening in the general population, such as colonoscopy, family genetic testing); tertiary prevention (hormone therapy). Even if prevention levels are established, patients with the syndrome have a high oncogenic potential, and it is not possible to predict and prevent the appearance of new neoplastic foci. Therefore, tertiary prevention begins with the aim of mitigating the clinical repercussions of diseases.[11]

As for secondary prevention, family members of a syndrome carrier should be offered a genetic profile, due to the close hereditary correlation.[11] In the current case report, family members were informed about the need for periodic examinations in the event of a positive result for the p53 mutation, which is why they chose not to undergo genetic sequencing.

CONCLUSION

This case study illustrates Li-Fraumeni syndrome from a clinical and molecular point of view, with the intention of spreading knowledge of this entity and its clinical, ethical and preventive implications. It is important discuss with family members the possible anguish generated by a disease that generates fear, periodic screening tests in the event of a positive result to enable damage to be reduced with early diagnosis of possible alterations. It is up to the relatives, together with the care team, to decide whether or not to carry out a genetic test.

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