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Li-Fraumeni syndrome in a young patient with colorectal carcinoma

Síndrome de Li-Fraumeni em paciente jovem com carcinoma colorretal

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ABSTRACT

Li-Fraumeni syndrome is characterized as a mutation of the TP53 gene, belonging to the tumor suppressor gene lineage. Patients with mutations in this gene accumulate, throughout their lives, a greatly increased probability for the development of several types of malignant tumors. The main objective of this report is to report a clinical case of a young patient with colon cancer, whose laboratory and anatomopathological tests indicated microsatellite instabilities. A search was carried out in the medical records of the consultations, exams and surgeries to which the patient was submitted in order to collect important data. The information obtained was compared as that which is present in the. Scientific and medical literature, and it was possible to conclude, although there is no specific genetic test that detects the mutation of the TP53 gene in this patient, that he presents significant alterations in DNA segments, compatible with Li-Fraumeni syndrome.

Keywords: Li-Fraumeni, TP53, neoplasia.

INTRODUCTION

The TP53 gene, located on chromosome 17p13.1, is an important tumor suppressor. Belonging to the group of P53 coders, they help in the maintenance of complex cellular functions, DNA repair, metabolism, apoptosis, genomic stability and other biological functions essential to life [1]. There is a fairly wide range of tumors that are predisposed

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in patients who have this genetic alteration, from brain tumors to adrenocortical carcinomas. Some specific molecular and genetic findings help in the screening and diagnosis of this syndrome [2].

TP53 mutations are an inherited condition, which is why Li-Fraumeni syndrome is known as "hereditary TP53-related cancer syndrome." The incidence is approximately 1:5000. There is a fairly wide variation between different regions and they carry the [mutation2,3,5]. In Brazil, for example, the frequency is as high as 1:300 in some regions of the country, due to specific combinations of successive mutations. On average, the first tumor in patients with Li-Fraumeni syndrome will appear at the age of 25. By the age of 30, the chances are 50%. By the age of 60, the chances are 90%. Women have a higher risk of cancer than men, due to the high incidence of breast cancer [4].

The manifestations of the syndrome in patients with the mutation do not have any phenotypic alteration resulting from it. Diagnosis, therefore, is guided by family history and tumor characteristics. There is a class of tumors, called central tumors, which correspond to 70% of the cancers resulting from the syndrome. Among the central tumors, breast cancer is the most frequent, with an incidence of around 30%. Sarcomas account for more than 25% of the remaining cases. Tumors from the central nervous system to adrenocortical carcinomas complete list [4].

Because it is a syndrome resulting from a very specific genetic mutation, and this field of medicine is not yet fully investigated and accessible, over time some criteria have been developed to diagnose patients as carriers, or not, of Li-Fraumeni syndrome. The classic criteria involve the diagnosis of a sarcoma before the age of 45, a first-degree relative diagnosed with cancer before the age of 45, and a relative up to the second degree with any cancer that appeared before the age of 45, or sarcoma at any age 3,6.

An important aspect to take into account in patients with Li-Fraumeni is epigenetics. It was observed that patients from the same family, carriers of the syndrome, have heterogeneous manifestations and different mean ages of the first tumor. It is known how the environment can modulate the risk of developing neoplasms, especially exposure to ionizing radiation. It has been shown that patients who underwent diagnostic tests or procedures using radiation had a high tendency for the appearance of primary tumors in the same exposed areas [3].

Cancers associated with TP53 gene mutations usually have a fairly early pre-symptomatic phase, which if detected before more severe manifestations, can ensure better therapy and a more favorable prognosis. Currently validated tests show that early diagnoses in patients with breast

cancer and colorectal cancer reduce lethality levels [3]. Early diagnosis requires family genetic follow-up and multidisciplinary support, a fact that faces obstacles in countries such as Brazil, where genetic tests are slowly being incorporated into the Unified Health System [6].

OBJECTIVE

Brazil is one of the countries with the highest incidence of patients with TP53 gene mutations [4]. A better understanding of this syndrome and the possibility of screening is important, especially in populations more predisposed to mutations, for early detection and appropriate treatment for various types of cancer that may arise as a result of Li-Fraumeni. Understanding how genetic screening can benefit thousands of patients in the country can change the way the higher spheres of health see the issue, and speed up its incorporation into the SUS, favoring more personalized treatments with better results.

METHODS

A search was conducted on the history of a male patient, based on medical records. In addition, a search was conducted in databases, such as Pubmed and Lilacs, to compare the findings with what is available in the most current literature. The following study was approved by the Ethics Committee of the Presidente Prudente Regional Hospital, and followed all the guidelines of the National Council for Research Ethics (CONEP).

CASE REPORT

A young patient, 20 years old on the date of the first consultation, male, was admitted, via referral from the primary health unit of his city, on August 14, 2020, for investigation of epigastralgia that persisted for 1 month. The patient had an upper gastrointestinal endoscopy reported in July of the same year, which did not show any evidence of ulcers or other lesions of the upper digestive tract. The patient had chronic gastritis and had a positive *Helicobacter pylori* (HP) test. In this consultation with gastroenterology, the outgoing diagnosis was gastritis and duodenitis, and the patient was prescribed standard treatment.

On 06/01/2021, less than 1 year after the first consultation with the hospital's gastroenterology, the patient returned to the service with a complaint very similar to the previous one: epigastralgia for 1 month, with globose abdomen. The most recent endoscopy was still in 2020, the gastritis condition remained moderate with the treatment, but the patient was anemic. To investigate the anemia, the patient was hospitalized. He was asked about his family history of

neoplasia, and he stated that there were no close relatives who had developed any cancer throughout his life.

On the same day of admission, the serology for PH was negative for immunoglobulin M (IgM) and positive for immunoglobulin G (IgG). The cause of epigastralgia continued to be associated with chronic gastritis and duodenitis, but a new endoscopy was requested, which was performed the next day. The examination report did not show any abnormality in the esophagus, stomach or duodenum. A urease test was performed, which showed a negative result.

The patient was then submitted to other examinations for further investigation, and all of them presented normal results, except for the CT scan of the abdomen and pelvis, which showed a "marked heterogeneous concentric wall thickening with hypoattenuating areas of intervening configuration configuring expansive formation of lobulated contours measuring about 10.9 cm x 10.5 cm in the descending colon in the hypochondrium and left flank associated with slight blurring of mesenteric fat and lymph node enlargement adjacent and small nodular formations suggesting a lesion of a primary neoplastic nature", as described in the examination report itself.

On the same day, the patient underwent a video colonoscopy for more precise investigation of the possibly neoplastic formation seen on the CT scan. The examination revealed an ulcer-vegetating lesion in the descending colon, with points of necrosis and covered by a fibrin net, classified by the physician who issued the report as Borrmann III. The material was collected and biopsied.

The anatomopathological report confirmed a colonic adenocarcinoma of epithelial origin, moderately differentiated, infiltrative and ulcerated. With the imaging evidence and laboratory confirmation, the surgical approach was considered the best option, and the surgery took place on 06/08, without any intercurrence or complication. A total colectomy was performed, with ileorectum-L-anastomosis. Part of the material was sent for another anatomopathological analysis. The result described a moderately differentiated, mucosecretory adenocarcinoma that infiltrates the subserosa of the colon, measuring about 14 cm in the longest axis. No affected pericolic lymph nodes were detected, and the omentum and surgical margins were also clean. According to Duke's criteria, the tumor was in category B (T3, N0, M0).

Immunomicroscopy was performed on the total colectomy material: the result showed microsatellite instability, suggestive of a germline mutation in the MS2 gene. The same test was performed on tissue from the descending colon, not from the tumor mass itself. The result reaffirmed an infiltrative colonic adenocarcinoma, but evidenced the loss of nuclear expression of the MSH2 and MSH6 genes, highly suggestive of Lynch Syndrome.

Image 1 – immunomicroscopy performed from the total colectomy material

IMUNOMICROSCOPIA

Material
PRODUTO DE COLECTOMIA TOTAL

Dados Clínicos
BLOCO: BHR-21/2623 (2)

Hipótese Diagnóstica
TUMOR DE CÓLON ESQUERDO

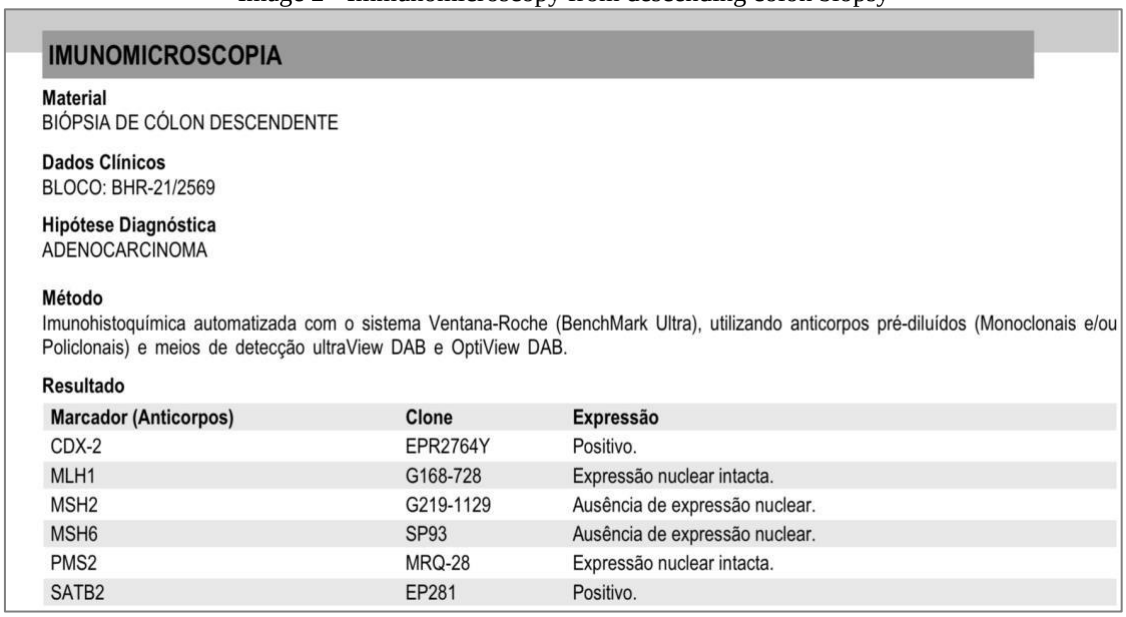
Método
Imunohistoquímica automatizada com o sistema Ventana-Roche (BenchMark Ultra), utilizando anticorpos pré-diluídos (Monoclonais e/ou Policlonais) e meios de detecção ultraView DAB e OptiView DAB.

Resultado

Marcador (Anticorpos)	Clone	Expressão
Cytoqueratin	AE1, AE3	Positivo.
MLH1	G168-728	Negativo.
MSH2	G219-1129	Negativo.
MSH6	SP93	Negativo.
PMS2	MRQ-28	Positivo.
Pten	SP170	Negativo.

Source: the authors.

Image 2 - Immunomicroscopy from descending colon biopsy



IMUNOMICROSCOPIA

Material
BIÓPSIA DE CÓLON DESCENDENTE

Dados Clínicos
BLOCO: BHR-21/2569

Hipótese Diagnóstica
ADENOCARCINOMA

Método
Imunohistoquímica automatizada com o sistema Ventana-Roche (BenchMark Ultra), utilizando anticorpos pré-diluídos (Monoclonais e/ou Policlonais) e meios de detecção ultraView DAB e OptiView DAB.

Resultado

Marcador (Anticorpos)	Clone	Expressão
CDX-2	EPR2764Y	Positivo.
MLH1	G168-728	Expressão nuclear intacta.
MSH2	G219-1129	Ausência de expressão nuclear.
MSH6	SP93	Ausência de expressão nuclear.
PMS2	MRQ-28	Expressão nuclear intacta.
SATB2	EP281	Positivo.

Source: the authors

The patient was then referred for outpatient follow-up with proctology, in addition to the support of social work, psychology and nutrition that were offered. The proctologist who received the case requested an appointment with the oncologist to discuss the need for chemotherapy. The patient was instructed on postoperative care and a carcinoembryonic antigen (CEA) test was requested.

The oncology appointment took place the following week; The patient reported being well, denied any previous comorbidity and said he was a social drinker and smoker. A relevant piece of information, which until then had not been mentioned in any previous consultation, and even disqualified the initial information that there was no history of neoplasia in the family, occurred in this consultation. The patient recalled that his maternal grandfather had died of colon cancer at the age of 50. In addition, his paternal grandfather also died as a result of cancer, but this one in his stomach, at the age of 60. The presence of malignant neoplasms in close relatives brought a new perspective to the outpatient follow-up of the patient. At this visit, which took place in July 2021, the patient's CEA was at 6.2 ng/mL.

In subsequent consultations, with the hospital's proctology and oncology, the patient reported being well, with normal bowel habits, good acceptance of the diet prescribed by the nutrition service and without any abnormal or worrying sign or symptom. CEA levels in August and September remained between 2.7 and 2.8 ng/mL. CT scans of the abdomen, thorax and pelvis performed during the period did not show recurrence of the neoplasm or problems in healing. At the September consultation, flexible rectosigmoidoscopy (RSF) and follow-up of the CEA were requested.

Flexible rectosigmoidoscopy, performed in November 2021, did not go as well as it could have, as there were problems in the preparation of the colon. However, polypoid lesions were observed in the colon. It was suggested that a colonoscopy be performed for better evaluation of the lesions, with the patient adequately prepared and sedated.

At the December proctology appointment, the patient's CEA had dropped to 1.0 ng/mL. In discussion with oncology, it was decided that chemotherapy would not be performed. In view of the results of the flexible rectosigmoidoscopy, the proctologist requested new CT scans and continued follow-up of the CEA. In the oncology consultation, held in the same month, colonoscopy was requested to investigate the hyperplastic polyps detected in the RSF. The oncology team prescribed acetylsalicylic acid to the patient, since there is evidence of benefits of using the medication in cases of new colonic tumors. It was not possible to refer the patient to a geneticist by the local regulatory center. **A return was scheduled for the month of March 2022, which at the time of writing, had not yet happened.**

In February 2022, a colonoscopy was performed, now with adequate preparation. Examination revealed the presence of sessile polypoid lesions in the rectum, ranging from 3 to 7 mm, covered with enanthematous mucosa. Polypectomies were performed, and there were no complications during the procedures.

RESULTS

Although this is a clinical case still in progress, it is possible to highlight important points in the inter-specialty approach that took place. The team's rapid decision-making between the suspicion of a neoplasm and the surgical approach adopted were decisive for the success of the treatment. The original tumor showed no signs of recurrence. The patient had good acceptance of the diet and recovered quality of life, being followed up on an outpatient basis only. Thepolyps detected in theretoxinthmoidoscopy Flexible were Removed uneventful during the last colonoscopy performed. Now, the patient should continue to be monitored on an outpatient basis and for evaluations of recovery from polypectomies and whether there will be a need for re-approach in the future.

Although it was not possible to follow up with a geneticist, immunomicroscopy showed DNA alterations that may have been responsible for the development of the malignant neoplasm in the patient. The presence of a positive family history for cancer in the grandparents and the early development of colonic adenocarcinoma speak volumes in favor of Li-Fraumeni syndrome in this patient.

DISCUSSION

Li-Fraumeni syndrome is characterized by a germline mutation in the TP53 gene, the gene responsible for encoding the tumor suppressor gene p53. With the genetic alterations that make up the syndrome, the individual carrying the mutation ends up being susceptible to several types of neoplasms throughout life, most of which manifest themselves early [6]. As there are no phenotypic alterations that help in the clinical suspicion, it is impossible, without genetic screening, to determine which children are carriers or not of the syndrome. A positive family history of cancer, especially at an early age, is the main warning sign, however, it does little to help in early diagnosis; Li-Fraumeni is usually suspected when the patient already has cancer [4].

The relationship between phenotype and genotype is at the center of scientific research on germline mutations of the TP53 gene. It is increasingly evident that different types of mutation are associated with different levels of risk of developing specific cancers. Acknowledging these differences is critical in the current era, since one can think of specific therapies, created individually for individuals carrying different mutations. It should also be taken into account that mosaicism, the difference in penetrance between mutations and distinct alleles, may favor the emergence of new non-classical forms of the syndrome, and therefore, a better understanding of the intrinsic characteristics of the mutations is essential to improve the prognosis of patients [3].

Recent multicenter studies have shown that patients with Li-Fraumeni syndrome who had an early diagnosis have a considerably higher survival rate than those who were not diagnosed early. Patients without screening and diagnosis had an overall survival of 59.6% at 5 years, compared to 88.8% of those whose diagnosis was made before any manifestation of syndrome [2]. Research shows that early detection of breast and colorectal cancer are positive prognostic factors in patients who develop these malignancies. Although there is no published study on this evidence specifically in patients with Li-Fraumeni, breast cancer is the most common cancer in women with the syndrome, and therefore, predicting the neoplastic manifestation can be extremely beneficial for this population [3,4].

Although genetic screening for early detection of Li-Fraumeni syndrome may be a palpable reality in some rich countries, in Brazil the reality is quite different. In the reported case, for example, it was impossible to refer the patient to a geneticist, due to the unavailability of professionals in the unified health system. The test that raised the suspicion of a syndrome at the DNA level was immunomicroscopy, which revealed microsatellite instability of the MS2 gene in the tissue coming from the tumor, and loss of gene expression in the MSH2 and MSH6 genes in the colonic tissue of the colectomy region.

Microsatellites are the part of DNA made up of "repeats" of very small sequences of nucleotides, with a maximum of 6 of them. These repeats permeate the genome, and help to make it unique among individuals: the way these repetitive sequences are arranged, their composition, and the frequency with which they appear make each individual unique. In addition, microsatellites are markers of the function of DNA repair genes. If many alterations are detected in the composition or arrangement of these small structures, there is an indication that the DNA repair mechanisms are not performing their functions well to prevent the proliferation of anomalous tissues [7].

In the reported case, microsatellite instability was detected in the tumor tissue, which reinforces the fact that the DNA repair mechanisms were dysfunctional, which allowed anomalous tissue to proliferate disorderly. In addition, immunomicroscopy performed on tissue from colon biopsy showed absence of nuclear expression of the MSH6 and MSH2 genes, which are linked to DNA repair. It is evidence that the patient is exposed to new cancers in the future, since his defense mechanisms against the emergence of these are practically silenced.

One of the main difficulties in the follow-up of these patients is the limited information about the type of mutation they carry, which hinders individualized treatment. Another important aspect is the interaction with the environment. Smoking makes carriers of TP53 mutations about

3 times more susceptible to lung cancer when compared to carriers who do not smoke. Another very important piece of evidence is the relationship of new tumors in regions exposed to ionizing radiation. Patients who had areas of the body exposed to radiation, either for diagnosis or treatment, and had Li-Fraumeni, had an above-average occurrence of new tumors in these same regions [3].

This is extremely relevant data, as it can completely change the treatment alternatives of some patients where radiotherapy was an option, for example. There are no quantitative studies that express the extent to which patients who have the TP53 gene mutation and are exposed to radiotherapy are more susceptible to the development of a new tumor, but the existence of this relationship may dictate the way treatment is managed [3]. The lack of studies on this topic is evident in the scientific community.

It is clear, therefore, that there is a need to promote scientific advances in medical genetics regarding Li-Fraumeni Syndrome. Brazil is one of the countries with the highest incidence of the syndrome in the population; while the average is from 1:2000 to 1:5000 between Europe and North America, some Brazilian regions have specific mutations of p53 that reach an incidence of 1:300 [4]. Developing ways to diagnose the syndrome early in patients, so that adequate family follow-up can be carried out, is essential to reduce mortality rates.

Studies have already proven the excellent impact of early diagnosis on the survival of patients with Li-Fraumeni syndrome [2]. In a country with one of the highest incidences of the mutation in the world, it is necessary to discuss ways to redistribute resources and make it possible to screen these patients before they become oncology patients in the country's hospitals.

CONCLUSION

Regarding the patient whose case was reported, he continues to be monitored by the hospital's proctology and oncology teams, being regularly monitored through imaging exams and carcinoembryonic antigen dosage. The most recent consultations and examinations do not show any tumor activity or recurrence in the colonic tumor surgically approached. The performance of the multidisciplinary team has been extremely satisfactory with the resources that are available and the patient continues to lead a life free of limitations, since his tumor was diagnosed in time to avoid further complications.

Conflicts of interest
The authors declare that there is no potential conflict of interest that could interfere with the impartiality of this scientific work.

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