



## Lynch syndrome: Diagnosis based on immunomicroscopy and family history of a young patient with colorectal carcinoma

### Síndrome de Lynch: Diagnóstico baseado em imunomicroscopia e antecedentes familiares de paciente jovem com carcinoma colorretal

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Mariana Rosso Franco Zanoni<sup>1</sup>, Matheus de Souza Camargo<sup>2</sup>, Daniela Bôscoli da Silva Noma Boigues<sup>3</sup>

#### ABSTRACT

Lynch syndrome is a genetic condition that alters the production of DNA compatibility genes, which are responsible for monitoring the process of formation of new cells in the body. Once compromised, this vigilant system begins to fail and allows the development of abnormal cells, which sometimes initiates a process of malignancy, resulting in the appearance of malignant tumors, especially in the colon and endometrial tissue. This text reports the clinical case of a young patient who was diagnosed with colorectal carcinoma and, after extensive outpatient and anatomopathological research, with association with a positive family history, was diagnosed with Lynch syndrome.

**Keywords:** Colorectal carcinoma, Syndrome, MLH1, MSH2.

#### INTRODUCTION

Lynch's syndrome was first described by Aldred Warthin in 1895, who described a syndrome related to the increased predisposition to colonic malignancies, which he called "hereditary nonpolypoid colorectal cancer", which was later associated with and named after its discoverer<sup>1</sup>. Basically, Lynch syndrome involves a set of alterations of deoxyribonucleic acid, or DNA, incompatibility repair genes. These genes are called MMR, an acronym for *mismatch repair*, and when dysfunctional, they favor the appearance of neoplasms, commonly colonic and endometrial<sup>2</sup>.

Because it is a genetic disorder, for a long time it was not possible to elucidate the mechanisms behind Lynch syndrome, however, advances in the field of molecular biology and genetics in recent decades have given rise to the possibility not only of understanding the machinery existing in MMR genes, but also of better understanding how their alterations create

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<sup>1</sup> Specialist in Internal Medicine, Universidade do Oeste Paulista, E-mail: marianarossofranco@hotmail.com

<sup>2</sup> Medical student at the University of Oeste Paulista, E-mail: matheusdesouzacamargo@gmail.com

<sup>3</sup> Doctor from the University of Oeste Paulista, E-mail: daniboigues@hotmail.com



an environment conducive to the proliferation of neoplastic cells. In a functional MMR gene system, there are several proteins responsible for the surveillance of nitrogenous bases that, due to the action of chemicals or physicists, have suffered injuries and become incompatible. They are: MLH1, PMS2, MSH2, MSH6, MLH3, MSH3, PMS1 and Exo 1<sup>3</sup>.

In the case of colorectal cancer, two specific proteins are the most altered among all the others: MLH1 and MSH2. Microsatellite instability is frequently observed, even serving as a screening and diagnosis for the syndrome in some patients. For those with colorectal cancer who are not carriers of the syndrome, the prevalence of microsatellite instability is around 20%, while for those with the genetic disorder, the prevalence rises to something around 90%<sup>4</sup>.

Lynch syndrome is the most common form of hereditary colorectal cancer. The disease in patients affected by the syndrome has a rapid evolution, and the polyps can become malignant in a short period of time, ranging from 1 to 3 years<sup>5</sup>. The high rate of malignancy of these small structures makes preventive diagnosis more difficult, but there are efficient ways to detect the presence of the genetic disorder before it translates into cancer.

Currently, there are two ways to make the diagnosis for Lynch syndrome: the first is based on familial genetic screening of individuals with a positive history of colorectal cancer and high suspicion for disease caused by genetic immunological alterations. The second depends on the molecular investigation of tissue from biopsies performed on existing tumors; in these tumors, alterations compatible with defective MMR genes are investigated, and therefore permissive to the development of local neoplastic tissue<sup>1</sup>.

Because it is a disorder that alters the patient's immune component, current therapies, including the most modern ones, focus precisely on ways to manipulate the patient's immune system, in order to obtain favorable results in reducing the appearance, growth and recurrence of malignant tumors. Although it is still an area of medicine and pharmacology that depend on further advances and clinical trials, what is currently available in the literature points to the fact that when the altered immunological mechanisms in the syndrome are known, it is possible to better predict the manifestations, potentiate the immune response, eliminate immunodepressive factors, and even manipulate the phenotype of cancer cells, making them more susceptible to immunotherapy<sup>5</sup>.

The main objective of this scientific text is to enrich the literature and favor gains in early diagnosis and treatment of patients who are in the same condition, through the description of a clinical case of a patient who was diagnosed with early colorectal cancer, at the age of 20, previously healthy, social drinker and smoker. There was a history of colorectal cancer in the



paternal family, which culminated in the death of a grandfather who was only 50 years old at the time. This and other information raised the suspicion of hereditary factors involved in this patient's case, which was later confirmed through laboratory and imaging investigations.

## 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 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 hypodensifying 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 intercurrentence or complication. A total colectomy was performed, with ileorectum-anastomosis L-L. Part of the material was sent for another anatomopathological analysis. The result described a moderately differentiated, mucosecretory, infiltrating adenocarcinoma up to 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 using the total colectomy material: the result showed microsatellite instability, suggestive of a germline mutation in the MSH2 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 showed the loss of nuclear expression of the genes, MLH1, MSH2 and MSH6, highly suggestive of Lynch Syndrome.

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. Faced with the results of the immunomicroscopy tests associated with the important family history, the team sealed the diagnosis of Lynch syndrome. 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. 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.

The polyps detected in flexible rectosigmoidoscopy were removed uneventfully 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.

The alterations found in the expression of MMR proteins, especially MLH1 and MSH2, associated with the history of other malignant neoplasms of the gastrointestinal tract in the patient's family, made Lynch's syndrome evident. Targeted and individualized treatment made it possible to recover quality of life and control the disease, which so far has not presented new recurrences.

## DISCUSSION

In view of the reported case and what is found in the recent literature, it is evident that Lynch syndrome is an entity strongly associated with the development of malignant colonic tumors. Because it is a genetic anomaly that affects the body as a whole, and is not restricted only to the colon or gastrointestinal tract, there are extracolonic neoplastic manifestations, often in endometrial, for example; however, when it comes to hereditary CRC, Lynch syndrome becomes the main causative factor of the disease<sup>4,5</sup>.

Another relevant related finding is the presence of microsatellite instability in these patients. Alterations in the expression of MMR genes are present in about 90% of patients with Lynch syndrome who develop colorectal cancer, compared to only 20% of those who do not have the same syndrome<sup>4</sup>. This is relevant to help make diagnoses of patients who have a family history of malignancies and who are suspected of having Lynch syndrome, which was the case of the patient reported in this text.

According to Yurgelun and Hampel, 2018, diagnosis can be made by searching for high-level microsatellite instability or MMR defects. Immunomicroscopy performed on portions of the tumor and also on healthy tissue after excision revealed the presence of this instability, with alterations in the expression of MLH1, MSH2 and MSH6.

As there was no diagnosis of the syndrome earlier, it was not possible to identify and remove colonic polyps before the first malignancy, however, the support offered to the patient resulted in resolution of the condition, without major complications. Subsequent examinations



revealed the formation of new polyps, which were removed as early as possible to prevent the development of new tumors, since the evolution in these patients is quite rapid.

Because it is a hereditary condition that often manifests itself in the form of CRC, early diagnosis for this syndrome is essential to prevent the development of these malignant tumors. As there is no phenotype associated with it, screening should take into account especially those patients who have a history of colorectal carcinoma in family members, and in the worst case scenario, in patients who develop CRC early and also have a family history of the disease.

We conclude, therefore, that because it is a genetic condition that does not manifest a specific phenotype, screening becomes complicated, and because of this most patients will be diagnosed with the syndrome when it manifests itself in the form of CRC. It is necessary that diagnostic methods become more accessible, aiming to reduce the incidence of these severe and aggressive manifestations in patients with Lynch, as a way to increase their life expectancy and quality of life, in addition to having greater outpatient care with the ascendants and descendants of patients who may have the diagnosis confirmed.

## **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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