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Case Report

Never too late: Lynch syndrome diagnosed at the age of 71

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ABSTRACT

Lynch syndrome is an autosomal dominantly inherited disease characterized by a mutation in one of the deoxyribonucleic acid mismatch repair genes. In consequence of this defect, patients have higher risk of developing early colorectal and endometrial cancer (among others types of cancer). This syndrome accounts for 3% of all colorectal cancers and 10% to 19% of colorectal cancers diagnosed before the age of 50. Total abdominal colectomy is the best treatment for patients with Lynch syndrome who develop colorectal cancer.

Keywords: Lynch syndrome, Colorectal cancer, Colorectal surgery

INTRODUCTION

Lynch syndrome, previously called hereditary nonpolyposis colorectal cancer, is caused by pathogenic germline mutations in the deoxyribonucleic acid (DNA) mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2.[1] These mutations predispose to early occurrence of colorectal tumours but also extracolonic malignancies (usually before 50 years of age).[2-4] Endometrial adenocarcinoma is the most common extracolonic cancer although ovarian, gastric, small bowel, urinary tract, brain and pancreas cancers are also frequently seen in these patients.[5,6]

The mean age of diagnosis for Lynch syndrome related colorectal cancer (CRC) is 45 to 60 years, compared with 69 years in patients with sporadic CRC.[6]

Estimates for CRC risk at the age of 70 in Lynch syndrome ranges from 25 to 70% compared with a lifetime risk of up to 5% in the general population.[7]

CRC in Lynch syndrome patients mostly arises proximal to the splenic flexure and has a propensity for synchronous and metachronous lesions.[3,6,8]

Surgery remains the preferred treatment for patients with Lynch syndrome who develop CRC. Surgery can be prophylactic (in very specific cases), therapeutic with curative intent (in the presence of CRC), or, in some cases, palliative.[8]

Herein, a case of Lynch syndrome diagnosed in a patient older than 70 years is reported. Management evolved total colectomy with hysterectomy and bilateral salpingo-oophorectomy.

CASE REPORT

A 71 years old woman was evaluated in a general surgery appointment due to colonoscopy alterations.

The patient had a history of chronic constipation, leukocytoclastic vasculitis, dyslipidaemia, dilated cardiomyopathy and chronic kidney disease. Familiar history included a son of 43 years old with synchronous colonic adenocarcinomas (right colon and lower rectum) treated with panprotocolectomy due to genetic confirmation of Lynch syndrome (MSH 2). No other family CRC history was present.

The patient underwent a routine total colonoscopy which revealed, at 23 cm from the anal verge, a sessile lesion of 12 mm in diameter. Mucosectomy was performed. Pathological examination revealed invasive adenocarcinoma and the immunohistochemistry study found loss of expression of MSH2 protein.

The patient denied haematochezia, abdominal pain or constitutional symptoms. Physical exam including rectal examination was normal. Laboratory parameters were within value ranges and carcinoembryonic antigen (CEA) was 3.6 ng/ml. A staging computed tomography was performed without evidence of metastatic disease.

Genetic study was performed and exon 7 deletion in MSH2 gene was confirmed by multiplex ligation-dependent probe amplification (MLPA), therefore confirming Lynch syndrome. Gynaecologist evaluation was normal.

Total colectomy (Figure 1) and ileo-rectal anastomosis as well as prophylactic abdominal hysterectomy with bilateral salpingo-oophorectomy (Figure 2) was performed without complications.

Pathological examination of the colon revealed no remaining adenocarcinoma and also two other lesions with characteristics of tubular adenoma with high grade dysplasia. Anastomotic rings and uterus presented no alterations.

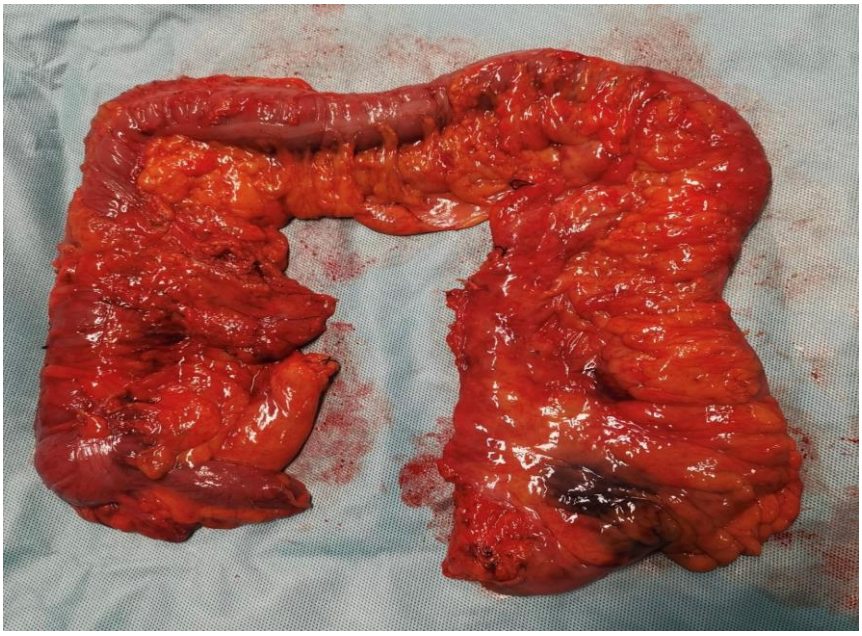

Figure 1: Total colectomy.

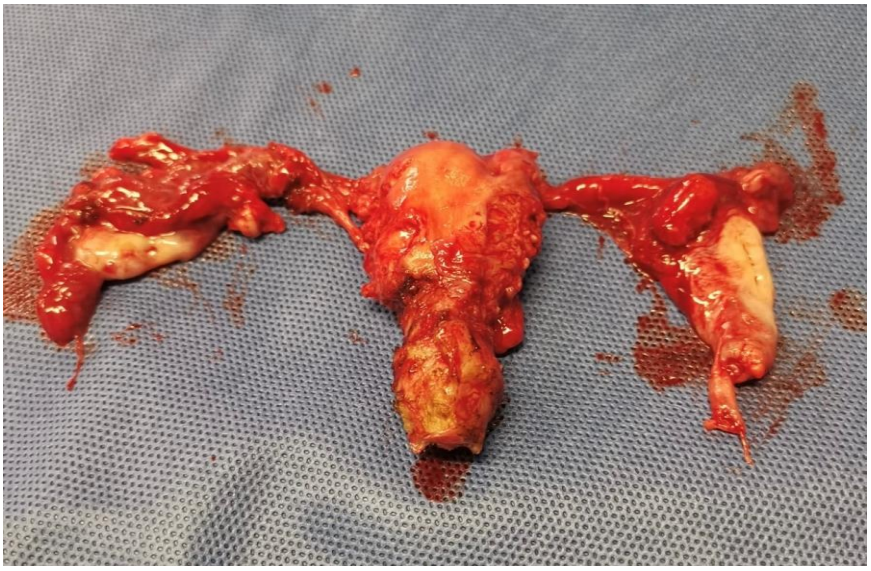

Figure 2- Hysterectomy with bilateral salpingo-oophorectomy.

DISCUSSION

In the basis of Lynch syndrome pathology are the mutations in the DNA MMR genes MLH1, MSH2, MSH6 and PMS2. The main function of these genes is to correct spontaneous insertions or deletions generated during DNA replication.[4] Loss of expression of MMR proteins leads to defective DNA mismatch repair and, consequently, to changes in the length of nucleotide repeat sequences and accumulation of mutations known as microsatellite instability (MSI).[2,9,10]

MLH1 and MSH2 gene mutations account for the majority of patients with Lynch syndrome and are associated with greater lifetime CRC risk and earlier age at CRC onset. On the other hand, MSH6 and PMS2 variants are often identified in older patients.[2,3] Thereby, this case becomes particularly interesting and rare, because of the time free from disease, despite the patient's phenotype was MSH2.

Although not imperative for the occurrence of CRC, adenoma is the main precursor of CRC in Lynch syndrome. However, compared to sporadic cancer, adenomas in Lynch syndrome patients appear earlier and present with a flat morphology that is harder to detect by colonoscopy. Also the adenoma-carcinoma sequence is accelerated in Lynch syndrome (2-3 years while in sporadic CRC it lasts 8-10 years).[3,4]

Recent studies have shown that patients with Lynch syndrome who have not developed cancer exhibit T cells that are reactive to MSI-induced neopeptids. Although the colonic crypts in these patients demonstrate MMR defects and MSI, cancer does not develop, which leads to the hypothesis that the healthy colon of patients with Lynch syndrome may act as a source of neopeptides that, through innate immune mechanisms, supresses MSI-induced carcinogenesis instead of inducing it.[1] Perhaps the protective factor of our patient is to harbour such T cells.

Several studies concluded that for MLH1 and MSH2 carriers, colonoscopy for CRC surveillance should start between ages 20 and 25 and performed every 2 years.[2,11,12] However, data from a large multinational registry found that a quarter of all incident CRCs developed in individuals who received their last colonoscopy 12-23 months ago, which contributes to advocate annual colonoscopies.[9] Recommendations for colonoscopy do not vary by gender.[12]

The median age for the diagnosis of gynaecologic malignancies (endometrium and ovarian cancer) is in the fifth to sixth decade of life.[8] Hence, annual endometrial biopsy and transvaginal ultrasound are also recommended, starting at the age 30-35.[9] Some factors have been associated with a significantly reduced risk of developing endometrium cancer, such as the use of hormonal contraceptives for 1 year or more, nulliparity and earlier onset of menarche.[1]

It has been argued that families with MSH2 mutations have higher risk of developing extracolonic cancers compared to MLH1 mutations families.[4] Interestingly and so far, neither the patient nor her son have been diagnosed with extracolonic malignancies despite their phenotype is MSH2. Prophylactic total abdominal hysterectomy with bilateral salpingo-oophorectomy should be offered to women undergoing colorectal surgery if childbearing is complete or if the patient is postmenopausal.[8] Also, esophagogastroduodenoscopy with gastric biopsy of the antrum and *Helicobacter pylori* testing is recommended at age 30-35 and then every 2–3 years. Eradication of *Helicobacter pylori* should be administered in patients who exhibit infection.[9,11]

Lifestyle factors have been proved to influence CRC development, which explains why in Lynch syndrome affected-families the expression of the syndrome varies.[7] In fact, in the present case, the patient developed cancer at the age of 71, while her son was diagnosed with synchronous colonic adenocarcinomas at the age of 43 years old. Similarly, to sporadic colonic cancer, smoking and obesity increase the risk of CRC in people with Lynch syndrome.[7] Although the patient was not a smoker she had an elevated BMI.

To reduce CRC incidence even further, evidence suggests that endoscopic surveillance can be paired with chemoprevention with high-dose aspirin which is proven to reduce the incidence of CRC in patients with Lynch syndrome (especially if taken for 2 or more years).[1,2,9] Interestingly a recent study revealed that in obese patients aspirin seems to be less effective in preventing cancer.[1]

Timing of Lynch syndrome diagnosis in suspected patients is critical, as early identification can help to choose the surgical options (according to the patients age, health status and tumour location) and look up for extracolonic cancers.[3,13]

Colonoscopy is the primary modality for screening for Lynch syndrome since it allows resection of preneoplastic and neoplastic lesions. Colonoscopies should be performed by expert endoscopists and under optimal conditions such as adequate bowel preparation. Other quality criteria include complete exam (defined by caecum intubation) and complete polyp resection when required. If these criteria are not met, a new colonoscopy must be rescheduled quickly.[3]

The diagnosis of Lynch syndrome was initially established by the Amsterdam criteria: history of at least 3 family members with histologically confirmed CRC, in 2 generations with at least 1 person diagnosed before age of 50 years.[11] Although this tool is very useful and specific, it is not free from pitfalls, such as the possibility of later-onset variants of the disease.[14] Asking about family history of CRC remains crucial when Lynch syndrome is suspected, but it is important to remind that only 43% of

patients with Lynch syndrome have a positive family history.[14]

As the molecular understanding of the syndrome improved, several diagnostic tests have appeared. Currently, three main tests are available: immunochemistry (IHC) to diagnose MMR deficiency (widely used because it is a fast and inexpensive method), polymerase chain reaction (PCR) to diagnose MSI and germline testing.[1,3,11] In fact, Bethesda criteria were initially established to indicate who should be tested for MSI, but nowadays, more specific screening methods are available, such as IHC and germline testing. Nowadays, germline testing is used to confirm the diagnosis as it is able to identify more cases of CRC attributed to Lynch syndrome than those based on 2-stage testing.[5,11,15]

Regardless of the test used, it is important to remind clinicians to screen all patients with newly diagnosed colorectal (CRC diagnosed at age ≤70 years and patients >70 years who have a family history concerning for Lynch syndrome) and endometrial cancer not only to identify patients with Lynch syndrome but also to screen these patients' relatives, allowing them to receive better cancer surveillance.[1,11] In fact, all family members in the present case were screened for Lynch syndrome. Of the two daughters, one does not have Lynch syndrome and the other is waiting for genetic results.

Due to high rates of metachronous CRC in Lynch syndrome patients undergoing partial colon resections total colectomy with ileorectal anastomosis (IRA) is preferred in patients with newly diagnosed CRC not only because of survival benefit but also because it is cost-effective.[8,11,13,16] Less-extensive surgery should be considered in older patients and in cases of pre-existing sphincter dysfunction.[11] In this case, despite the patient's age, total colectomy was performed due her overall good status and concerning familiar history, as well as patient´s desire.

After total colectomy with IRA, patients still have risk of developing cancer in the rectum. Therefore, endoscopic surveillance of the rectum is recommended every 6 to 12 months after surgery.[6] The most frequent complaint reported by patients submitted to IRA is the increased frequency of bowel movements.[8,11] Nevertheless, over time, most patients are able to adapt.[8]

Patient's concerns regarding bowel function and quality of life after surgery sometimes limit the performance of more extensive surgery.[13] In this case, patient is well adapted to her bowel function.

CONCLUSION

Lynch syndrome is the most common hereditary CRC syndrome. A careful family history in the workup of patients presenting with CRC is fundamental but criteria for the diagnosis of Lynch syndrome often fail to detect the syndrome in many patients, especially when the diagnose occurs later in life and in patients with few family members. In this case report, family screening for CRC should have started when our patient's son was diagnosed with synchronous colonic adenocarcinomas at an early age. In fact, the goal is to diagnose Lynch syndrome in healthy individuals instead of identify it in new cancers, since a considerable amount of cases can be missed, and screening work-up in these families delayed. Surgery is the main treatment when cancer develops. Although several surgical options exist, total colectomy with ileorectal anastomosis is recommended for most patients because it is the one that offers superior cancer risk reduction. A topic for further research is the hypothesis that MSI neopeptides act as autovaccines, suggesting immune based mechanisms for primary cancer prevention are a promising possible target in the future.

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