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Hereditary colorectal cancer: synchronous presentation of colorectal cancer and cholangiocarcinoma in a patient with familial adenomatous polyposis

Cáncer colorrectal hereditario: presentación sincrónica de cáncer colorrectal y colangiocarcinoma en un paciente con poliposis adenomatosa familiar

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Familial adenomatous polyposis, Lynch syndrome, hereditary colorectal cancer.

Palabras clave:
Poliposis adenomatosa familiar, síndrome de Lynch, cáncer colorrectal hereditario.

ABSTRACT

Gastrointestinal polyposis syndromes are characterized by the presence of multiple polyps in the gastrointestinal tract preferentially affecting the colon and rectum. They account for about 5% of colorectal cancers, the most common being familial adenomatous polyposis and hereditary non-polyposis colon cancer (Lynch syndrome). They are a group of diseases of low incidence with variable characteristics that require a correct individualization for their most appropriate treatment. Within the genetic syndromes there are presentations with typical molecular variations that typecast the most frequent groups; however, there is the possibility that these syndromes show genetic similarities whose predominance determines the evolution and presentation of the disease.

RESUMEN

Los síndromes de poliposis gastrointestinales se caracterizan por la presencia de múltiples pólipos en el tubo digestivo que afectan preferentemente el colon y recto. Representan alrededor de 5% de los tipos de cáncer colorrectal, siendo los más comunes la poliposis adenomatosa familiar y el cáncer de colon no polipósico hereditario (síndrome de Lynch). Son un grupo de enfermedades de escasa incidencia con características muy variadas que precisan una correcta individualización para su tratamiento más adecuado. Dentro de los síndromes genéticos hay presentaciones con variaciones moleculares típicas que encasillan a los grupos más frecuentes; sin embargo, existe la posibilidad de que dichos síndromes muestren similitudes genéticas cuya predominancia determine la evolución y presentación de la enfermedad.

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INTRODUCTION

Worldwide, colorectal cancer (CRC) represents the third most common malignancy and the fourth leading cause of cancer-related mortality, with recognized familial syndromes accounting for about 5% of cases.[1,2] There are two broad classes of hereditary colorectal cancer, depending on the predominant location of the cancer: distal and proximal. Familial adenomatous polyposis (FAP) and most sporadic cases can be considered a paradigm for the distal class, whereas hereditary nonpolyposis colorectal cancer

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(Lynch syndrome) more clearly represents the proximal class.[3,4]

PAF is an autosomal dominant syndrome caused by a germline mutation of the adenomatous polyposis coli gene.[5] It affects 1:10,000 people and accounts for approximately 1% of colorectal cancer. Its main characteristic is the appearance of more than 100 colorectal adenomatous polyps, which can number in the thousands, starting at a young age, with a cancer risk close to 100% if not treated promptly. Most cases begin as benign adenomatous colonic adenomatous polyps.[2,6,7]

The complexity of the possible clinical presentations of these syndromes includes, in addition to severe or attenuated colorectal disorders, various extracolonic manifestations such as gastric and duodenal polyposis and desmoid tumors, which may require additional endoscopic or surgical treatment that complicates the therapeutic process and imposes continuous surveillance even when the colorectal disease is eradicated.[8]

CASE PRESENTATION

The patient is a 56-year-old man under medical treatment for long-standing arterial hypertension and ischemic heart disease treated with coronary stent placement two years ago, with a hereditary family history of colon cancer in two first-degree relatives under 50 years of age. He came for external evaluation due to a history of three months of evolution with lower gastrointestinal tract bleeding (LGITB) accompanied by anemic syndrome; a colonoscopy was performed, and multiple polyposis was observed (more than 200 polyps), with neoplastic lesions in the sigmoid colon and transverse colon *(Figure 1)*. No abnormal skin or bone lesions were found, nor was the presence of hypertrophy of the retinal epithelium pigment identified.

The study was complemented with an endoscopy of the upper gastrointestinal tract showing a diffuse micronodular surface in the upper portion of the body of the stomach, without duodenal polyps *(Figure 2)*, and a thoracoabdominal computerized tomography (CT) scab with IV contrast revealed a transverse colon tumor with peri-colonic fat infiltration conditioning partial obstruction, as well as the presence of para-aortic lymphadenopathies *(Figure 3)*. Laboratory studies showed hemoglobin: 9.0 g/dl, total protein: 5.8 g/dl, albumin: 3.0 g/dl and carcinoembryonic antigen: 131 ng/ml.

During the second day of hospitalization, the LGITB persisted with a decrease in hemoglobin to 7.0 g/dl. An intestinal occlusion was diagnosed, so it was decided to schedule surgery.

Total colectomy with terminal ileostomy was performed by hand-assisted four-port laparoscopy, finding multiple peritoneal and hepatic implants, of which biopsies were taken. Postoperatively, the patient developed adynamic ileus that resolved after 18 days

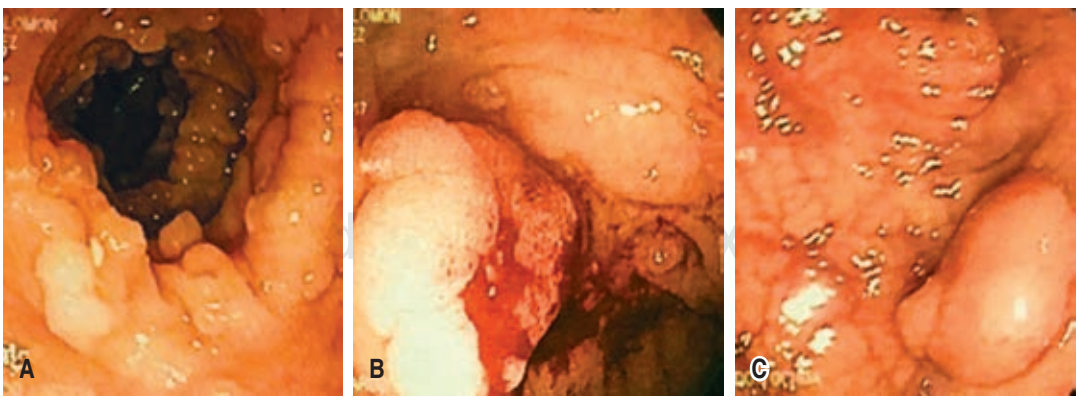

Figure 1: *Colonoscopy showing multiple polyposis* ***(A)****, with neoplastic lesions in the transverse colon* ***(B)*** *and in sigmoid colon* ***(C)****.*

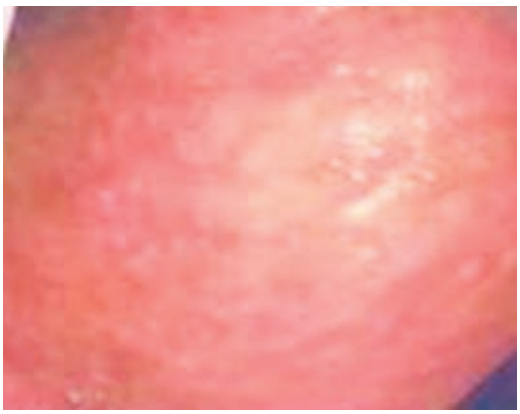

Figure 2: *Endoscopy image: diffuse micronodular surface in the upper portion of the body of the stomach, without duodenal polyps.*

with parenteral nutrition. Later, the patient tolerated the oral route. He was discharged with a functional ileostomy, after placement of a Port-a-Cath catheter.

The pathology department reported more than 200 tubular adenomatous polyps with low-grade dysplasia, as well as the presence of intestinal adenocarcinoma with mucinous component in the transverse and sigmoid colon. Liver biopsy revealed type I cholangiocarcinoma (CCA). Immunohistochemistry panel was performed for microsatellite instability with the following findings: MLHI, MSH2, MSH6 and PMS2 with conserved nuclear expression, and loss of nuclear expression of the APC gene, negative molecular test for identification of KRAS gene mutation, with CK7 (+), CK9 (+) and CK20 (-) in liver biopsy, suggesting FAP associated with primary cholangiocarcinoma *(Figure 4)*.

The patient was readmitted for adjuvant FOLFOX + bevacizumab-based chemotherapy administration in six cycles, with good tolerance. He is currently asymptomatic.

DISCUSSION

Most CRCs develop from benign preneoplastic lesions: adenomatous polyps or adenomas. Vogelstein proposed a multistep model of carcinogenesis for the development of CRC that describes the progression from a benign adenoma to a malignant carcinoma through a series of well-defined histological stages, known as the adenoma-carcinoma sequence model. Accordingly, it is understood that the etiology of CRC is multifactorial and is likely to involve the actions of genes at multiple levels, among which p53, APC, transforming growth factor (TGF)-β, SMAD, MLH1, MSH2, MSH6, PMS2, AXIN, STK11, PTEN, DCC and KRAS have been implicated.[9]

In 1991 the gene responsible for FAP, called Adenomatous Polyposis Coli or APC gene, was discovered.[10] More than 300 different mutations have been discovered in this gene that can cause this type of polyposis *(Annex 1)*. It was been shown that the risk of developing specific manifestations of FAP, as well as the severity of the disease in the large intestine are related to the type of genetic

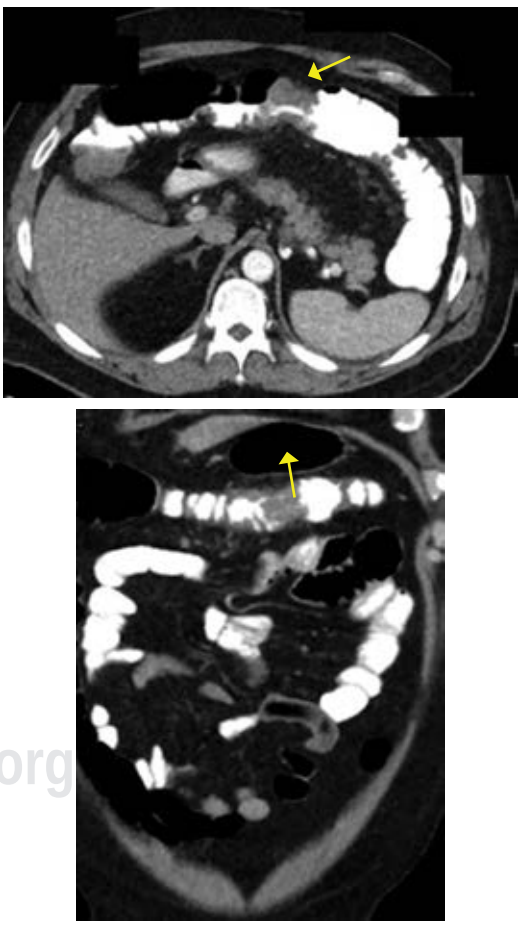

Figure 3: *Partially occlusive transverse colon tumor (yellow arrow).*

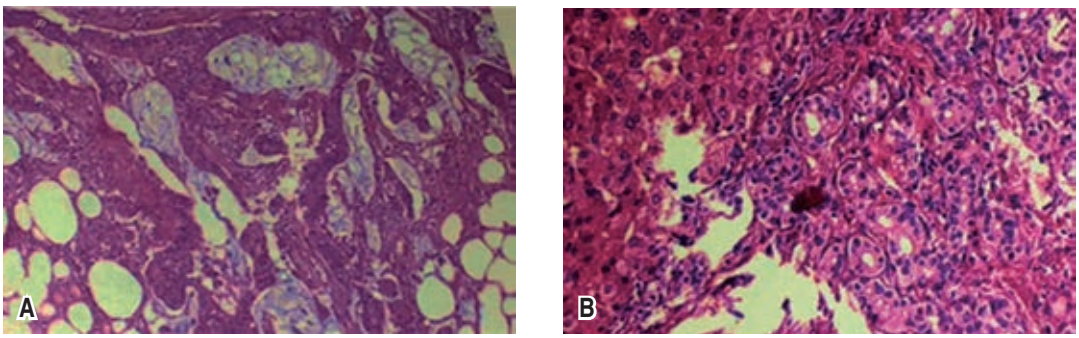

Figure 4: ***(A)*** *Muco-secretory colonic adenocarcinoma with signet ring cells,* ***(B)*** *well-differentiated hepatic adenocarcinoma.*

mutation. The most severe are most frequently observed in mutations between codons 1250 and 1464. This implies an early onset with symptoms (abdominal pain, diarrhea, blood in the stool) even before the age of 20 years, a high number of polyps in the colon and rectum, and an early progression to malignancy. Although clinically proven, FAP has no recognizable genetic mutation. There are many extracolonic manifestations of FAP, including osteomas, epidermoid cysts, desmoid tumors, gastroduodenal involvement, congenital hypertrophy of the pigmented epithelium of the retina, among others.[11]

The management of this type of hereditary diseases or syndromes should start with genetic counseling to inform about the type of pathology, the best therapy, and the necessary follow-up, thus reducing the morbimortality attributable to these syndromes. Prevention will be aided by specific identification of the causative germline mutation in the patient's family, which classifies the risk and sets the tone for the therapeutic and surveillance plan. Currently, prophylactic surgery is mandatory; however, the type of surgical technique will depend on the severity of the manifestations and the genotype presented.[12,13]

CCA is a malignant tumor arising from the biliary epithelium anywhere in the bile duct system, from the bile ducts to the ampulla of Vater. It is often associated with inactivation of tumor suppressor genes, e.g., p53, SMAD4, Bcl-2 and p16. Mutations in oncogenes, including KRAS, p53, c-ErbB-2 and c-Neu, have also been described. Although mutations may lead to detectable phenotypic changes, molecular profiles in biliary cytology currently have no established diagnostic or prognostic role.[14]

Distinguishing intrahepatic CCA from metastatic adenocarcinoma and other primary liver tumors can be difficult. Differentiation requires gastrointestinal tract metastases that often cannot be performed by histology. Other modalities, especially imaging, are essential. Immunohistochemistry panels including CK7, CK19, CK20, CDX-2, TTF-1, estrogen/progesterone receptors and prostatic specific antigen (PSA) may be useful, depending on the clinical context. CCAs are usually CK7 positive and CK20 negative,[15,16] as was found in our patient.

Currently there are no specific serum markers for bile duct neoplasms in healthy patients or carriers of genetic polymorphisms. There are promising studies of markers such as different mucins, interleukin-6, sialic acid, and matrix metalloproteinases used in combination, but more research is needed.[17]

The ideal gold standard for preventing complications or delaying the development of colorectal cancer would be a genetic technique that allows the deletion of the diseased gene and the implantation of a disease-free gene. Currently, this remains pure speculation. Most of the research deals with systems for screening for germline mutations in the adenomatous polyposis coli gene that predispose to susceptibility and disease in familial adenomatous polyposis. Today there are technical systems that detect mutations

in the APC gene, which could be useful in the molecular diagnosis of pre-symptomatic cases in families with FAP;[18] however, there are other interesting ways to approach the problem of pre-symptomatic carrier risk assessment in familial adenomatous polyposis such as the combined use of molecular markers and biomarkers, with a detailed understanding of the process of carcinogenesis being necessary.[19]

CONCLUSION

Familial adenomatous polyposis may not be considered a single disease entity with standard guidelines for surgical treatment. However, prophylactic colectomy after the manifestation of polyps, but before the development of colorectal cancer, remains the most effective preventive measure. Nowadays, refinement genetic analysis techniques and new targeted therapies with the possibility of identifying the mutation carried by the patient (whether it is related to a severe phenotype or not) have assumed a fundamental role in the indication of the type of surgical treatment in terms of radicality. Some bioinformatics tools aim to predict the sensitivity of the tumor to drugs based on its molecular characteristic, as well as in the short and long-term follow-up of both the patient and his first-degree relatives, have been developed.[20,21]

Surgical options are proctocolectomy with end ileostomy, subtotal colectomy with ileorectal anastomosis and restorative proctocolectomy with ileoanal reservoir. The decision should be based on the estimation of the risk of colorectal cancer, so that patients at high risk such as those with more than 20 adenomas in the rectum, more than 1,000 adenomas in the colon, rectal adenomas larger than 3 cm in diameter or with severe dysplasia, or in patients with a confirmed diagnosis of colon or rectal cancer, restorative proctocolectomy with ileoanal pouch could be the procedure of choice.[22]

The application of various intermediate biomarkers to chemoprevention studies increases the ability of investigators to analyze the effects of new chemo-preventive agents in the colon and other organs.

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Annex 1: Main characteristics of allelic heterogeneity of mutations in Adenomatous Polyposis Coli, Lynch Syndrome and Neoplasia associated with chronic non-specific ulcerative colitis (CNSUC).

	FAP	AFAP/HFAS	HNPCC/Lynch	UCAN
Mean age at diagnosis of colorectal cancer	32-39	45-55	42-49	40-70
Distribution of cancer	Random	Mainly right colon	Mainly right colon	Mainly left colon
No. of polyps	> 100	1-100	1 (i.e., tumor)	
Sex ratio (male:female)	1:1	1:1	1.5:1	1:1
Endoscopic view of polyp	Pedunculated	Mainly flat	Pedunculated (45%); flat (55%)	None
Lag time (years) from early adenoma to occurrence of cancer	10-20	10	5	?<8
Proportion (%) of colonic cancer	1	0.5	1-5	< 0.5
Superficial physical stigmata	80% have retinal pigmentation None	None	Only in Muir-Torre syndrome	None
Distribution of polyps	Distal colon or universal	Main proximal to splenic with rectal sparing	Mainly proximal to splenic flexure	None
Carcinoma histology	More exophytic growth	Non-exophytic but very variable	Inflammation increased mucin	Mucosal ulceration and inflammation
Other associated tumors	Duodenal adenoma cerebral and thyroid tumors, medulloblastoma and desmoids	Duodenal adenoma	Endometrial ovarian, gastric cancer, glioblastoma, many other cancers	
Gene (chromosome) mutation	APC (5q 21) distal to 5	APC (5q 21) proximal to 5	MHS2 (2p), MLH1 (3p21), PMS1 (2q31), PMS2 (7p22)	Multiple mutations, 17p (p53), 5q (APC), 9p (p16)

FAP = familial adenomatosis polyposis coli; AFAP = attenuated familial adenomatous polyposis coli; HFAS = hereditary flat adenoma syndrome; HNPPC = hereditary non-polyposis colon cancer; UCAN = ulcerative colitis associated neoplasia.
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