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Colorectal Adenocarcinoma in A Young Patient: A Case Report

Camejo Natalia[1,4*], Diego Santana[2], Castillo Cecilia[3], Dörner Carolina[4], Krygier Gabriel[5]

[1]Department of Clinical Oncology, School of Medicine, University of Uruguay, Montevideo, Uruguay. https://orcid.org/ 0000-0002-8684-0291

[2]Department of Clinical Oncology, School of Medicine, University of Uruguay, Montevideo, Uruguay. https://orcid.org/0009-0009-8408-1269

[3]Department of Clinical Oncology, School of Medicine, University of Uruguay, Montevideo, Uruguay. https://orcid.org/0000-0002-0417-0512

[4]Department of Clinical Oncology, School of Medicine, University of Uruguay, Montevideo, Uruguay. https://orcid.org/0000-0003-3758-2545

[5]Department of Clinical Oncology, School of Medicine, University of Uruguay, Montevideo, Uruguay. https://orcid.org/0000-0002-0518-1854

[*]**Corresponding Author:** Camejo Natalia, MD, Department of Clinical Oncology, School of Medicine, University of Uruguay, Montevideo, Uruguay. https://orcid.org/ 0000-0002-8684-0291. & https://orcid.org/0000-0003-3758-2545.

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Abstract

Introduction: Colorectal cancer (CRC) has established itself as one of the significant medical challenges of our time, especially with an increase in incidence among individuals under 50 years old. Globally, CRC is the third most common cancer and the second leading cause of cancer-related death. Most of these cases are reported in countries with a high Human Development Index (HDI), attributed to lifestyle factors and an aging population. Alarmingly, incidence has increased in individuals under 50 years of age, especially in Western countries.

Case presentation: A 39-year-old male patient presented with abdominal pain and was subsequently diagnosed with an intestinal occlusion due to a right colon adenocarcinoma. Following a colectomy, adjuvant treatment was administered for 3 months. Due to the patient's unusual age at diagnosis, a genetic study was conducted. While no pathogenic mutations were found, two variants of uncertain clinical significance were identified in the MSH6 and MSH2 genes.

Conclusions: CRC is a significant medical challenge worldwide, particularly in Uruguay. Although screening typically starts at 50 years, the uptick in cases among younger individuals is concerning. The presented case underscores the importance of considering genetic predisposition in early diagnoses, although the clinical significance of specific genetic variants remains uncertain.

Introduction

Cancer has emerged as one of the most significant medical challenges of our times. Thanks to medical advancements that have controlled and prevented infectious diseases and improved quality of life, we have witnessed a notable increase in life expectancy during the past century. This has led to a shift in the epidemiological landscape wherein, during the latter half of the 20th century, chronic and degenerative diseases—with emphasis on cardiovascular problems and cancer—became the leading causes of mortality **[1]**. Recent figures from the International Agency for Research on Cancer (IARC) indicate that in 2018 over 18 million new cancer diagnoses were identified, excluding non-melanoma skin cancer. Over 9 million individuals succumbed to this disease that year **[2]**.

Globally, colorectal cancer (CRC) ranks third in incidence and second in mortality for both sexes. In 2018 over 1.8 million new CRC cases were diagnosed, with a tragic tally of approximately 881,000 deaths. This translates to nearly 1 in every 10 cancer diagnoses and deaths attributed to this disease **[2]**.

The risk of CRC increases with age, with over 90% of cases detected in individuals older than 50. In addition to age, the main factors associated with elevated risk include a hereditary predisposition to CRC and a history of chronic ulcerative colitis or Crohn's disease. A small percentage (< 5 %) of CRCs occur in individuals with a hereditary predisposition of autosomal dominant transmission, such as familial adenomatous polyposis and non-polyposis hereditary CRC (Lynch Syndrome types I and II). When present, these constitute the primary risk factor. Genetic alterations in MLH1 and MSH2 genes lead to Lynch Syndrome, also known as Hereditary Non-Polyposis CRC, while mutations in the APC gene cause the condition known as Familial Adenomatous Polyposis. Both conditions are hereditary forms of colorectal cancer and are transmitted following an autosomal dominant pattern **[3-5]**.

It's worth noting that most cases, approximately 65 %, are recorded in nations with a high or very high Human Development Index (HDI). This can be understood demographically, given that susceptibility to CRC increases with age and the prolonged presence of disease-associated risk factors. These include smoking, lack of physical activity, obesity, alcohol consumption, and a diet rich in processed red meats and sausages. Such factors are often more prevalent in societies with elevated living standards **[2,6,7]**.

There's an uptick in CRC incidence among individuals under 50, particularly in Western countries. These figures are especially alarming since traditional CRC screening recommendations typically begin at age 50 for average-risk individuals. Although the reason behind this increase isn't fully understood, it's speculated that lifestyle-related factors, such as obesity, a diet low in fiber and high in fats, sedentary behavior, and consumption of tobacco and alcohol, might contribute to the rising incidence in younger individuals. Diagnosing CRC in more youthful individuals can present specific challenges. These cancers are often detected at more advanced stages, potentially resulting from diagnostic delays due to the lack of suspicion in this younger population **[8,9]**.

We present the case of a young patient who consulted for abdominal pain and was diagnosed with an intestinal obstruction due to a right colon adenocarcinoma. A colectomy was performed, and adjuvant treatment was administered for 3 months, based on the ACHIEVE-2 study. Given the patient's early age of colon cancer diagnosis, a hereditary predisposition was suspected, leading to genetic research. While no confirmatory pathogenic mutations were found, two variants of uncertain clinical significance were identified in the MSH6 and MSH2 genes.

Case presentation

A 39-year-old male patient, single, a driver from Mercedes, with a personal history of being an ex-smoker and a family history of a paternal aunt diagnosed with kidney cancer at 61.

He consulted for abdominal pain and underwent medical treatment without improvement. Upon consulting again, a right colon obstruction with an incompetent ileocecal valve was diagnosed due to a tumor in the right angle of the colon. An exploratory laparoscopy revealed a tumor in the right angle of the colon. No peritoneal nodules or hepatic lesions were observed. A conversion was opted for, followed by a laparotomy and right colectomy with ileo-transverse anastomosis.

The pathological anatomy (PA) showed a moderately differentiated tubulopapillary adenocarcinoma, infiltrative and transmural. 12 nodes were examined, none with metastatic involvement. Vascular-lymphatic or perineural invasion was not observed—pT3 pN0 Stage II.

Tumor markers, CEA, and CA 199 were within normal limits. A thorax, abdomen, and pelvis CT scan was conducted without evidence of lesions, and a total fibro colonoscopy showed a polyp in the remaining colon, which was resected. The PA showed a tubular adenoma with mild low-grade atypia. Given that the patient had a Stage II colon adenocarcinoma with risk factors (excluding T4, perforation, and insufficient nodal resection with <12), and according to the ACHIEVE-2 study, adjuvant treatment was carried out for 3 months with capecitabine and oxaliplatin. In this study, the 3-month adjuvant versus 6 months in the previously mentioned patients showed similar efficacy to the 6-month adjuvant without detriment in disease-free survival (DFS) at 3 years and with an improvement in the toxicity profile.

Given the diagnosis of colon cancer in a 38-year-old patient, a possible hereditary predisposition to cancer was suspected. Therefore, a genetic study was conducted using a multi-gene panel covering 35 known genes related to the diagnosis observed in the family. This assessment was carried out using massive sequencing technology, including detecting large genomic rearrangements.

The germinal genetic study results from a blood sample reported the absence of a pathogenic mutation that confirms the clinical suspicion. Therefore, neither our patient nor his family are at risk of developing hereditary cancer linked to said genes. However, two variants of still uncertain clinical significance were detected. The variant c.4002-15_4002-10del; p.(?) in the MSH6 gene (NM_000179.3) in heterozygosity and the variant c.2210+11_2210+22del; p.(?) in the MSH2 gene (NM_000251.3) in heterozygosity were identified.

Discussion

In Uruguay, colorectal cancer (CRC) is the second most frequent cancer in both sexes, surpassed only by breast cancer, with approximately 1,800 new cases annually. Moreover, it is the second leading cause of cancer death, following lung cancer, with over 1,000 yearly fatalities. The five-year relative survival rate is 55 %. Regrettably, over 50 % of these tumors are diagnosed at advanced stages, making it a significant public health issue in the country **[10,11]**.

While there are hereditary cases of CRC, the vast majority are sporadic. Despite potential genetic vulnerabilities, primarily modifiable "exogenous" risk factors play a critical role **[12]**. For the average-risk population, evidence-based national guidelines recommend commencing screening at age 50, continuing until 74-75, and conducting occult blood in stool tests every two years. If this test returns positive, a follow-up with a fibro colonoscopy is advised. However, for those at high risk—due to a personal or familial history of CRC, genetic predisposition, or chronic inflammatory bowel diseases such as ulcerative colitis or Crohn's disease—a colonoscopy screening should begin before age 50. These recommendations are just a portion of a broader algorithm for CRC prevention and early detection **[13-15]**.

The increase in cases among adults under 50 in countries like the USA and Australia, ages for which screening isn't typically recommended, is noteworthy. Although a well-substantiated explanation for this phenomenon is lacking, our statistics also reflect this trend **[8,9]**.

It's estimated that 5 % of CRC cases originate from identifiable hereditary syndromes. Considering this possibility in young patients diagnosed with colon cancer is vital, as syndromes like Lynch or familial adenomatous polyposis (FAP) are linked to genetic mutations. Early recognition of these syndromes is essential for determining treatment, follow-up, and providing appropriate genetic counseling. It's worth noting that specific genetic syndromes

associated with CRC may increase the risk of other cancers. Knowing a patient's genetic profile is crucial for preventing and monitoring potential additional malignancies. Once a genetic mutation or hereditary syndrome is identified in a patient, offering genetic counseling to other family members to evaluate and, if relevant, apply preventive or surveillance measures is imperative.

Lynch syndrome is the most common hereditary cause of CRC, accounting for 1 to 3 % of all cases. It arises from mutations in DNA repair genes, such as MLH1, MSH2, MSH6, and PMS2. These mutations can cause DNA replication errors, particularly in repetitive sequences known as microsatellites. Those with this syndrome have a high risk of developing CRC (40-80 %) and endometrial cancer (40-60 %), typically at younger ages. While other cancers, like stomach or urinary tract cancers, may emerge due to the syndrome, their prevalence is lower (cumulative risk below 10 %). Molecularly, tumors in patients with Lynch syndrome display specific features, such as the loss of gene expression and microsatellite instability. It should be noted that around 15 % of all CRCs exhibit microsatellite instability or loss of MLH1/PMS2 for non-hereditary reasons, often in older patients without familial CRC history **[16,17]**.

Familial adenomatous polyposis (FAP) is a hereditary genetic condition characterized by the formation of numerous adenomas in the colon and rectum (more than 100 in its classic form and 10 to 20 in its attenuated variant). These adenomas significantly increase the risk of developing CRC, up to 100 % in its traditional form. Mutations in the APC or MUTYH genes are commonly responsible for this condition, with the latter sometimes referred to as "MUTYH-associated polyposis." While the colon is the primary manifestation site, polyps can also appear in the stomach (mainly fundic gland polyps, which are generally benign) and the duodenum, where polyposis represents a major mortality cause due to duodenal cancer risk. Furthermore, individuals with FAP can develop desmoid tumors, certain thyroid cancer types, and other conditions **[18,19]**.

Our patient detected the c.4002-15_4002-10del; p. (?) variant in the MSH6(NM_000179.3) gene in heterozygosity. It's located in an intronic region and doesn't have impact information at the splicing site, thus meeting the specifications for scoring the ACMG criteria: the variant is absent from the gnomAD and 1000Genomes population databases. In silico prediction algorithms predominantly concur that such a variant may not impact the protein. This variant is probably benign in the ClinVar database (ID:24428867)—variants without description in specialized literature. Based on the considered criteria, this variant is classified as of uncertain clinical significance.

The c.2210+11_2210+22del; p. (?) variant in the MSH2(NM_000251.3) gene in heterozygosity was also detected. Located in an intronic region, it doesn't have impact information at the splicing site and, thus, meets the specifications for scoring the ACMG criteria: variant with low frequency in the gnomAD and 1000Genomes population databases—intronic variant with no splicing site prediction. In silico prediction algorithms predominantly agree that this variant might not impact the protein. The variant has conflicting pathogenicity classification in the ClinVar database (a variant of certain clinical significance, benign/probably benign) (ID: 1826062)—variants without description in specialized literature. This variant is classified as of uncertain clinical significance according to the criteria.

The identified variants do not possess an adverse medical effect. According to current literature, they are labeled as uncertain but benign according to well-informed computational models. Nevertheless, they will be included in a variant monitoring system to track any potential reclassification.

Given the family history, we recommend first-degree relatives undergo control fibro colonoscopy starting at 30, with frequency contingent upon the findings.

Conclusion

Colorectal cancer (CRC) is one of the primary causes of cancer-related morbidity and mortality worldwide. In Uruguay, it poses a significant public health concern, ranking as the second most common cancer and the second leading cause of cancer deaths. Although screening typically commences at age 50, there has been a discernible rise in CRC cases among individuals under 50 in various countries, including Uruguay. This report discussed the case of a 39-year-old patient diagnosed with stage E II adenocarcinoma of the colon. Given the patient's age at diagnosis, a genetic study was undertaken to identify a potential hereditary predisposition to cancer. While no pathogenic mutations were identified, two variants were found in the MSH6 and MSH2 genes, currently classified as having uncertain clinical significance.

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