Sporadic colorectal adenocarcinoma in children: an uncommon diagnosis

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Keywords

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Abstract

Colorectal cancer (CRC) is rare in the pediatric population. Low incidence and disease awareness among pediatricians often leads to delayed diagnosis. Compared with adult CRC, pediatric CRC is characterized by an advanced clinical stage at diagnosis and a higher frequency of unfavorable histopathology. We report the case of an 11-year-old boy diagnosed with an adenocarcinoma of the ascending colon without any predisposing factors.

Introduction

In the European Union, colorectal cancer is estimated to account for 12.7% of all new cancer diagnoses and 12.4% of all cancer deaths in 2020. It is the second most common cancer in adults after breast cancer and the second most common cause of cancer death in adults after lung cancer (1). In contrast, CRC is rare in children and adolescents, with an estimated annual incidence of one case per million (2).

Many small series and case reports suggest that children are more likely to present with advanced-stage disease than adults. This phenomenon can be explained by the non-specific symptoms and low awareness of the disease, leading to delayed diagnosis, and by the fact that the tumors found in children are often aggressive with unfavorable histology, suggesting a different pathophysiology.

Clinical case

An 11-year-old boy presented to the emergency department with a 3-month history of abdominal pain and weight loss of 2 kg.

He had been referred 1 month earlier by his general physician for hematochezia. Constipation was diagnosed at that time based on the history and the presence of a small anal fissure scar. A treatment was initiated. On admission, the pain had been increasing for one week and was associated with vomiting, nausea, and fever. He had no medical history except for asthma and no history of travel.

Physical examination revealed a relatively distended abdomen with diffuse rebound and tenderness, right lumbar pain and palpable stool. His vital signs were normal.

Abdominal ultrasound showed a distension of the right colonic frame with suspicion of paralytic ileus. The evaluation was completed with abdominal radiography and a computed tomography, which demonstrated the presence of a right colic flexure-centered mass causing intestinal subocclusion (Figures 1 A and B). Intestinal wall thickening and multiple adenopathies were also seen. A malignant lesion was suspected, yet tumor markers (CEA (carcinoembryonic antigen) and NSE (neuron-specific enolase)) were negative.

Figure 1:
A. An Abdominal X-ray was done at first showing air-fluid levels and a right paravertebral calcification at L2 level.
B. Abdominal computed tomography showed the presence of a right colic flexure centered mass causing intestinal subocclusion.

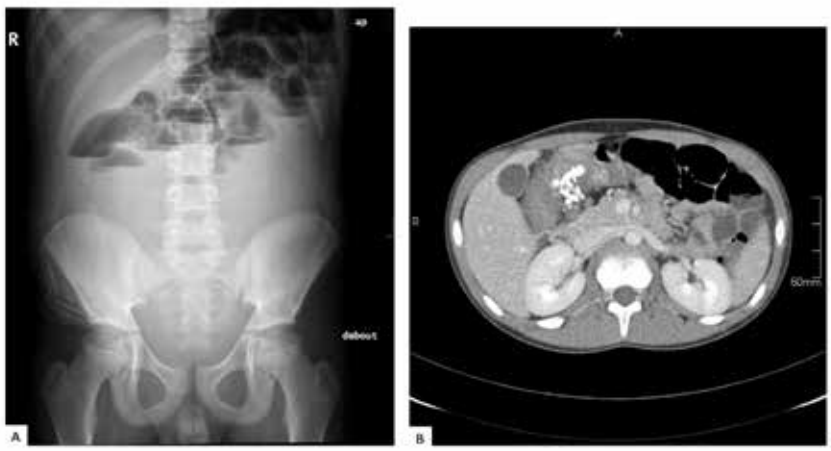


Figure 2:
A and B : Colonoscopy showed an annular, irregular mass with an ulcerated aspect totally obstructing the lumen.

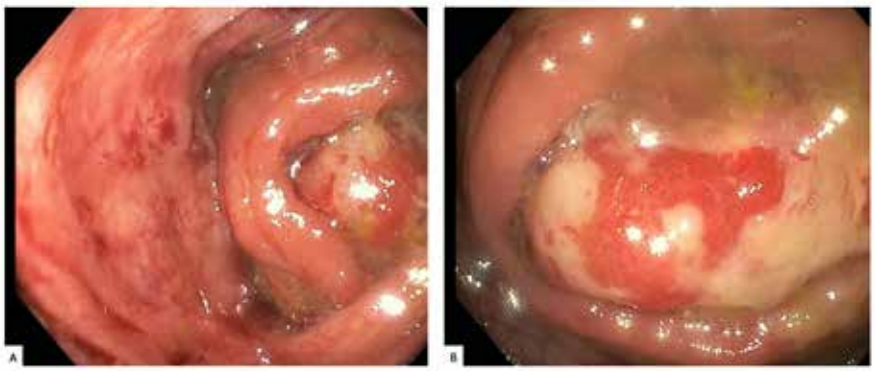
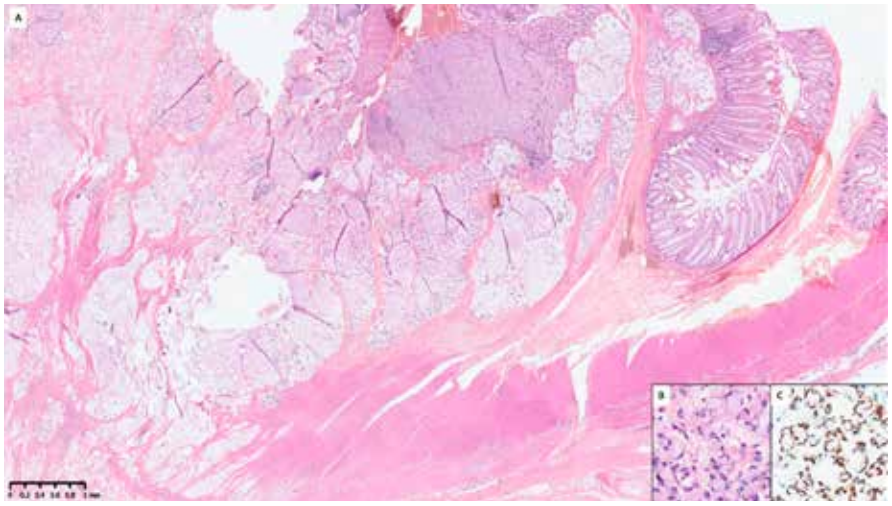


Figure 3:
A. Histopathology of the lesion. H&E staining of the tissue showing tumoral lesions characterized by abundant extracellular mucin with numerous floating signet-ring cells.
B. H&E staining - x40- Isolated tumor cells with an eccentric nucleus and mucus vacuole.
C. x40- Immunohistochemical stains are positive for Anti-CDX2, which is a transcription factor expressed in case of intestinal differentiation.
H&E = hematoxylin and eosin.



A diagnostic laparoscopic surgery with concomitant colonoscopy was scheduled. An annular colon tumor with an ulcerated aspect was found in the right colonic frame, obstructing the lumen (Figures 2 A and B). Pathology of the tumor and lymph node biopsies revealed abundant extracellular mucin with numerous floating signet-ring cells, supporting the diagnosis of mucinous adenocarcinoma (Figure 3 A and B).

A right hemicolectomy was performed. Final pathology results confirmed high-grade mucinous adenocarcinoma extending through the visceral peritoneum. Seven lymph nodes out of the sixty-three removed were metastatic. There was no evidence of metastatic disease to the liver, and the preoperative PET scan was negative. The final staging was pT4aN2bMx according to the 8th edition of the Union for International Cancer Control.

The immunohistochemical profile of the tumor was CK20/CDK2/MUC2 confirming the colic origin, but no evidence of microsatellite instability was found (Figure 3C). Next-generation sequencing of the samples revealed no mutations in the *NRAS*, *KRAS* and *BRAF* genes, but identified a presumed pathogenic point mutation in the tumor suppressor gene *TP53*, a gene associated in about 40 to 50% of sporadic colorectal cancer cases in adults.

A constitutional mutation of TP53 was ruled out.. Further genetic testing for inherited cancer susceptibility syndromes (Hereditary Non-Polyposis Colorectal Cancer, Familial Adenomatous Polyposis (FAP), MUTYH-associated polyposis, Peutz-Jeghers syndrome, Juvenile polyposis syndrome and Cowden syndrome) was also negative.

The patient underwent a FOLFOX chemotherapy regimen consisting of 1 cycle of intravenous 5-fluoruracil and oxaliplatin every 2 weeks. To date, he has completed thirteen cycles of chemotherapy without complication. Follow-up imaging studies have shown no evidence of recurrent disease.

Discussion

While it is one of the most frequent malignancies among adults, colorectal cancer is a rare tumor in the pediatric population, with an incidence of approximately 1 per million. A recently published population-based study using the SEER database (1973-2005) calculated an age-adjusted incidence rate of 0.38 and 802 per million for children/adolescents and adults respectively (2).

Much of the existing literature focuses on young adults or "early-onset" colorectal cancer (< 50 years of age), while fewer series or studies focus on children or adolescents. The largest database study to date was published by Poles et al. in 2015. Using the National Cancer Database, they compared pediatric, early-onset, and older adult patients with a total of 918 pediatric patients (≤ 21 years) (3).

Common presenting signs and symptoms are abdominal pain, vomiting, altered bowel habits, weight loss and hematochezia. However, these are often underestimated because they are nonspecific and can mimic many common functional gastrointestinal disorders in children. In our case, the patient had a history of hematochezia with presence of a small anal fissure scar caused by constipation, itself due to the tumor.

As illustrated by our case, pediatric colorectal cancer is unanimously characterized in the literature by a high occurrence of aggressive histologic subtypes: poorly differentiated, signet-ring or mucinous adenocarcinoma. The cause of this observation has not been elucidated to date. Still, it is suggested that pediatric CRC may have a different pathophysiological process compared to the well-known multistep development described in adult CRC (which usually occurs over approximately 10 years) (4). It has been demonstrated that even in adult CRC, there are significant differences in molecular alterations between mucinous and non-mucinous colorectal adenocarcinoma. Mucinous colorectal adenocarcinoma is characterized by an overexpression of the MUC2 and MUC5AC proteins, high-frequency microsatellite instability and mutations of the *RAS/MAPK* pathway (5).

High-frequency microsatellite instability (MSI) is caused by defects in the mismatch repair system (MMR). It has been found mainly in Hereditary Non-Polyposis Colorectal Cancer (HNPCC) but also in about 15% of sporadic CRC in adults. Few articles suggest a more frequent occurrence of MSI in early-onset sporadic colorectal carcinomas than in late-onset tumors. Furthermore, a different pattern of genetic alterations between both groups has been suggested to cause the altered function of the MMR system. (6-7)

An advanced stage at diagnosis is also a hallmark of pediatric CRC. This is illustrated in the population-based study by Poles et al., in which 62% of

pediatric patients presented with stage 3 and 4 disease at presentation, compared to 49.7% and 37.3% in the early-onset adult and older adult populations respectively (3).

The reason why children present more often at a later stage than adults is still unclear, but the possible explanations include an intrinsically more aggressive behavior of the disease and a delayed diagnosis, itself due to low incidence, non-specific symptoms and lack of awareness by physicians. In their review, Hill et al. compared patients whose time to diagnosis was less than 2 months (20 patients) with those whose diagnosis occurred 2-6 months (12 patients) after symptom onset. This comparison showed that patients with a longer delay to diagnosis tended to have a lower disease stage (p= 0.063) and better overall survival (p=0.014), making it less likely that delayed diagnosis alone explains advanced disease at presentation (8).

CRC most frequently develops sporadically in children. The main known predisposing factors are inflammatory bowel disease and inherited cancer susceptibility syndromes such as FAP and HNPCC, which are inherited autosomal dominant disorders associated with early-onset tumors. However, they seem less frequent in the pediatric population, representing an average of 10% of the cases (9). Several authors, such as Weber et al., have presented evidence suggesting that pediatric patients with predisposing syndromes (mainly HNPCC) have a better prognosis than those with sporadic disease (10).

However, in the case of HNPCC, strict adherence to follow-up guidelines does not seem to explain this observed better prognosis as there are currently no specific recommendations for the follow-up of children. The onset of surveillance colonoscopy is advised to be stratified based on the associated gene, with 25 years being the earliest recommended age.

To date, there are no therapeutic recommendations specific to pediatric CRC, so adult protocols are used. Surgery is considered the keystone of the treatment and should be radical. Complete surgical resection and lymph node dissection are decisive for cure. Saab et al. reported that the common factors among long-term survivors of pediatric CRC were low-stage disease and complete resection.

Depending on the disease stage, surgery may be followed by adjuvant chemotherapy. Oxaliplatin and 5–fluorouracil–based antineoplastic agents are commonly used chemotherapy combinations. For patients with metastatic disease, resection of all metastatic lesions is needed. Therefore, neoadjuvant chemotherapy may be advised (9).

Predictors of poor outcome in addition to disease stage are incomplete resection, mucinous histology, proportion of signet-ring cells > 10 %, and the absence of an in-situ component (2, 8).

Pediatric CRC is also characterized in the literature by a poorer survival rate than in adults. In the population-based study by Sultan et al. using the SEER database, the estimated 5 and 10 years overall survival rates were 40% ± 4,2% and 31% ± 4,4% respectively, in the children/adolescent population. This compares to 60 % ± 0,1% and 54 % ± 0,1% in the adult population. They also observed an improved outcome over time in adults, while no major differences were observed in children and adolescents (2).

Conclusion

Pediatric CRC differs from adult-onset CRC in several aspects. It is characterized by a high occurrence of aggressive histologic subtypes, an advanced clinical stage at diagnosis and, probably due to these aforementioned aspects, a poorer prognosis than adults.

There is evidence that an intrinsically different tumor biology may partially explain these features. In the absence of specific pediatric treatment recommendations, adult protocols are currently used. However, given the possibility of a different pathogenesis, the response to treatment may also be different from adult cancers. This is supported by the fact that even within adult populations, early-onset colorectal cancer is associated with differences in tumor behavior. With this in mind, further studies are needed to adapt the management of pediatric CRC, starting with a better understanding of the physiopathological process.

Due to its rarity and the non-specific nature of the symptoms, it is challenging to provide specific recommendations to general pediatricians regarding suspicion of CRC. Our suggestion is to be vigilant for warning signs and to emphasize the need to re-evaluating the outcomes of any therapeutic intervention.

Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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