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Case Series and Review of the Literature

Colorectal Carcinoma in Children and Adolescents - Case Reports and Literature Review

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ABSTRACT

Colorectal carcinoma (CRC) is extremely rare among pediatrics, particularly before puberty. It usually begins with nonspecific signs and symptoms, so the index of suspicion is low, consequently, the diagnosis may be delayed. Reports in the literature indicate that poor prognostic factors are more common in children than in adults, resulting in a worse outcome. Our objective is to report clinical profile, treatment and prognosis of CRC in children and adolescents admitted in our institution, and to perform a systematic review of reports in the bibliography.

Introduction

Colorectal adenocarcinoma (CRC) is the third most common malignancy in the adult population, surpassed only by lung and breast cancers. However, only 1-4 % of all CRC occurs in patients younger than 25-30 years old, being extremely rare among children, particularly before puberty. However, it is the most common gastrointestinal primary malignancy after liver tumors according to the Surveillance, Epidemiology, and End Results (SEER) database [1, 2].

Initial signs and symptoms may be nonspecific. Available data showed that the most common symptom was abdominal pain (54%), change in bowel habits (38%), rectal bleeding (31%), weight loss (19.7%), nausea and vomiting (17%), and iron deficiency anemia (77%). In advanced disease there may be intestinal obstruction and perforation associated with a poor prognosis. The acute onset is more common in pediatrics (>20%) [1].

Because of the rarity of the pathology, these signs and symptoms are often underestimated or misunderstood as other more common childhood problems such as gastroenteritis, which may lead to a delay in diagnosis; the median time elapsing between the first symptoms and diagnosis was reportedly 3 months for patients younger than 20 years old, as opposed to 1 month for those over 20 [1, 3-4]. Furthermore, it has been hypothesized that the delay in diagnosis could partly explain the advanced stages in children [5]. CRC in children differs from adults mainly in higher incidence of aggressive histological features (poorly differentiated, signet-ring or mucinous adenocarcinoma subtypes), advanced stage, more microsatellite instability and worse survival rate [1].

Patients and Methods

We retrospectively analyzed all patients younger than 20 years old with diagnosis of CRC referred to Hospital de Pediatría Dr. J.P. Garrahan, Buenos Aires, Argentina between September 1987 and December 2020. A systematic review of the literature was performed using keywords and MeSH terms "Adolescent" AND/OR "Child" AND "Colorectal Neoplasms". Case reports were qualitatively assessed and analyzed according to predefined criteria: n >5 and younger than 30 years old.

Result / Case Reports

Fifteen patients younger than 20 years old (range 11-19) were admitted during the study period (Table 1). Ten were male and five were female. The median time of delay in diagnosis was 2.37 months (range 8 days-5 months). The most common symptoms were abdominal pain and weight loss; 5 patients reported acute surgical abdomen.

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Table 1: Case reports.

	Age	Sex	Predisposing factors	Signs & Symptoms	Delay	Location	Histology	Dukes stage	Survival
1	11y10m	M	Ulcerative colitis	Ulcerative colitis	Colonoscopy control	Sigmoid-Rectum	Mucinous	D	alive
2	15y4m	M	-	Gastrointestinal bleeding + weight loss	3m	Sigmoid-Rectum	Mucinous + Signet-ring cells	C	Dead (OS 19.9m)
3	15y7m	F	-	Diarrhea + weight loss	2m	Hepato-colic angle	Mucinous	D	Dead (OS 6.2m)
4	13y11m	M	NF1 -High grade glioma	Abdominal pain + gastrointestinal bleeding	1.5m	Sigmoid	Mucinous	D	Dead
5	14y10m	M	-	-	-	Colon	Mucinous + Signet-ring cells	D	Dead (OS 11.3m)
6	15y5m	M	-	Abdominal pain + rectal bleeding + diarrhea + weight loss	4m	Rectum	Mucinous	-	Dead (OS 5.3m)
7	14y7m	F	-	Abdominal pain + anemia + weight loss	5m	Sigmoid-Rectum	Poorly differentiated	D	Dead (OS 7.9m)
8	19y	M	High grade glioma / glioblastoma	Lower gastrointestinal bleeding	-	-	-	-	Dead
9	17y	F	Crohn's disease	Crohn's disease	Colonoscopy control	Rectum	Well - differentiated	A	Dead (OS 10.3m)
10	16y	F	-	Acute surgical abdomen (occlusion) + anemia	8d	Hepatic flexure	Moderately differentiated	C	Dead (OS 18.5m)
11	14y9m	F	-	Acute surgical abdomen (pain + vomiting)	11d	Cecum	Signet-ring cells	D	Dead (OS 5.8m)
12	11y9m	M	-	Abdominal pain + change in bowel habits	3m	Sigmoid	Mucinous + Signet-ring cells	-	Dead
13	12y3m	M	-	Acute surgical abdomen + abdominal pain	3 m	Sigmoid	Signet-ring cells	-	Dead (OS 1.7m)
14	14y8m	M	-	Abdominal pain + weight loss + intestinal obstruction	3 m	Transverse	Mucinous	C	Dead
15	14y	M	-	Abdominal pain + vomiting + change in bowel habits	1m	Hepatic flexure	Moderately differentiated	C	Alive

y: Years; m: Months; d: Days; M: Male; F: Female; NF1: Neurofibromatosis type 1; OS: Overall Survival.

Two patients had been previously diagnosed and treated for a high-grade glioma, one of them with Neurofibromatosis type 1. Other two patients had increased risk factors for developing CRC: One with Crohn's disease and one with ulcerative colitis.

Unfavorable histotypes were more frequent: mucinous adenocarcinoma was observed in 9 patients, 5 being signet ring cell carcinoma. Poorly differentiated and undifferentiated tumors (grades III and IV) were seen in 6 of the 15 patients. Rectosigmoid was the most common primary site (8 patients). Fourteen patients reported an advanced stage of the disease (Dukes stage III-IV); more than half had distant metastases, seen in 9 of the 15 patients. At the moment of this analysis only 2 patients were alive, thirteen died because of the disease. The 1-year progression-free survival was 28,5%. Median mortality time was 9.8 months. An important limitation for our series is the lack of adequate immunohistochemical and genetic analyses on our patients.

Literature Review

Twenty-six full-text articles were retrieved (Table 2). The youngest reported patient was a 9-month-old girl [6]. Most reports confirm that pediatrics have unfavorable histotypes, advanced stages and double rates of metastases than adults, as we observed in our series. The 5 years overall survival reported for children is between 10-48% vs 60-81% for adults [2, 5, 7-9]. In our series only two patients were alive at the time of this study. The risk factors with statistical significance identified were: aggressive histological features, advanced Dukes stages, metastasis, lymph node involvement, complete surgical resection, use of adjuvant chemotherapy [1, 3, 10-11].

The median delay in diagnosis reported is between 1 and 4.5 months, coincident with our series [5, 10-15]. This worse prognosis than in adults may be due to the aggressive behaviour and/or the delayed diagnosis resulting in an advanced stage of the disease, with a lower chance of complete resection, the mainstay of its treatment [5, 23, 27, 30].

Table 2: Systematic literature review of case reports.

Author	n	Age (y)	Family History of CRC or Genetic Syndromes	Pathology	Stage	Survival/ Comments
Mathey, 2021, Argentina	15	< 20 (r:11-19)	2 history of HGG (1 NF1) 1 Crohn 1 UC	Mucinous: 9 Signet-ring cells: 5 Poorly differentiated: 6	Dukes C/D: 14 M1: 9	2 pts alive
Cortez-Pinto, 2019, Portugal [29]	5	< 18 (r:9-17)	4/5 had family history of cancer in 2nd-degree relatives (2 CRC history) No MSI or MMRD	3/5 signet ring cells/mucinous histology		
Khan SA, 2016, USA [7]	94	<30 (r:11-30)	Family history in 43% (vs. 26% in adults)	Poorly differentiated 37% Signet-ring cells 13% Advanced stages 76%		OS 5-y 40-48% (vs. 70-81%) compared with adults
Poles GC, 2015, USA [16]	918 (SEER)	<21	FAP 2.6% (p<0.001) compared with adults	Signet-ring cells 15.4% Mucinous 17.5% Poorly differentiated 30%	Stages III-IV 62% (vs. 37%)	
Weber ML, 2016, German [17]	31	≤18	11 pts: 8 HNPCC - 1 FAP - 2 other			OS 100% vs 36-50% without Genetic Syndromes 6 pts developed other malignancies: 3 NHL-T, 3 Glioblastoma
Du F, 2015, China [8]	19	10-20	MMRD in 2 of 9 pts analyzed	Signet-ring cells 37% Mucinous 26%	Stages: III 52.6% y IV 26.3%. Nodes + 89%.	OS 5-y 23%
Rahman M, 2014, Bangladesh [18]	7	6-10	2 FAP	2 Signet-ring cells 5 Poorly differentiated	Dukes Stages: 4 pts D, 1 pt By 2 pts A (both with FAP)	
Kaplan MA, 2013, Turkey [1]	76	<25	15 family history of CRC (21.7%) 5 (6.8%) APC			OS 16.3 m (r: 1-107 m).
Tay CH, 2012, Taiwan [19]	8	0-18	-		87.5% Dukes stages C/D	25% CEA high level.
Sultan I, 2010, Jordan, SEER [2]	159	4-20	10% APC	Mucinous 22%. Signet-ring cells 18%. Poorly differentiated / undifferentiated 31.9%.	Localized 19%	OS 5-y 40% vs 60% adults
Salas-Valverde S, 2009, Costa Rica [13]	11	7-17	2 APC, 1 Turner syndrome	Mucinous 64%		0 Dukes A and 2 Dukes B: alive 9 Dukes C/D: OS: < 17 m Delay in diagnosis: 6 days - 1 y (media: 3.9 m).
Ferrari A, 2008, Italy [9]	27	<30	3 pts MSI (1 family history of HNPCC) vs. 6 FAP + 5 HNPCC in adults		Stages III-IV 86% vs 40% in adults	Delay in diagnosis: 1-12 m. PFS 5-y 18% and OS 5-y 23% vs. PFS 62.5% and OS 73% in adults.
Hill DA, 2007, USA [3]	77	7-19	1 FAP, 6 juvenile polyps, 1 UC, 1 NF1,	Mucinous 62%	Advanced stages 86%, M1 51%.	OS 10-y: 20.1%; EFS 10-y: 17.7%.

			2 history of irradiation because of RMS. 3 pts 2nd malignancy			21% pts alive with medial survival of 12.2 y.
Kravarusic D, 2007, Israel [20]	7	2-18	-	4 Mucinous +/- Signet-ring cells		Delay in diagnosis 2-12m 3 pts alive
Durno C, 2005, Canada [21]	16	9-24	8/11 MSI 6/14 CMMRD 1 CMMRD: homozygous MLH-1 - brother (11y) with duodenal adenocarcinoma			7/16 developed 2nd malignancies
Chantada GL, 2005, Argentina [5]	21	10-30	3 family history of CRC		Pts <20 years old: Staged III and IV	11/14 died OS 5-y 10% vs. 72% in adults Delay in diagnosis: 2-24 m
Radhakrisshnan CN, 2003, England [22]	8	<16	-	Poorly differentiated 50%	All Dukes stage C	All died (1-12 m from diagnosis)
Vastyan AM, 2001, Hungary / UK [14]	7	<15 (r:9-15)	1: 2nd malignancy (Astrocytoma previous) 1: later presented 2nd malignancy (AML)	5/7 aggressive histological	5 Dukes stage C 2 Dukes stage D *1 case: metastasis in ovaries (Kruckenberg tumors)	6 pts died (6m-5y from diagnosis) Delay in diagnosis: 1-12 m (media 4 m)
Datta RV, 2000, USA [11]/ La Quardia MP, 1992, USA [10].	29	<21	7 family histories of CRC 1 HNPCC 1 FAP 1 UC 6/16 MSI 1 previous irradiation because of Wilms´ tumor	Signet-ring cells 45%. Poorly differentiated 24%.	76%: lymph node involvement 24 % metastasis.	Median delay in diagnosis: 2 m OS 3-y: 24%. Median OS: 16 m If complete resection: median OS 33 m
Karnak I, 1999, Turkey [23]	20	<16 (r:7-16)	3 family histories of CRC 1 Bloom Syndrome	16/20 (80%) Mucinous		100% advanced stage (35% Dukes C, 65% Dukes D) 17/20 died Delay in diagnosis: 2-15 days in Acute surgical abdomen; 1-24m in other clinical presentations.
Steinberg, 1988, USA [24]	9	10-20	1 Turcot syndrome	6 Poorly differentiated or Mucinous		5 pts delayed diagnosis (>3 m, median delay in diagnosis 11,6 m): 2 pts Dukes C and 3 pts Dukes D, median OS 4 m. 4 pts early diagnosis (median 20 days): 3 Dukes C and 1 Dukes D, median OS 24 m.

Andersson, 1976, Sweden [25]	6	< 15	-			2 pts Acute surgical abdomen All died. Longest survival 3y9m
Chabalco, 1975, USA [26]	76	<20	1 family CRC 4 FAP- 3 UC - 1 colitis granulomatous 1: Mangioendothelioma 1: Astrocytoma previous (Turcot syndrome)	32% Mucinous.		
Brown, 1992, South Africa [15]	7	10-15	-	5 Mucinous 4 Poorly differentiated 2 Signet-ring cells.		4 pts initial diagnosis: Acute surgical abdomen Delay in diagnosis 4.5m (r:2-6 m).
Lamego CMB, 1989, Brazil [27]	11	6-15	1 FAP	8 pts Mucinous	7 pts stages III and IV. 5 pts metastasis	Delay in diagnosis: 2-360 days
Goldthorn JF, 1983, Taiwan [28]	7	11-20	3 pts with predisposition (FAP o UC)	1 Mucinous	3 pts Dukes stage D	5 pts died
Indini, 2017, Italy [12]	12	< 18	2 pts MMRD.	5 Poorly differentiated 4 Mucinous 2 pts Signet-ring cells	All stages II/IV 6 pts metastasis.	6 pts alive with survival of 51.7 m 6 pts disease progression OS of 17 m (r:3-34 m) Delay in diagnosis: 1-12 m

Pts: Patients; y: Years; m: Months; HGG: High Grade Glioma; FAP: Familial Adenomatous Polyposis; HNPCC: Hereditary Non-Polyposis Colorectal Cancer; MMRD: Mismatch Repair Deficiency; CRC: Colorectal Carcinoma; APC: Adenomatous Polyposis Coli gene; MHL-1 + MSH-2 ; UC: Ulcerative Colitis; NF1: Neurofibromatosis type 1; RMS: Rhabdomyosarcoma; MSI: Microsatellite Instability; CMMRD: Constitutional Mismatch Repair Deficiency; LMA: Acute Myeloid Leukemia; OS: Overall Survival ; NHL: Non Hodgkin Lymphoma; PFS: Progression-Free Survival; M1: Metastasis to distant organs; EFS: Event Free Survival.

CRC in children and adolescents has a strong association with inherited cancer susceptibility syndromes [1, 7, 9, 17, 21, 29]. In our series, we report 2 cases with previous diagnosis of inflammatory bowel disease (1 Crohn's disease and 1 ulcerative colitis), and 2 patients with previous diagnosis of High-grade glioma, one of them with Neurofibromatosis type 1.

Conclusion

CRC poses many challenges to pediatric oncologists because of the low incidence, the delay in diagnosis may substantially contribute to the poorer prognosis, added to the higher prevalence of worse prognosis factors. Also, there is a strong association with hereditary cancer predisposition syndromes such Lynch Syndrome or Familial adenomatous polyposis, with manifestations that, even when mostly appear in adults, the adequate early screening allows its prevention and timely treatment. Added to that, it is important for the pediatrician and the pediatric oncologist to be able to provide genetic counseling for all the family.

Conflicts of Interest

None.

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