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Colorectal Dysplasia and Cancer in Pediatric-onset Ulcerative Colitis Associated with Primary Sclerosing Cholangitis

Wael El-Matary,
University of Manitoba, Winnipeg, Manitoba, Canada

Stephen L Guthery,
University of Utah and Intermountain Primary Children's Hospital, Salt Lake City, UT

Achiya Z. Amir,
The Dana-Dwek Children's Hospital, The Tel-Aviv Medical Center, Tel-Aviv University, Tel Aviv, Israel

Matthew DiGuglielmo,
Nemours Alfred I duPont Hospital For Children, Wilmington, DE

Laura G. Draijer,
Amsterdam University Medical Center, The Netherlands

Katryn N. Furuya,
University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI

Nitika Gupta,
Emory University School of Medicine, Atlanta, GA

Jessica T Hochberg,
University of Miami, Miami, FL

Simon Horslen,
University of Washington, Seattle, WA

Nanda Kerkar,
University of Rochester Medical Center, Rochester, NY

Bart GP Koot,
Amsterdam University Medical Center Amsterdam, The Netherlands

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Corresponding Author: Dr. Wael El-Matary, MBBCh, MD, MSc, FRCPCH, FRCPC, Professor, Department of Pediatric and Child Health, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, AE 408 Children's Hospital, Health Sciences Centre, 840 Sherbrook St., Winnipeg, Manitoba, R3A 1S1, Canada. Tel: +1-204-787-1039. Fax: +1-204-787-1045. welmatary@exchange.hsc.mb.ca.

Author contributions:
WE: Conceptualization, interpretation of data, and writing original draft.
SG, AA, MDG, LGD, KNF, NG, JTH, SH, NK, BGPK, TJL, KML, CM, MM, AM, TM, DM, SM, S Moroz, NO, ERP, GR, AR, PS, KBS, US, RS, NS, PLV, AZ, : Data curation and reviewing and editing of manuscript.
MD: Conceptualization, investigation, methodology, formal analysis, and reviewing and editing of manuscript

Trevor J Laborda,
University of Utah and Intermountain Primary Children's Hospital, Salt Lake City, UT

Kathleen M Loomes,
Children's Hospital of Philadelphia, Philadelphia, PA

Cara Mack,
University of Colorado School of Medicine, Aurora, CO

Mercedes Martinez,
Columbia University, New York, NY

Alexander Miethke,
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Tamir Miloh,
University of Miami, Miami, FL

Douglas Mogul,
Johns Hopkins University, Baltimore, MD

Saeed Mohammed,
Lurie Children's Hospital, Chicago, IL

Stacy Moroz,
University of Southern California, Los Angeles, CA

Nadia Ovchinsky,
Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY

Emily R Perito,
University of California, San Francisco

Girish Rao,
Indiana University, Indianapolis, IN

Amanda Ricciuto,
University of Toronto, Toronto, Ontario, Canada

Pushpa Sathya,
Memorial University, St. John's, Newfoundland and Labrador, Canada

Kathleen B Schwarz,
University of California San Diego, San Diego, CA and Johns Hopkins University, Baltimore, MD

Uzma Shah,
Massachusetts General Hospital, Harvard Medical School, Boston, MA

Ruchi Singh,
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Nisreen Soufi,
University of Southern California, Los Angeles, CA

Pamela L. Valentino,

Yale University School of Medicine, New Haven, CT

Andréanne Zizzo,
London Health Sciences Center, Western University, London, Ontario, Canada

Mark R. Deneau
University of Utah and Intermountain Primary Children's Hospital, Salt Lake City, UT

Introduction

Inflammatory bowel disease (IBD) especially when associated with primary sclerosing cholangitis (PSC) is a risk factor for developing colorectal cancer (CRC).[1–3] We aimed to determine the incidence of CRC in a large cohort of pediatric-onset PSC-ulcerative colitis (UC) patients.

Methods

Data on persons diagnosed with PSC-UC (0–18years) were collected from 54 centers through the Pediatric PSC Consortium. A full description of the methodology to identify persons with PSC was previously published.[4,5] Diagnosis of colonic dysplasia and adenocarcinoma was confirmed through reviewing pathology reports of all colonoscopy and colectomy specimens. The incidence of colorectal dysplasia/cancer in pediatric PSC-UC/IBD-U (unclassified) was calculated. (Details in supplemental material)

Results

We identified 509 patients with PSC-UC/IBD-U and complete data including colonoscopy and colectomy (if performed), 75% with a UC phenotype and 25% with an IBD-U phenotype, observed for 2894 person-years from diagnosis of IBD to time of colectomy or last follow-up [median duration 5 years, IQR [2.4–8 years] per patient]. The median age at IBD diagnosis was 12.6 years [IQR 8.8–15.3]. Clinically, PGA scores at diagnosis were severe in 16%, moderate in 55%, mild in 23.4%, and quiescent in 5.6% (diagnosed during routine screening colonoscopy for PSC diagnosis). On endoscopy, 96% had pancolitis or extensive colitis. The majority of patients had mild endoscopic disease at diagnosis with Mayo endoscopic severity of 3 in 17.0%, 2 in 6.6%, and 1 in 36.4%. The median age at PSC diagnosis was 13.2 years [IQR 9.3–15.6]. PSC involved the large ducts in 79% and 31% had features of overlap with autoimmune hepatitis.

Over the follow up period, 36 (7%) patients underwent colectomy at median 3 years after diagnosis of IBD (figure 1). The five-year probability of colectomy in PSC-IBD was 6.5% (95%CI 4.4–9.4%). The ten-year probability of colectomy in PSC-IBD was 10.1% (95%CI 6.9–14.5%) (Supplemental Figure 1).

All patients had at least one follow-up colonoscopy at median 2.4 [IQR 1.1–4.7] years after diagnosis. Eight patients were diagnosed with colorectal dysplasia/cancer (Table 1) with 5 of them diagnosed with adenocarcinoma or dysplasia in screening colonoscopy and 3 additional patients underwent colectomy for colitis that was resistant to medical therapies

and had evidence of dysplasia in colectomy specimens. No mortality or metastasis was reported.

Four patients (50%) had very early onset (VEO) IBD (<6years at diagnosis of IBD). Approximately 1% of VEO and non-VEO IBD patients required colectomy annually, yet the rate of CRC/dysplasia was higher in VEOIBD patients (5.8 vs. 1.8 cases per 1000 person-years, incidence rate ratio 3.4), suggesting that VEO-IBD may be an independent risk factor for CRC. Except for VEO-IBD, there was no statistically significant difference between those who developed cancer/dysplasia as compared to those who did not in base-line demographic or IBD clinical or endoscopic severity (Supplementary Table 2). VEO-IBD patients had longer median follow-up in our cohort (7.5 vs. 4.6 years), potentially biasing towards more time to identify CRC.

The incidence of colorectal dysplasia/cancer in pediatric PSC-UC/IBD-U was 2.8 cases per 1000 person-years. The 5-year probability of CRC was 0.8% (95%CI 0.3–2.7%). The ten-year probability of developing CRC after diagnosis was 4.8% (95%CI 2.0–11.1%).

Discussion

We reported the incidence of colorectal dysplasia/cancer in pediatric PSC-UC/IBD-U to be 2.8 cases per 1000 person-year. The longer duration of inflammation may explain that 50% of those who developed CRC/dysplasia were diagnosed with IBD before the age of 6 years although VEO-IBD could be an independent risk factor for developing CRC/dysplasia. The incidence we reported is higher than that reported in recent pediatric reports.[1,6] A recent study reported 12 CRC in pediatric-onset IBD (8 UC/IBD-U and 4 with colonic Crohn disease) after a median follow-up of 9.3 years with an incidence of 171 per 1000,000.[6] On the other hand, a retrospective analysis by Shah et al.[7] reported the incidence of CRC in adults with PSC-IBD to be 1.3 /100 patient-years over a mean duration of follow up of 4.8 years.

Concordant with our colectomy rates, in a retrospective analysis by Ricciuto et al.[8] risk of colectomy was lower in children with PSC-IBD than those with isolated UC. Only 1 of 74 with PSC-IBD patients underwent colectomy, as compared to 11% in controls.

Our study is limited by retrospective analysis, lack of controls and data on family history of CRC, more details of dysplasia/CRC and the exact frequency of screening colonoscopy in different centers. However, the incidence of CRC in pediatric PSC-UC/IBD-U is under-reported. We recruited the largest cohort of PSC-IBD to date. Further research is needed to define the optimal surveillance colonoscopy onset and interval in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

IBD	Inflammatory bowel disease
CRC	Colorectal cancer
PSC	Primary sclerosing cholangitis
UC	Ulcerative colitis
VEOIBD	Very early-onset IBD
PGA	Physician Global Assessment

References

1. El-Matary W, et al. Gastroenterology 2020 (accepted for publication) 2020 Mar 29. pii: S0016–5085(20)30402–9. doi: 10.1053/j.gastro.2020.03.048. [Epub ahead of print].
2. Claessen MM, et al. J Hepatol. 2009;50:158–64. [PubMed: 19012991]
3. Soetikno RM, et al. Gastrointest Endosc. 2002;56:48–54 [PubMed: 12085034]
4. Deneau MR, et al. Hepatology. 2017;66:518–527. [PubMed: 28390159]
5. Deneau MR, et al. Hepatol Commun 2018;2:1369–1378 [PubMed: 30411083]
6. Joosse ME, et al. Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN. Aliment Pharmacol Ther 2018;48:523–537. [PubMed: 29984520]
7. Shah SC, et al. Clin Gastroenterol Hepatol. 2018;16:1106–13 e3. [PubMed: 29378311]
8. Ricciuto A, et al. Clin Gastroenterol Hepatol. 2019 Sep 4. pii: S1542–3565(19)30970-X. doi: 10.1016/j.cgh.2019.08.048. [Epub ahead of print]

Table 1:

Disease characteristics in PSC-IBD patients who developed colon cancer/dysplasia

Case	Sex	UC classification	Backwash ileitis?	Type	Age at IBD diagnosis (y)	Age at PSC diagnosis (y)	Age at cancer/ dysplasia (y)	Medications	PSC phenotype	PSC complications
1	F	E3	No	Adenocarcinoma	5.5	8.2	19	UDCA, 5-ASA, IFX	Large duct	none
2	F	E4	Yes	Adenocarcinoma	4.1	4.1	14.9	UDCA, steroids, 5-ASA, MTX, IFX, VDZ	Large duct with AIH overlap	Esophageal varices at 9.5y
3	F	E4	Yes	Dysplasia	5.2	12.6	15.2	UDCA, steroids, AZA	Small duct with AIH overlap	none
4	M	E3	No	Dysplasia	8.8	9.2	13.2	UDCA, OVT, steroids, 5-ASA, AZA, IFX	Large duct	Dominant biliary stricture ballooned at 13.5y
5	F	E4	No	Dysplasia	18	12.4	24	UDCA, 5-ASA, AZA	Large duct with AIH overlap	Esophageal varices at age 19.4y, liver transplantation at 28y
6	M	E3	No	Dysplasia in colectomy	18	18	26.9	UDCA, steroids, 5-ASA, AZA, MTX, IFX	Large duct	Esophageal varices at 20y, liver transplantation at 26y
7	M	E3	Yes	Dysplasia in colectomy	5.6	5.8	6.7	Steroids, 5-ASA, IFX, VDZ	Large duct	none
8	F	E4	Yes	Dysplasia in colectomy	12	11.9	12.3	UDCA, OVT, steroids, MMF, tacrolimus	Large duct with AIH overlap	Esophageal varices at 12.5y, liver trasnplantation at 13y

E3 extensive colitis, E4 pancolitis, UDCA Ursodeoxycholic acid, 5-ASA 5-aminosalicylate, IFX infliximab, MTX methotrexate, VDZ vedolizumab, AIH autoimmune hepatitis, aza azathioprine, OVT oral vancomycin therapy, MMT Mycophenolate mofetil.