A Clinicopathologic Comparison Between Early-Onset and Late-Onset Small Bowel Adenocarcinoma: A Multicenter International Study

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INTRODUCTION: **Early-onset small bowel adenocarcinoma (EO-SBA) is a rare and poorly characterized entity.**

METHODS: **This retrospective study conducted on an international multicenter cohort of 208 patients with SBA aimed at comparing clinicopathologic features of EO-SBA (age younger than 50 years at SBA diagnosis) and late-onset SBA (age 50 years or older at SBA diagnosis).**

RESULTS: **The presence of predisposing pathologic conditions was significantly more common in the EO-SBA group compared with that in the late-onset SBA group ($P = 0.003$, Fisher exact test; relative risk: 1.50, 95% confidence interval: 1.20–1.86). This difference is mainly due to the significantly higher prevalence of celiac disease among patients with EO-SBA.**

DISCUSSION: **EO-SBA is strongly associated with predisposing conditions, particularly with celiac disease, highlighting the importance of routine screening for celiac disease in patients with EO-SBA.**

KEYWORDS: celiac disease; Crohn's disease; immune-mediated disorders; small bowel cancer; mismatch repair

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INTRODUCTION

Recent epidemiologic studies have described a worrisome surge in early-onset gastrointestinal cancer incidence (1). In young patients, gastrointestinal tumors are usually diagnosed at later stages compared with the older patients, carrying several implications in terms of patient management and quality of life. Most of early-onset gastrointestinal carcinomas are sporadic. However, very few data are available for early-onset cancers arising in the small intestine and particularly for nonampullary early-onset small bowel adenocarcinoma (EO-SBA). Although SBA is a rare neoplasm, representing <2% of all gastrointestinal cancers, its incidence has lately increased in Western countries, with an estimated annual percentage change of 3.7% in the period 1999–2013 (2) and a 20-year period increase in incidence of 16% in men and 38% in women (3). SBA is an aggressive neoplasm with a 5-year survival rate of 25% and a median survival rate of 13–14 months (2). Although most SBA seem to be sporadic, numerous predisposing conditions have been recognized, including both inflammatory diseases, i.e., celiac (CeD) and Crohn's disease (CD), and inherited tumor syndromes, e.g., Lynch syndrome (LS) and familial adenomatous polyposis (FAP1) (4). The median age at SBA diagnosis is 69 years for SBA as a whole, with younger ages reported for SBA related to Crohn's disease (CD-SBA) (58 years of age) and to celiac disease (CeD-SBA) (53.5 years of age) (2,5). Although a non-negligible fraction (10%) of SBA has been reported to have an onset before 50 years in a Dutch epidemiological investigation (2), no study comparing this early-onset subgroup with patients with late-onset SBA (LO-SBA) has yet been published. To fill this gap, our group decided to perform this study.

METHODS

A descriptive observational retrospective study (Ethical Committee 20140003980) was conducted on an international multicenter cohort including 208 patients with surgically resected SBA from 31 tertiary referral centers from 3 countries. Following the threshold used to define other early-onset gastroenteropancreatic carcinomas (2,6), we set the cutoff at the age of 50 years, so as to divide our study population into 2 groups: EO-SBA (age younger than 50 years at SBA diagnosis) and LO-SBA (age 50 years or older at SBA diagnosis). All cases were reviewed for the following clinicopathologic features: sex, age at SBA diagnosis, etiology, site, pathological tumor-node-metastasis stage (according to the eighth edition American Joint Committee on Cancer), histologic grade, histotype, and mismatch repair (MMR) proteins status, as previously

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Table 1. Clinicopathologic features of the 208 SBA investigated, divided into EO-SBA and LO-SBA

Variable	Total (n = 208, 100%)	EO-SBAs (n = 41, 20%)	LO-SBAs (n = 167, 80%)	*P* value
Age at SBA diagnosis, yr, ±SD	61.6 ± 13.9	40 ± 1.0	66.9 ± 0.8	<**0.001**
Sex, n (%)				
Male	129 (62)	20 (49)	109 (65)	0.072
Female	79 (38)	21 (51)	58 (35)	
Etiology, n (%)				
Crohn's disease	58 (28)	13 (32)	45 (27)	<**0.001**
Celiac disease	41 (20)	13 (32)	28 (17)	
Lynch syndrome	17 (8)	3 (7)	14 (8)	
Familial adenomatous polyposis 1	2 (1)	2 (5)	0	
Hereditary breast and ovarian cancer syndrome	1 (1)	1 (2)	0	
Sporadic	89 (42)	9 (22)	80 (48)	
Any predisposing condition, n (%)				
Yes	119 (57)	32 (78)	87 (52)	**0.003**
No (sporadic)	89 (43)	9 (22)	80 (48)	
Any hereditary tumor syndrome, n (%)				
Yes	20 (10)	6 (15)	14 (8)	0.240
No	188 (90)	35 (85)	153 (92)	
Celiac disease, n (%)				
Yes	41 (20)	13 (32)	28 (17)	**0.047**
No	167 (80)	28 (68)	139 (83)	
Tumor site, n (%)				
Duodenum	39 (19)	8 (19)	31 (19)	0.459
Jejunum	83 (40)	13 (32)	70 (42)	
Ileum	86 (41)	20 (49)	66 (39)	
Histotype, n (%)				
Glandular	144 (69)	23 (56)	121 (72)	0.173
Mixed-poorly-cohesive-glandular	36 (17)	9 (22)	27 (16)	
Poorly cohesive	18 (9)	7 (17)	11 (7)	
Medullary	9 (4)	2 (11)	7 (4)	
Undifferentiated rhabdoid	1 (1)	0	1 (1)	
Histologic grade, n (%)				
Low	130 (62)	24 (59)	106 (63)	0.592
High	78 (38)	17 (41)	61 (37)	
Stage (AJCC 8th ed), n (%)				
I	14 (7)	2 (5)	12 (7)	0.492
II	90 (43)	18 (44)	72 (43)	
III	78 (37)	13 (32)	65 (39)	
IV	27 (13)	8 (19)	19 (11)	
MMR status, n (%)				
MMRp	142/207 (69)	28 (68)	114/166[a] (69)	1
MMRd	65/207 (31)	13 (32)	52/166[a] (31)	

Bold type indicates significant *P* values.
AJCC, American Joint Committee on Cancer; EO-SBA, early-onset small bowel adenocarcinoma; LO-SBA, late-onset small bowel carcinoma; MMRd, mismatch repair deficient; MMRp, mismatch repair proficient; SBA, small bowel adenocarcinoma.
[a]In 1 case, microsatellite instability status could not be assessed.

described (7–9). The underlying inflammatory conditions (CeD and CD) were ascertained/excluded by clinical, serological, radiological, and histologic findings in all patients, while an SBA was regarded as hereditary cancer syndrome related when patients were diagnosed with a known inherited tumor syndrome, which was suspected based on clinical criteria or by histopathologic findings (MMR deficiency) and confirmed by the identification of specific germline mutations. Data were described with the mean and SD if continuous and with counts and percentages if categorical and compared between groups with the Student t test or the Fisher/χ^2 test, respectively. A 2-sided P value <0.05 was considered statistically significant. Bonferroni correction for multiple comparisons was not applied given the exploratory nature of the study.

RESULTS

The study cohort included 41 (19.7%) EO-SBA and 167 (80.3%) LO-SBA. Clinicopathologic findings of the 2 groups are summarized in Table 1. Patients with EO-SBA and LO-SBA had a mean age of 40 years (SD ± 1.0) and 66.9 years (SD ± 0.8) at SBA diagnosis, respectively. A predisposing condition was identified in 119 (57.2%) cases: 58 CD-SBA, 41 CeD-SBA, 17 LS-related SBA, 2 FAP1-associated SBA, and 1 SBA arising in a patient with hereditary breast-ovarian cancer syndrome (harboring the *BRCA2* germline mutation c.5645C>A(p.Ser1882Ter)). Predisposing conditions resulted significantly more frequent in EO-SBA when compared with those in LO-SBA (78% vs 52%, $P = 0.003$). Association with CD, CeD, FAP1, LS, and hereditary breast-ovarian cancer syndrome was found in 13 (32%), 13 (32%), 2 (5%), 3 (7%), and 1 (2%) EO-SBA and in 28 (17%), 45 (27%), 0, 14 (8%), and 0 LO-SBA, respectively. EO-SBA showed a significantly higher prevalence of patients with CeD compared with LO-SBA (32% vs 17%, $P = 0.047$). Patients with CeD-SBA had a concomitant diagnosis of CeD and SBA in 30% of cases with EO-SBA and 10% of cases with LO-SBA. No significant difference in sex, site, stage, histotype, histologic grade, and MMR protein status was noted between the 2 subgroups.

DISCUSSION

To our knowledge, this is the first study to analyze a relatively large international multicenter cohort of EO-SBA. We found that predisposing conditions as a whole, and particularly CeD, are strongly related to EO-SBA. There is evidence showing a shorter time span between immune-inflammatory disease diagnosis and SBA development for CeD-SBA in comparison with CD-SBA (7). Of interest, among hereditary conditions–related SBA, we found a case with a *BRCA2* germline mutation, a gene only recently linked to SBA (10). In this regard, a limitation of this investigation is that genetic testing for the detection of hereditary tumor syndromes has not been thoroughly performed; thus, we cannot exclude that the actual prevalence of hereditary syndrome–associated SBA may be underestimated. However, we performed universal screening for LS by immunohistochemistry for MMR proteins in all cases, followed by MMR gene germline test in MMR-deficient cases without MLH1 promoter hypermethylation. We identified LS in approximately 8% of patients with SBA, a proportion similar to that reported by Latham et al (11), without significant difference in LS prevalence between patients with EO-SBA and LO-SBA. Moreover, we showed an EO-SBA prevalence approximately 2-fold higher than data reported by Legué et al (2), an observation that may reflect a still ongoing evolution of SBA epidemiology.

In conclusion, our study suggests that, in contrast to other early-onset gastrointestinal cancers, EO-SBA are frequently associated with an immune-inflammatory or hereditary predisposing condition, and particularly, it stresses the importance of routine screening for CeD in patients with a diagnosed SBA at an age younger than 50 years.

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CONFLICTS OF INTEREST

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REFERENCES

1. Ben-Aharon I, van Laarhoven HWM, Fontana E, et al. Early-onset cancer in the gastrointestinal tract is on the rise-evidence and implications. Cancer Discov 2023;13(3):538–51.
2. Legué LM, Bernards N, Gerritse SL, et al. Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013: A population-based study in The Netherlands. Acta Oncol 2016;55(9-10):1183–9.
3. Bouvier AM, Robaszkiewicz M, Jooste V, et al. Trends in incidence of small bowel cancer according to histology: A population-based study. J Gastroenterol 2020;55(2):181–8.
4. Aparicio T, Henriques J, Manfredi S, et al. Small bowel adenocarcinoma: Results from a nationwide prospective ARCAD-NADEGE cohort study of 347 patients. Int J Cancer 2020;147(4):967–77.
5. Giuffrida P, Arpa G, Grillo F, et al. PD-L1 in small bowel adenocarcinoma is associated with etiology and tumor-infiltrating lymphocytes, in addition to microsatellite instability. Mod Pathol 2020;33(7):1398–409.
6. Patel SG, Karlitz JJ, Yen T, et al. The rising tide of early-onset colorectal cancer: A comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. Lancet Gastroenterol Hepatol 2022;7(3):262–74.
7. Vanoli A, Di Sabatino A, Furlan D, et al. Small bowel carcinomas in coeliac or crohn's disease: Clinico-pathological, molecular, and prognostic features. A study from the small bowel cancer Italian Consortium. J Crohns Colitis 2017;11(8):942–53.
8. Vanoli A, Di Sabatino A, Martino M, et al. Small bowel carcinomas in celiac or crohn's disease: Distinctive histophenotypic, molecular and histogenetic patterns. Mod Pathol 2017;30(10):1453–66.
9. Vanoli A, Guerini C, Grillo F, et al. Poorly cohesive carcinoma of the nonampullary small intestine: A distinct histologic subtype with prognostic significance. Am J Surg Pathol 2022;46(4):498–508.
10. Hänninen UA, Katainen R, Tanskanen T, et al. Exome-wide somatic mutation characterization of small bowel adenocarcinoma. PLoS Genet 2018;14(3):e1007200.
11. Latham A, Shia J, Patel Z, et al. Characterization and clinical outcomes of DNA mismatch repair-deficient small bowel adenocarcinoma. Clin Cancer Res 2021;27(5):1429–37.