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Association between serrated epithelial changes and colorectal dysplasia in inflammatory bowel disease

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Abstract

Background and Aims—Serrated epithelial change (SEC) is a histologic finding in longstanding colitis that may be associated with dysplasia. Our primary aim was to determine the incidence of dysplasia and colorectal cancer (CRC) in inflammatory bowel disease (IBD) patients with SEC. Secondary aims were to determine the rate of location concordance between SEC and dysplasia/CRC and to identify other risk factors associated with dysplasia in IBD patients with SEC.

Methods—A retrospective, descriptive, observational study was performed by searching the Pathology Data System at a single tertiary referral center for a histologic finding of “serrated epithelial change.” The patient’s first pathology specimen with SEC was designated the index SEC. All subsequent pathology reports were evaluated for the occurrence and location of dysplasia or CRC. Univariable and multivariable logistic regression were performed to identify predictors of dysplasia.

Results—There were 187 patients with confirmed IBD and 1 or more histologic findings of SEC without prior dysplasia. Mean IBD duration was 16 years, and median follow-up time was 28 months. The rate of high-grade dysplasia or CRC was 17 per 1000 patient-years. Thirty-nine of 187 patients (21%) had synchronous or metachronous dysplasia or CRC. Location concordance

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was 68%. Multivariable analysis found SEC on follow-up examinations, older age at IBD diagnosis, male gender, and a first-degree relative with CRC were associated with dysplasia in IBD patients with SEC.

Conclusions—This uncontrolled study describes a high frequency of dysplasia in patients with a histologic finding of SEC. SEC seen on successive endoscopic examinations further increased the risk of dysplasia. Further controlled studies are needed to determine if SEC is a precancerous lesion in IBD patients and if SEC can be endoscopically identified. (*Gastrointest Endosc* 2016;84:87-95.)

The risk of developing colorectal cancer (CRC) after 30 years of inflammatory bowel disease (IBD) ranges between 10% and 18%.¹⁻⁴ The American Gastroenterological Association 2010 guidelines recommend commencing surveillance colonoscopy after 8 to 10 years of colitis that affects at least one third of the colon and every 1 to 2 years thereafter.⁵ Low-grade dysplasia (LGD) is an accepted precursor of high-grade dysplasia (HGD) and CRC⁶⁻⁸ and requires closer surveillance if not colectomy. In 2015 the SCENIC consensus statement⁹ offered further recommendations on the improved detection and management of dysplasia in IBD.

The histologic finding of serrated epithelial change (SEC) in the setting of IBD has been described but incompletely studied.¹⁰⁻¹⁴ SEC is synonymous with hyperplastic-like mucosal change and flat serrated change, although it is a separate entity from sessile serrated adenomas/polyps. Sessile serrated adenomas in the general population are flat yet visible lesions shown to follow a distinct “serrated pathway” that leads to colorectal cancer in an accelerated manner. By contrast, SEC is a histologic diagnosis most often found on flat mucosa during routine surveillance in IBD patients but can appear as nodular mucosa grossly indistinguishable from LGD (Fig. 1A). Microscopically, SEC is characterized by distorted architecture without classic features of dysplasia. It is histologically distinct from both hyperplastic polyps and LGD (Fig. 1B).

The role of SEC in IBD patients is unclear. In 2000, Kilgore et al¹² studied Crohn’s colectomy specimens and found that patients with CRC had an increased prevalence of SEC compared with Crohn’s patients without CRC. SEC may represent a separate dysplasia pathway in IBD patients. Molecular alterations in SEC are comparable with mutations found in the serrated neoplasia pathway.^{10,12} More recent studies have yielded conflicting results about the role of SEC.^{11,12} Our goal was to further understand the significance of SEC and its relationship to dysplasia in IBD patients. Therefore, we investigated the incidence of dysplasia or CRC in IBD patients with SEC, the concordance between the locations of SEC and dysplasia or cancer, and other predictive risk factors of dysplasia or cancer in this population.

METHODS

This study was approved by the Johns Hopkins Institutional Review Board.

Population

The Johns Hopkins Pathology Data System was searched for a histologic finding of the validated term “serrated epithelial change” between January 1, 2000 and December 31, 2008. These patients were confirmed to meet criteria for a diagnosis of ulcerative colitis (UC), Crohn’s disease (CD), or IBD undetermined type (IBDU) based on chart review. The patient’s first finding of SEC was defined as the index SEC. Both colonoscopic biopsy samples and surgical resection specimens were included. During this study period at our institution standard white-light endoscopy without chromoendoscopy was performed on all IBD patients; random and targeted biopsy sampling was performed in patients undergoing dysplasia surveillance. In our study the term “dysplasia” includes LGD, HGD, or CRC.

Patient data

Medical and endoscopy records were reviewed to determine the occurrence of LGD, HGD, or CRC before, at the time of, and after the index SEC. An additional pathology search was performed for dysplasia to ensure cases were not missed. Patients’ histories of IBD were recorded, including date of diagnosis, smoking status (never smoker, former smoker, and current smoker at the time of index SEC), the coexistence of primary sclerosing cholangitis, family history of IBD, and family history of CRC in a first-degree relative.

Prevalence of SEC

The prevalence of SEC in our IBD population was calculated in 2 separate years within our search: 2004 and 2008. The number of unique patients with a pathologic finding of “serrated epithelial change” was divided by the number of unique patients with a pathologic finding of “chronic active/inactive colitis.” Full colonoscopies or colectomy specimens were included. Pouchoscopies and flexible sigmoidoscopies were excluded.

Disease characteristics

Disease extent was defined for UC/IBDU (proctitis only, left-sided disease only, or extensive colitis) and for CD (<50% or ≥50% colonic involvement). Gross endoscopic disease activity (inactive/mild or moderate/severe disease as abstracted from colonoscopy reports) and medication usage (antitumor necrosis alpha antibody, thiopurine, corticosteroid, and mesalamine-containing medications) at the time of the index SEC were recorded.

SEC histology

Pathologists at Johns Hopkins have been diagnosing SEC consistently since 2000. Histologically, it is recognized by distorted architecture but lacking typical features of dysplasia (Fig. 1B). In contrast to hyperplastic polyps, the crypts in SEC lose orientation to the lumen and are no longer perpendicular to the muscularis mucosae nor do they necessarily reach the muscularis mucosae. Serrations of the epithelium and enlarged goblet cells both extend to the base of the crypts. Additionally, cytoplasmic eosinophilia can be noted, although the nuclei have no atypia. SEC is goblet-cell rich, in contrast to most hyperplastic polyps, which typically display microvesicular cytoplasm (occasional examples have been described as goblet-cell type and mucin-poor type, although these forms still display straight crypts that reach the muscularis mucosae)¹⁵ (Fig. 1B). By contrast, LGD

contains hyperchromatic, elongated basal nuclei without surface maturation and involves a loss of goblet cells.¹⁶ Criteria used to separate SEC from sessile serrated adenoma/polyp, hyperplastic polyp, low-grade colitis-associated dysplasia, and high-grade colitis-associated dysplasia appear in Table 1. To further validate the findings of SEC (because this is a rare and emerging finding), 10 slides of SEC were sent to the University of Chicago and the diagnosis was confirmed by their pathologist (J.H.).

SEC characteristics

SEC lesions were further described: multifocal index SEC was defined as evidence of SEC in more than 1 segment of the colon at index colonoscopy. Follow-up SEC was defined as either SEC not present or SEC present in subsequent pathology specimens (designated as 0, 1, or >1 specimens with SEC). Lesions undergoing biopsy sampling were characterized as targeted or nontargeted based on endoscopic description. The presence or absence of microscopic active inflammation in the specimen demonstrating SEC was recorded from the pathology specimen containing SEC. Location concordance between the index SEC and synchronous or metachronous dysplasia was recorded. Location concordance was defined as dysplasia located in the same segment of colon as the index SEC. Because it was not possible to confirm that an area of dysplasia was located at the site of the index SEC, we defined “same segment” based on colonoscopic biopsy sample jar labeling.

Statistical analysis

Descriptive statistics were used to evaluate patient demographics, clinical characteristics, rate of dysplasia, and location concordance between SEC and dysplasia. Univariable logistic regression was performed to evaluate possible predictors of dysplasia, including age, family history of CRC or IBD, smoking status, primary sclerosing cholangitis diagnosis, disease extent and activity, and medication usage at the time of the index SEC. Five univariable analyses were performed, 1 with the entire cohort of patients (UC and CD) divided into “dysplasia” (including synchronous and metachronous dysplasia) or “no dysplasia,” 2 with only CD patients or only UC patients, and 3 using the entire cohort of patients (CD and UC) but dividing patients by presence of synchronous or metachronous dysplasia. Selection of predictors for adjustment in the multivariable model was based on a $P < .10$ in the univariable analyses and an a priori determination of relevant variables regardless of univariable P value. The number of follow-up colonoscopies was not included in the multivariable model because of collinearity with follow-up time. Because of possible minimization or recall bias in patients reporting smoking status, sensitivity analysis was performed without smoking status as a covariate. A $P < .05$ was considered to be statistically significant. Statistical analyses were performed using Stata 12.1 (StataCorp, College Station, Tex).

RESULTS

Search results

A search of the Johns Hopkins Pathology Data System for “serrated epithelial change” between the years 2000 and 2008 yielded 293 patients. Of these, 77 patients without a confirmed IBD diagnosis were excluded. Of the remaining 216 IBD patients, 29 patients

(13.4%) had prior dysplasia (6 CRC, 4 HGD, 19 LGD), leaving 187 patients who underwent primary analysis (Fig. 2). The prevalence of SEC in our IBD pathology specimens (biopsy sample or resection) was found to be 12 of 477 (2.5%) for the year 2004 and 14 of 455 (3.0%) for the year 2008.

Patient characteristics

Table 2 outlines the baseline characteristics of the 187 IBD patients with histologic findings of SEC without prior dysplasia. Ninety-eight patients (52%) had UC, 73 (39%) had CD, and 16 (9%) had IBDU. The mean duration of disease was 16 years. One hundred patients (53%) had extensive disease and 105 (56%) had moderate-to-severe gross endoscopic disease activity at the index SEC. Median endoscopic follow-up time was 28 months, and 112 patients (60%) had at least 1 follow-up pathology specimen (colonoscopy biopsy samples or surgical resection) after the index SEC.

SEC characteristics

In total, 247 discrete index SEC lesions were found in 187 patients, with 10.4% located in the ascending colon, 7.9% in the transverse colon, 37.1% in the left side of the colon, 37.8% in the rectum, and 6.8% unknown. Most were nontargeted, random biopsy samples of flat mucosa (73.4%); however, 22% were endoscopically visible lesions. There was no surrounding active microscopic inflammation in 55% of the SEC cases.

Synchronous and metachronous dysplasia

Fifteen of 187 patients (8.0%) had synchronous SEC and dysplasia. Of these, 13 patients had LGD (6 UC, 6 CD, 1 IBDU) and 2 had CRC (both of whom had UC and both of whom underwent surgical resections that were reviewed). Additionally, 3 patients with LGD (2 UC, 1 CD) developed HGD or CRC on further follow-up.

Of the 172 patients analyzed for metachronous dysplasia on follow-up, 60 patients had no follow-up pathology, leaving 112 patients for further analysis (Fig. 2). Twenty-four of 112 (21%) patients had *new* dysplasia on follow-up; 6 (5%) had HGD or CRC and 18 (16.1%) had LGD. Five of 6 patients with HGD or cancer had UC.

The median time from SEC to any metachronous dysplasia was 34 months, with a range of 4 to 101 months. The median time from SEC to metachronous HGD or cancer was 23.5 months, with a range of 4 to 108 months. One patient developed HGD 4 months after the finding of SEC; this most likely represents a missed synchronous lesion. However, all other dysplastic lesions were found 6 months after SEC was detected. Supplemental figure 1 (available online at www.giejournal.org) depicts a Kaplan-meier dysplasia free survival curve in SEC patients.

HGD and CRC

Eleven patients developed HGD or CRC during the study: 2 patients with synchronous SEC and CRC, 6 patients with metachronous HGD/CRC, and 3 patients with synchronous SEC and LGD who then developed HGD/CRC on follow-up. Most of the HGD/CRC specimens were colectomy specimens (9/11). Overall, 11 of 187 patients (6%) developed HGD or

cancer with a rate of 17 per 1000 patient-years. One patient developed appendiceal mucinous adenoma 45 months after index SEC; this patient was not included among the patients who developed metachronous dysplasia.

Location concordance

All 40 patients who had synchronous or metachronous dysplasia were evaluated for concordance between location of the index SEC and any dysplasia. There was location concordance of SEC and synchronous or metachronous dysplasia in 27 of 40 patients (68%). The location of the corresponding SEC and dysplasia was predominantly found in the sigmoid/descending colon (44%), with 22% in the transverse colon, 19% in the ascending colon, and 15% in the rectum.

Risk factors of dysplasia

Table 3 compares baseline characteristics between patients with SEC who developed dysplasia versus patients with SEC who did not develop dysplasia. Patients who developed dysplasia were older (53.4 vs 46.3 years, $P = .01$), male (74% vs 53%, $P = .02$), and had at least 1 follow-up SEC (53% vs 15%; $P = .001$). The patients with SEC and dysplasia had a later age at IBD onset (37 vs 30 years, $P = .01$), a longer median endoscopic follow-up time (55 vs 18 months, $P < .001$), and a greater median number of colonoscopies performed (4 vs 2, $P < .001$). The disease duration was similar between the 2 groups (17 vs 16 years, $P = .55$). No difference was found in the presence of prior indefinite dysplasia, multifocal SEC lesions, SEC acquisition (targeted vs nontargeted biopsy samples), surrounding active microscopic inflammation, or medication usage between the 2 groups. Subanalyses by UC or CD phenotypes were remarkable for the following: in the UC subgroup, the gender disparity favoring males for dysplasia was no longer evident; in the CD subgroup, SEC patients who developed dysplasia were not significantly older than those who did not develop dysplasia. All other variables had similar trends in both the UC and CD subgroups. Subanalyses by synchronous or metachronous dysplasia found no significant factors in the synchronous dysplasia group, but older age at IBD diagnosis and follow-up SEC were significant in the metachronous dysplasia group.

Multivariable analysis demonstrated several independent predictors of dysplasia: older age at IBD diagnosis (odds ratio, 1.06; 95% confidence interval, 1.01-1.10), male gender, family history of CRC (odds ratio, 6.48; 95% confidence interval, 1.31-31.97), and follow-up SEC (odds ratio, 1.43; 95% confidence interval, 1.06-1.94) (Table 4). A sensitivity analysis that did not consider smoking status as a covariate yielded similar findings, except gender was no longer significantly associated with dysplasia.

DISCUSSION

SEC is an emerging histologic finding whose clinical significance in the development of dysplasia in IBD patients is unclear. Our results suggest an association between SEC and dysplasia. Of all patients with SEC (216), 13% of patients had a prior history of dysplasia. Additionally, 21% of patients with SEC without a history of dysplasia had synchronous or metachronous dysplasia with a rate of 60 per 1000 patient-years. The development of

HGD/CRC was mostly specific to UC patients: 9 of 98 UC patients (9%) had synchronous or metachronous HGD or cancer. Only 1 case of HGD/CRC was seen in a CD patient and 1 in an IBDU patient. SEC lesions are not consistently recognized endoscopically, with only 22% seen on targeted biopsy sampling. Finally, there was a high concordance between the location of the SEC and the dysplasia.

SEC data currently available suggest an association with dysplasia. Kilgore et al,¹² in 2000, evaluated Crohn's patients with hyperplastic-like mucosal change, now known as SEC. Two groups of colectomy specimens were compared: 30 Crohn's colitis patients with associated adenocarcinoma and 30 without adenocarcinoma. They found that 33% of colectomy specimens with adenocarcinoma had SEC (both adjacent to and distant from the adenocarcinoma) compared with only 10% in the group without adenocarcinoma.

Recently, Johnson et al¹¹ found that IBD patients with SEC were more likely to have clinical risk factors for CRC such as primary sclerosing cholangitis, older age, and longer disease duration. Seven of 36 patients (19%) without prior or concomitant dysplasia who had at least 1 follow-up colonoscopy developed metachronous dysplasia compared with 3 of 76 patients (4%) in the IBD non-SEC group. The 1-year and 3-year dysplasia rates were not significantly different between the SEC and non-SEC group when controlling for confounding factors. The authors recognize they may have been underpowered to detect a difference.¹¹ Notably, our study found a similar rate of metachronous dysplasia (~20%) in patients with SEC.

In a separate abstract, Atwaibi et al¹⁴ demonstrated that IBD patients with "flat serrated change" (synonymous with SEC) had an increased risk of developing dysplasia compared with IBD patients without SEC (12.8% vs 4.3%). When adjusting for confounding variables, the presence of flat serrated change was not found to be an independent risk factor for dysplasia. This study may also have been underpowered to show an effect.

Our study has the largest number of IBD patients with a histologic finding of SEC: 187 patients compared with 79 in the Johnson study and 94 in Atwaibi study. The prevalence of SEC in our IBD population within 2 separate years was 2.5% in 2004 and 3.0% in 2008. Johnson et al had a lower prevalence of about 1%, and Atwaibi et al did not report a prevalence of SEC. All IBD pathology slides were interpreted by an expert GI-trained pathologist (E.M.) and reviewed in clinical conference for interobserver agreement.

Our results suggest an association between SEC and dysplasia in IBD patients. In our study patients with 1 or more follow-up SEC lesions after the initial, index SEC were more likely to develop dysplasia. Additionally, males, older patients, and later age at IBD diagnosis increased the likelihood of a dysplasia diagnosis. A multivariable analysis confirmed that the presence of 1 or more follow-up SEC lesions was independently associated with dysplasia.

Surprisingly, no statistical difference was noted in the disease duration at the time of index SEC between the dysplasia and no-dysplasia groups, although the duration was >15 years in both groups. Furthermore, no difference was seen in extent of disease or microscopic/macroscopic inflammation between groups. This may be explained by most of our patients having extensive as well as active disease. These findings do not rule out that SEC may be

associated with other known risk factors for IBD-associated dysplasia or may simply be a marker of longstanding inflammation. It is also possible that sporadic adenomas may have contributed to the high rate of LGD and the older age association with dysplasia.

SEC has been sparsely mentioned in the literature, perhaps because its significance has not been confirmed. Histologically, SEC has some features of hyperplastic polyps and therefore may be underreported. Endoscopically, it cannot yet be clearly delineated from hyperplastic or LGD lesions.

The association between SEC and dysplasia remains just that: a path of causality has not been delineated. However, there is some evidence of a unique genetic pathway that may exist for serrated lesions in IBD.¹⁷ In examining an array of neoplastic lesions in IBD, Bossard et al¹⁷ first described serrated lesions in this population. The serrated lesions in their study exhibited *BRAF* mutations with normal *KRAS* genes, which was specific to the serrated lesions and not found in surrounding inflammatory mucosa, conventional adenoma, or adenocarcinomas. The serrated lesions had *BRAF* mutations as early as the hyperplastic polyp stage and then progressed to microsatellite instability in the carcinoma stage. An earlier study confirmed that UC-related carcinomas had a lower rate of *KRAS* mutations than sporadic carcinomas (*BRAF* testing was not performed) and therefore concluded there may be another unrecognized pathway of dysplasia in IBD patients.¹⁸

The primary limitation of our study is the lack of a control group of IBD patients without SEC to compare the rates of dysplasia, thus limiting the evaluation of SEC as an independent predictor of dysplasia. The SEC patients who developed dysplasia had a longer follow-up time and a greater number of colonoscopies performed, thus pointing to the possibility of a detection bias. Many patients only had 1 pathology specimen in our system that may have caused a selection bias toward those more prone to develop dysplasia; this limits our ability to determine the risk of dysplasia in SEC patients. However, because of the novelty of SEC, we found these descriptive results to be important to create awareness and stimulate further research. This study was performed at a tertiary and surgical referral center with patients who have more complex and extensive disease, but these factors were controlled for in the multivariate analysis. Additionally, the indications for the colonoscopy were not necessarily for dysplasia surveillance because over half of the patients had moderate-to-severe disease activity (not necessarily at the site of the SEC or dysplasia). Patients with more severe disease are more likely to have subsequent colonoscopies and a greater number of biopsy samples obtained; this can introduce a selection bias. In terms of location concordance, SEC and dysplasia located in the same segment of colon was labeled as concordance, although we cannot be certain the dysplasia arose from the exact site of the prior SEC. Finally, as a retrospective study, there were incomplete data on some patients' demographics and medical history.

Future prospective studies are needed to compare IBD patients with and without SEC and quantify the risk of dysplasia between these 2 groups. In the last 5 years of our practice, we have been treating SEC findings as indefinite for dysplasia with heightened surveillance of every 6 to 12 months. Most colonoscopies included in this study were conducted using standard white light. Since then, high-definition endoscopes and/or chromoendoscopy are

more commonly used to better delineate the mucosal abnormalities. Confocal endomicroscopy is also emerging in the field of IBD. With these new technologies, SEC may be a visible change in the mucosa, not just a histologic diagnosis, which can be targeted for biopsy sampling.

In conclusion, the association between SEC and dysplasia needs to be studied further because the presence of SEC may change our surveillance protocols. The endoscopic recognition of SEC needs further evaluation with more advanced imaging techniques. In most cases location concordance exists between the SEC lesion and the area of dysplasia. SEC should be evaluated further as a potential precursor lesion for dysplasia in IBD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CD	Crohn's disease
CRC	colorectal cancer
HGD	high-grade dysplasia
IBD	inflammatory bowel disease
IBDU	inflammatory bowel disease undetermined
LGD	low-grade dysplasia
SEC	serrated epithelial change
UC	ulcerative colitis

Figure 1.

A, Endoscopic picture of SEC. **B,** Histologic picture of serrated epithelial change.

Figure 2.
Flowchart of patient inclusion. *IBD*, inflammatory bowel disease.

TABLE 1

Diagnostic criteria

Feature or diagnosis	SEC	HP	SSA	LGD	HGD
Surface maturation	+	+	+	-	-
Architecture	Distorted; some crypts do not reach muscularis mucosae	Intact; crypts are straight and reach muscularis mucosae	Distorted; crypts are "L," or inverted T" shapes at interface with muscularis mucosae and reach the muscularis mucosae	Intact to mild alteration	Intact to marked alteration [‡]
Cytology	Serrated epithelium at base and surface Goblet cell rich, not microvesicular, no gastric-like mucin, monolayer of nuclei	Serrated epithelium at surface not at base Monolayered bland nuclei at the base, more disorganized at surface Microvesicular cytoplasm, especially at surface	Serrated epithelium at base and surface Monolayered bland nuclei at the base, more disorganized at surface Gastric-like mucin prominent	Mild to moderate atypia with enlarged hyperchromatic nuclei	Marked atypia with enlarged nuclei and loss of nuclear polarity

SEC, serrated epithelial change; HP, Hyperplastic polyp; SSA, sessile serrated adenoma; LGD, low-grade dysplasia; HGD, highgrade dysplasia.

* Mild architectural alteration: Glandular crowding, some degree of loss of parallel crypt arrangement.

[‡]Marked architectural alteration: Very crowded glands, back-to-neck glands, fused or cribriform growth, dilated glands with luminal necrosis and/or zones of coagulative necrosis confined to mucosa.

TABLE 2

Patient characteristics of all 187 patients with SEC included in study

Key demographics	Value
Mean age at index SEC (SD)	48.4 (15.0)
Male gender	108 (57.8%)
White race	167 (89.3%)
Mean age at IBD diagnosis (SD)	31.5 (15.3)
Mean duration of IBD, y (SD)	16.0 (10.9)
Patients with >1 specimen	112 (59.9%)
Median follow-up time, mo (range)	28 (0-172)
Median number of endoscopes (range)	2 (0-18)
Pathology specimen	
Colonoscopy biopsy sample	175 (93.6%)
Surgery resection	12 (6.4%)
Diagnosis	
UC	98 (52.4%)
CD	73 (39.0%)
IBDU	16 (8.6%)
Smoking status	
Never	107 (57.2%)
Former	37 (19.8%)
Current	15 (8.0%)
Unknown	28 (15.0%)
PSC	12 (6.4%)
Diabetes	15 (8.0%)
Family history of IBD	31 (16.6%)
Family history of CRC (first degree)	19 (10.2%)
Multifocal SEC	38 (20.3%)
SEC morphology	

Key demographics	Value
Nontargeted biopsy specimen	134 (71.7%)
Targeted biopsy specimen	33 (17.6%)
Unknown	20 (10.7%)
Active microscopic inflammation	92 (49.2%)
Extensive disease *	100 (53.5%)
Endoscopic disease activity	
Inactive to mild	68 (36.4%)
Moderate to severe	105 (56.1%)
Unknown	14 (7.5%)
Medications at SEC	
Oral 5-ASA	128 (68.4%)
Rectal 5-ASA	27 (14.4%)
Steroids	52 (27.8%)
Immunomodulators	55 (29.4%)
Biologics	11 (5.9%)

SD, Standard deviation; *UC*, ulcerative colitis; *CD*, Crohn's disease; *IBDU*, inflammatory bowel disease undetermined; *PSC*, primary sclerosing cholangitis; *IBD*, inflammatory bowel disease; *CRC*, colorectal cancer; *SEC*, serrated epithelial change; *5-ASA*, 5-aminosalicylic acid.

* Extensive disease was defined as >50% colonic mucosa involvement.

TABLE 3

Univariable analysis of characteristics in SEC patients with and without dysplasia

	Dysplasia (n = 39)	No dysplasia (n = 148)	Odds ratio (95% CI)	P value
Median follow-up, mo (range)	55 (0-144)	18 (0-172)	1.01 (1.00-1.02)	<.01
Median number of colonoscopies (range)	4.0 (0-18)	2.0 (0-11)	1.36 (1.19-1.54)	<.01
Duration of IBD years (diagnosis of IBD to index SEC)	17.1 (10.6)	15.6 (11)	1.01 (.98-1.04)	.54
Mean age at IBD diagnosis	36.7 (18)	29.7 (14)	1.03 (1.01-1.06)	.01
Mean age at SEC diagnosis	53.4 (16)	46.3 (15)	1.03 (1.01-1.06)	<.01
Gender (% male)	29 (74%)	79 (53%)	2.53 (1.2-5.7)	.02
Race				
White	35 (90%)	132 (89%)	1.0	
Non-white	4 (10%)	16 (11%)	.9 (.3-3.0)	.92
Diagnosis				
UC	21 (54%)	77 (52%)	1.9 (.4-9.1)	.42
CD	16 (41%)	57 (39%)	2.0 (.4-9.6)	.40
IBDU	2 (5%)	14 (9%)	1.0	
Smoking status				
Current	3 (8%)	12 (8%)	.9 (.2-3.3)	.83
Prior	11 (28%)	26 (18%)	1.5 (.6-3.4)	.37
Unknown	1 (3%)	27 (18%)	.1 (.0-.1)	.04
Never	24 (62%)	83 (56%)	1.0	
PSC	5 (13%)	7 (5%)	3.0 (.9-9.9)	.08
Diabetes	3 (8%)	12 (8%)	.9 (.3-3.5)	.93
Family history of IBD	7 (18%)	24 (16%)	1.1 (.4-2.9)	.80
Family history of CRC (first degree)	7 (18%)	12 (8%)	2.5 (.9-6.8)	.08
Prior indefinite dysplasia	2 (5%)	6 (4%)	1.28 (.25-6.6)	.77
Multifocal SEC	11 (28%)	27 (18%)	1.8 (.8-4.0)	.17
Follow-up SEC				
0	19 (49%)	126 (85%)	1.0	

	Dysplasia (n = 39)	No dysplasia (n = 148)	Odds ratio (95% CI)	P value
1	7 (18%)	10 (7%)	4.6 (1.6-13.7)	<.01
2+	13 (33%)	12 (8%)	7.2 (2.8-18.0)	<.01
SEC morphology				
Nontargeted biopsy specimen	29 (74%)	105 (71%)	1.0	
Targeted biopsy specimen	5 (13%)	28 (19%)	.6 (.2-1.8)	.41
Unknown	5 (13%)	15 (10%)	1.2 (.4-3.4)	.80
Active microscopic inflammation	23 (59%)	69 (47%)	1.6 (.8-3.4)	.17
Extensive disease	21 (54%)	79 (53%)	1.02 (.5-2.1)	.96
Endoscopic disease activity				
Inactive to mild	12 (31%)	56 (38%)	1.0	
Moderate to severe	27 (69%)	78 (53%)	1.6 (.8-3.5)	.22
Unknown	0 (0%)	14 (10%)	.2 (.0-2.8)	.21
Medications at SEC				
Oral 5-ASA	30 (77%)	98 (66%)	1.7 (.7-3.9)	.20
Rectal 5-ASA	5 (13%)	22 (15%)	.8 (.3-2.4)	.75
Steroids	15 (38%)	37 (25%)	1.9 (.9-3.9)	.10
Immunomodulators	12 (31%)	43 (29%)	1.1 (.5-2.3)	.83
Biologics	3 (8%)	8 (5%)	1.5 (.4-5.8)	.59

CI, Confidence interval; *PSC*, primary sclerosing cholangitis; *5-ASA*, 5-aminosalicylic acid; *IBD*, inflammatory bowel disease; *SEC*, serrated epithelial change; *UC*, ulcerative colitis; *CD*, Crohn's disease; *IBDU*, inflammatory bowel disease undetermined; *CRC*, colorectal cancer.

TABLE 4

Multivariable analysis of predictors of dysplasia

	Odds ratio	95% Confidence interval	P value
Duration of IBD years (diagnosis of IBD to index SEC)	1.04	.98-1.10	.19
Follow-up time, mo	1.00	.98-1.01	.62
Older age at IBD diagnosis	1.06	1.01-1.10	.02
Male gender	3.86	1.15-12.94	.03
Race (white vs non-white)	3.06	.51-18.20	.22
IBD diagnosis (CD vs UC)	2.84	.82-9.88	.10
Smoking status			
Never smoker	Ref	–	–
Former smoker	1.44	.40-5.15	.57
Current smoker	.10	.01-1.42	.09
Family history of CRC	6.48	1.31-31.98	.02
Follow-up SEC	1.43	1.06-1.94	.02
Disease activity (inactive/mild vs moderate/severe)	.92	.30-2.78	.88

IBD, inflammatory bowel disease; *SEC*, serrated epithelial change; *CD*, Crohn's disease; *UC*, ulcerative colitis; *IBDU*, inflammatory bowel disease undetermined; *CRC*, colorectal cancer.