HHS Public Access

Author manuscript

Hum Pathol. Author manuscript; available in PMC 2023 April 19.

Published in final edited form as:

Hum Pathol. 2021 June ; 112: 9–19. doi:10.1016/j.humpath.2021.03.002.

Targeted next-generation sequencing supports serrated epithelial change as an early precursor to inflammatory bowel disease–associated colorectal neoplasia ☆

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Summary

Serrated epithelial change (SEC) manifests in patients with long-standing inflammatory bowel disease (IBD) and is characterized by disorganized crypt architecture, irregular serrations, and goblet cell–rich epithelium. The serrated nature of SEC is reminiscent of serrated colorectal polyps, which frequently harbor *KRAS*/*BRAF* mutations. SEC is, however, not only histologically distinct from sporadic serrated polyps but also associated with colorectal neoplasia. Whether SEC is a precursor to IBD-associated neoplasia remains unclear. To further define the relationship of SEC with serrated colorectal polyps and IBD-associated neoplasia, we performed targeted next-generation sequencing on colorectal specimens to include the following: SEC without dysplasia/neoplasia (n = 10), SEC with separate foci of associated dysplasia/adenocarcinoma from the same patients (n = 17), and uninvolved mucosa (n = 10) from 14 patients. In addition, we molecularly profiled sessile serrated lesion (SSL)–like or serrated lesion, not otherwise specified (SL-NOS), specimens, from 11 patients who also had IBD. This control cohort included SSL-like/SL-NOS without dysplasia/neoplasia (n = 11), SSL-like/SL-NOS with

☆Competing interests: A.D.S. has received an honorarium from Foundation Medicine, Inc. The remaining authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2021.03.002.

associated low-grade dysplasia (n = 2), and uninvolved mucosa (n = 8). By next-generation sequencing, the most frequently mutated gene in SEC without neoplasia and associated dysplasia/adenocarcinoma from separate foci in the same patients was *TP53*. Recurrent *TP53* mutations were present in 50% of SEC specimens without dysplasia/ neoplasia. In addition, alterations in *TP53* were detected at a prevalence of 71% in low-grade dysplasia, 83% in high-grade dysplasia, and 100% in adenocarcinoma. Paired sequencing of SEC and associated neoplasia revealed identical *TP53* missense mutations for 3 patients. In contrast, 91% of SSL-like/SL-NOS specimens without dysplasia/neoplasia harbored *KRAS /BRAF* mutations, which were conserved in associated low-grade dysplasia. No genomic alterations were found in uninvolved mucosa from either patients with SEC or patients with SSL-like/SL-NOS. Based on our findings, we conclude SEC is distinct from SSL-like serrated colorectal lesions in patients with IBD and an early precursor to IBD-associated neoplasia that warrants colonoscopic surveillance.

Keywords

Serrated dysplasia; Hyperplastic polyp; Sessile serrated adenoma/lesion; Crohn disease; Ulcerative colitis; Colon cancer

1. Introduction

Patients with inflammatory bowel disease (IBD) have an increased risk of developing colorectal adenocarcinoma [1,2]. Although the overall prevalence of colorectal adenocarcinoma in patients with IBD is only 3–5%, the cumulative risk of cancer increases with duration of disease [3]. Based on published studies, the incidence rates of IBD-associated colorectal adenocarcinoma range between 0.2% and 2.0% at 10 years, 1.4 and 8.0% at 20 years, and 3.1 and 18.0% at 30 years after diagnosis [4,5]. However, many of these studies were performed before the introduction of modern pharmacologic control of inflammation [6,7]. In addition, colonoscopic surveillance has resulted in increased detection of IBD-associated colorectal adenocarcinoma, but outcomes have improved with early diagnosis [8,9]. An estimated 15% of IBD-associated deaths are attributed to colorectal adenocarcinoma [3]. Consequently, current guidelines advocate surveillance colonoscopy to begin 8–10 years from disease onset and to continue surveillance within 1- to 5-year intervals thereafter [10,11]. The time interval of surveillance can be highly dependent on risk factors associated with the development of colorectal neoplasia in patients with IBD. These risk factors include extent of disease involvement, degree of histologic inflammation, the presence of a stricture, mucosal dysplasia, and a family history of colorectal adenocarcinoma in a first-degree relative.

Although dysplasia is a well-established risk factor for the development of colorectal adenocarcinoma in the setting of IBD, the diagnostic entity known as serrated epithelial change (SEC) has also been described as a potential risk factor for colorectal neoplasia in patients with IBD [12]. For decades, peculiar serrated proliferations adjoining IBD-associated colorectal adenocarcinoma have been described in the literature, thus raising the suspicion of SEC as a precursor lesion [13,14]. In fact, in a standardization study that attempted to codify the evaluation of dysplasia in patients with IBD, Riddell et al. [15]

noted the presence of unusual serrated lesions and introduced the concept that such lesions may be regarded as indefinite for dysplasia. SEC is detected in both the flat and nodular colonic mucosa and, microscopically, characterized by disorganized crypt architecture, irregular serrations, and a goblet cell–rich epithelium. In a report by Parian et al. [12], the authors found that 8% of patients with SEC had synchronous colorectal dysplasia or adenocarcinoma. Furthermore, 21% of patients with SEC and no history of colorectal neoplasia developed dysplasia or adenocarcinoma on follow-up. As acknowledged by the authors, a limitation of their study was the absence of a control group for patients with IBD and without SEC to compare rates of colorectal neoplasia. Another point of contention is whether SEC is analogous to sporadic serrated colorectal polyps and sessile serrated lesions (SSLs) that arise in patients with IBD [16]. However, based on macroscopic and microscopic findings, we believe that SEC is histologically distinct from conventional serrated colorectal polyps. Ko et al. [17] reported their experience with serrated colorectal polyps in patients with IBD and detected frequent alterations in *BRAF* and *KRAS*, which have been previously described in conventional serrated colorectal polyps. The authors concluded that these polyps in the absence of dysplasia did not confer an increased long-term risk of neoplastic progression as compared with control patients with no dysplasia at baseline. It is, however, plausible that these authors were studying a different lesion than the one that has been termed SEC.

To further characterize SEC and its relationship with colorectal neoplasia, we performed targeted next-generation sequencing of SEC diagnosed using strict criteria and/or neoplastic specimens from the same patients for genes commonly altered in both sporadic and IBD-associated colorectal adenocarcinoma. In addition, we molecularly evaluated SSL-like and serrated lesion, not otherwise specified (SL-NOS), in patients with IBD that morphologically overlapped with SEC, but did not exhibit all of the key histologic features that define SEC [18]. The sequencing results between SEC and SSL-like/SL-NOS were compared to determine if SEC truly represents a distinct pathologic entity or should be classified within the spectrum of serrated colorectal polyps.

2. Materials and methods

2.1. Study population

Study approval was obtained from Institutional Review Boards at Cedars-Sinai Medical Center, Johns Hopkins University, and the University of Pittsburgh (STUDY19110319). The anatomic pathology archives from the Departments of Pathology at Cedars-Sinai Medical Center, the Johns Hopkins Hospital, and the University of Pittsburgh Medical Center were queried for the diagnosis of SEC in patients with a history of IBD. Both colonoscopic biopsy and surgical resection specimens were included. Corresponding hematoxylin and eosin–stained slides were evaluated (by A.D.S., K.M.W., and E.A.M.) for histologic findings associated with SEC as previously described [12]. Histologically, SEC is recognized as colonic mucosa that is characterized by a distorted architecture. The crypts in SEC lose their orientation to the lumen and are neithers perpendicular to the muscularis mucosae nor necessarily reach the muscularis mucosae. The serrations in SEC are also irregular, but

present throughout the lesion. In addition, SEC is rich in goblet cells with enlarged goblet cells that extend to involve the bases of the crypts.

Fourteen patients with SEC were identified, and for a subset of these patients, available samples included an associated synchronous and/or metachronous low-grade dysplasia (n = 7), high-grade dysplasia (n = 6), and/or colorectal adenocarcinoma (n = 4). The corresponding formalin-fixed paraffin-embedded (FFPE) tissue blocks were retrieved for subsequent molecular analysis. In addition, 10 of the 14 patients had sufficient uninvolved colonic mucosa lacking SEC, dysplasia, or adenocarcinoma for further testing. Upon review for molecular analysis, the following number of specimens from 14 patients was sufficient for DNA microdissection: 10 uninvolved colonic mucosa specimens, 10 SEC specimens without dysplasia, 7 low-grade dysplasia specimens, 6 high-grade dysplasia specimens, and 4 colorectal adenocarcinoma specimens. The 4 colorectal adenocarcinoma cases were conventional in appearance without specific morphologic findings (eg, mucinous features, signet ring cells, and so on). As a control cohort, SSL-like/SL-NOS lesions from 11 patients with IBD were identified based on previously published criteria and chosen owing to their histologic overlap with SEC [18–22]. However, SSL-like/SL-NOS lesions lacked the full complement of all the aforementioned microscopic criteria and conventional dysplasia. Associated synchronous (n = 1) and metachronous (n = 1) low-grade dysplasia specimens were identified for 2 patients with SSL-like/SL-NOS. For 8 of 11 patients with SSL-like/SL-NOS lesions, uninvolved colonic mucosa was also available for further testing. The corresponding FFPE tissue blocks were obtained for molecular analysis and included the following specimens that were sufficient for DNA microdissection: 8 uninvolved colonic mucosa specimens, 11 SSL-like/SL-NOS specimens without dysplasia, and 2 low-grade dysplasia specimens. In addition, 35 surgical resection specimens of sporadic, primary colorectal adenocarcinomas were randomly selected from our surgical pathology archives to include juxtaposed uninvolved colonic mucosa. Both non-neoplastic and neoplastic tissues from these 35 surgical resections were also submitted for molecular analysis. For each patient, demographic data, clinical history, colonoscopic reports, and follow-up data were collected.

2.2. Targeted DNA next-generation sequencing

A total of 129 specimens were submitted for PancreaSeqV2 testing, an amplification-based targeted DNA next-generation sequencing panel (Supplementary Table 1) [23,24]. In brief, FFPE tissue was microdissected from 8.4-mm unstained histologic sections under stereomicroscopic visualization using an Olympus S=61 microscope (Olympus, Center Valley, PA). Genomic DNA was isolated using the DNeasy Blood and Tissue Kit on the automated QIAcube (Qiagen, Germantown, MD) instrument according to the manufacturer's instructions. Extracted DNA was quantitated on the Glomax Discover Fluorometer using the QuantiFluor ONE dsDNA system (Promega, Madison, WI). PancreaSeqV2 includes customized AmpliSeq primers for targeted regions within the following genes associated with gastrointestinal tract and hepatopancreatobiliary neoplasms: *AKT1*, *APC*, *BRAF*, *CTNNB1*, *GNAS*, *HRAS*, *IDH1*, *IDH2*, *KRAS*, *MEN1*, *MET*, *NF2*, *NRAS*, *PIK3CA*, *PTEN*, *RNF43*, *SMAD4*, *STK11*, *TERT*, *TP53*, *TSC2*, and *VHL*. Amplicons were bar-coded, ligated with specific adapters, and purified. DNA

library quantity and quality checks were performed using the 4200 TapeStation (Agilent Technologies, Santa Clara, CA). The Ion Chef was used to prepare and enrich templates and enable testing via Ion Sphere Particles on an Ion 540 semiconductor chip. Massive parallel sequencing was carried out on an Ion GeneStudio S5 System according to the manufacturer's instructions (Thermo Fisher Scientific, Carlsbad, CA, USA), and data were analyzed using Torrent Suite Software version 5.8 for point mutations, small insertions/deletions, and copy number alterations. Variant Explorer (UPMC) was used for variant annotation and interpretation. Each variant was prioritized as per the 2017 Association for Molecular Pathology /American Society of Clinical Oncology/ College of American Pathologist joint consensus guidelines for interpretation of sequence variants in cancer using a tier-based system [25]. Tier I, tier II, and tier III variants were reported; however, only tier I and tier II variants were used for subsequent analysis. The limit of detection of the assay was at 2% mutant allele frequency (AF). The minimum depth of coverage for testing was 1000×. For each mutation identified, an AF was calculated based on the number of reads of the mutant allele versus the wild-type allele and reported as percentage [24]. Copy number variation analysis was performed as previously described [26]. The total depth of sequencing coverage of each sequenced region was normalized by the normal controls and calculated per sequenced case. A decrease in sequencing coverage below established cutoffs with simultaneous presence of sequence variant at high AF was considered a copy number loss. In contrast, an increase in sequencing coverage above established cutoffs was interpreted as a copy number gain. A gene amplification was defined by the presence of ≥6 copies of a variant as previously described and validated using fluorescence in situ hybridization analysis [26,27].

3. Results

3.1. Patient study cohort

The clinical and pathologic features of 14 patients with SEC are summarized in Table 1. At the time of initial diagnosis of SEC, patients ranged in age from 24 to 85 years (mean, 54.6 years; median, 55.5 years) and were predominantly men (10 of 14, 71%). All patients had a history of colitis that included either ulcerative colitis (n = 10, 71%) or Crohn disease (n = 4, 29%). Data regarding duration of colitis were available for 13 of 14 (93%) patients. Except for 1 patient known to have colitis for only one month, the remaining patients had a history of colitis that ranged between 7 and 38 years (mean, 18.5 years; median, 15 years) in duration. The presence or absence of coexisting primary sclerosing cholangitis (PSC) was documented for 13 patients, with 1 patient remarkable for a history of PSC. By colonoscopy, SEC was identified within the colon and located within the transverse colon (n = 4), descending colon (n = 3), sigmoid colon (n = 3), rectosigmoid colon (n = 1), and rectum (n = 3).

Consistent with findings reported by Parian et al. [12], SEC arose in both the flat and nodular colonic mucosa. Microscopically, the colonic mucosa was characterized by a strikingly distorted architecture with crypts showing loss of orientation, such that they were no longer perpendicular to the muscularis mucosae (Fig. 1A). For a subset of cases, the crypts did not touch the muscularis mucosae and were separated by chronic

inflammation (Fig. 1B). Epithelial serrations were found at both the base and surface of the colonic mucosa. However, the serrations were irregular and not as prominent as those that characterize sessile serrated adenomas/SSLs and hyperplastic polyps. The colonic epithelium was also rich in goblet cells, which were enlarged and present throughout the mucosa (Fig. 1C). Cytoplasmic eosinophilia was seen, but nuclear atypia was absent. Other pathologic findings included neoplasia for 11 patients that consisted of low-grade dysplasia (n = 7, Fig. 1D), high-grade dysplasia (n = 6, Fig. 1E), and/or colorectal adenocarcinoma (n = 4, Fig. 1F). The dysplasia/neoplasia was detected close to the SEC in all 11 patients. Among the remaining three patients, one patient developed high-grade dysplasia upon follow-up colonoscopy.

As a control cohort, SSL-like/SL-NOS lesions, which had some morphologic overlap, but lacked the full complement of diagnostic features of SEC, were collected from 11 additional patients with IBD (Table 2). At initial diagnosis, patients with SSL-like/SL-NOS were 41–69 years in age (mean, 54.6 years; median, 59.0 years), and the majority were men (n = 9, 82%). Similar to patients with SEC, all patients with an SSL-like/SL-NOS had a history of IBD that included either ulcerative colitis (n = 9, 82%) or Crohn disease (n = 2, 18%). The duration of IBD ranged from 10 to 57 years (mean, 28.2 years; median, 25.0 years). Two (18%) patients also had a history of PSC. Except for 3 cases with lesions within the cecum (n = 1) and ascending colon (n = 2), the SSL-like/SL-NOS lesions were detected within the left colon and found in the sigmoid colon (n = 2) and rectum (n = 6).

By colonoscopy, SSL-like/SL-NOS lesions were described as either flat or nodular. Histologically, these lesions were reminiscent of SEC, but displayed notable differences in that they either resembled conventional serrated colorectal polyps or assumed a bulbous appearance. There was no architectural distortion for 5 cases. Three cases had a villous or bulbous architecture (Fig. 2A). While serrations were present in all 11 SSL-like/SL-NOS lesions, there was focal dilation at the base in 3 cases. In addition, another 3 cases exhibited serrations that were more prominent at the mucosal surface (Fig. 2B). A goblet cell–rich epithelium was present in 7 cases, but for 3 cases, there were fewer goblet cells and a higher proportion of absorptive cells (Fig. 2C). Adjacent low-grade dysplasia was identified in a single case of SSL-like/SL-NOS (Fig. 2D). Among the remaining 10 patients, one patient developed low-grade dysplasia upon follow-up colonoscopy.

3.2. Molecular analysis of SEC and SSL-like/SL-NOS without neoplasia

Among 14 patients with SEC, 10 specimens with SEC and no associated neoplasia were available for targeted next-generation sequencing (Fig. 3). Genomic alterations were identified in 5 of 10 (50%) cases, with *TP53* alterations identified in all 5 cases. The *TP53* alterations consisted of missense mutations (n = 4) and a nonsense mutation (n = 1). Mutant AFs for *TP53* varied between 2% and 39%. In addition, case 1 and case 2 harbored co-occurring missense mutations in *KRAS* with mutant AFs of 3% and 10%, respectively, as compared with *TP53* mutant AFs of 16% and 39%, respectively. Uninvolved colonic mucosa was available from the same patients for all 10 cases of SEC without neoplasia, and no genomic alterations were found by targeted next-generation sequencing.

In contrast to SEC, genomic alterations were detected in nearly all (10 of 11, 91%) cases of SSL-like/SL-NOS without dysplasia/neoplasia. The most frequently mutated gene was *KRAS* (n = 9) and consisted of missense mutations with mutant AFs of 4–44%. Two different *KRAS* missense mutations with similar mutant AFs were identified for case 22. In addition, case 23 harbored a missense mutation in *GNAS*, with a mutant AF equivalent to *KRAS*. Although case 24 was *KRAS* wild-type, a class 3 *BRAF* missense mutation was identified. For 8 SSL-like/SL-NOS cases, the surrounding uninvolved colonic mucosa was available for molecular testing, and no genomic alterations were found.

As a separate control cohort, genomic profiling was performed for 35 resected primary, sporadic colorectal adenocarcinomas (Supplementary Fig. 1). Detectable genomic alterations involved the following genes from the most to least prevalent: *TP53* (n = 24, 69%), *KRAS* (n = 22, 63%), *SMAD4* (n = 14, 40%), *BRAF* (n = 6, 17%), *PIK3CA* (n = 6, 17%), *PTEN* (n = 5, 14%), *NRAS* (n = 2, 6%), *RNF43* (n = 2, 6%), *CTNNB1* (n = 2, 6%), and *GNAS* (n = 1, 3%). Considering genes classified into the mitogen-activated protein kinase pathway, 30 of 35 (86%) cases harbored missense alterations in *KRAS*, *BRAF*, or *NRAS*. Of note, juxtaposed, non-neoplastic colonic mucosa was also evaluated and was negative for genomic alterations.

3.3. Molecular analysis of colorectal neoplasia found in patients with SEC and SSL-like/SL-NOS

Targeted next-generation sequencing was also performed for 17 colonic neoplastic specimens from 12 patients with SEC. These specimens consisted of 7 cases of low-grade dysplasia, 6 cases of high-grade dysplasia, and 4 cases of colorectal adenocarcinoma. Similar to SEC specimens without neoplasia, *TP53* alterations were the most frequent finding, with a prevalence of 71% in low-grade dysplasia (n = 5), 83% in high-grade dysplasia (n = 5), and 100% in colorectal adenocarcinoma (n = 4). Among the low-grade dysplastic cases, except for missense mutations in *TP53*, no additional genomic alterations were identified. Furthermore, two different *TP53* missense mutations were found for a single case (case 12). The mutant AFs for *TP53* ranged between 3% and 21%. In comparison, cases of high-grade dysplasia and colorectal adenocarcinoma were characterized by *TP53* missense mutations (n = 7) with mutant AFs of 23–70% and *TP53* deletions (n = 6). For 5 cases, both missense mutations and deletions in *TP53* were identified. Other genomic alterations included *RNF43* deletion (n = 4), *SMAD4* deletion (n = 4), and *PIK3CA* missense mutation (n = 2). Case 9 was the only specimen with high-grade dysplasia that lacked *TP53* mutations and harbored a *BRAF V600E* mutation.

A comparative analysis of matched SEC and neoplastic specimens from the same patient was able to be performed for 8 cases (Supplementary Fig. 2). For all 3 cases wherein the SEC without neoplasia had a *TP53* alteration, *TP53* missense mutations were identified within both SEC and colorectal neoplastic samples. These missense mutations in *TP53* were conserved between matched specimens. Of note, for case 1, *TP53* missense mutations were shared between SEC and high-grade dysplasia samples, but the missense mutations in low-grade dysplasia and adenocarcinoma were different. In addition, for case 6 and case 7, matched neoplastic specimens harbored identical *TP53* alterations. Only two patients with

SSL-like/SL-NOS lesions were found to have neoplasia, and both had low-grade dysplasia. A molecular analysis of case 15 and case 25 revealed *KRAS* missense mutations for both low-grade dysplastic samples. For case 15, a *TP53* missense mutation was also detected with a mutant AF of 6% as compared with a mutant AF of 35% for *KRAS*. Furthermore, the *KRAS* missense mutations in the matched SSL-like/SL-NOS and low-grade dysplasia for case 15 were identical.

4. Discussion

Next-generation sequencing has been an invaluable tool in defining the genomic basis of not only invasive carcinomas but also precursor lesions. Identifying key genomic alterations in precursor lesions and determining their relationship with carcinoma allows for improvements in early detection strategies, development of surveillance protocols, and potentially guides subsequent management. Herein, alterations in *TP53* were the most frequent genomic abnormality identified in patients with SEC. Furthermore, half of the tested SEC specimens without dysplasia or adenocarcinoma harbored *TP53* mutations. Alterations in *TP53* to include gene deletions were also detected in colorectal neoplasia, at a prevalence of 71% in low-grade dysplasia, 83% in high-grade dysplasia, and 100% in colorectal adenocarcinoma from patients with SEC. Furthermore, among 3 patients with SEC, paired analysis of SEC and colorectal dysplasia or adenocarcinoma revealed identical missense mutations in *TP53*. In comparison, no genomic alterations involving *TP53* or other genes within the targeted next-generation sequencing panel were identified in the uninvolved colonic mucosa.

TP53 mutations are a common finding in colorectal adenocarcinoma and play a pivotal role in tumor initiation, promotion, and progression [28]. However, depending on etiology, mutations in *TP53* can occur at different phases within the multistep progression model from normal colonic mucosa to carcinoma. For instance, in sporadic colorectal adenocarcinoma, *TP53* mutations are a late genomic event and are unusual in adenomatous precursor neoplasms [29,30]. Conversely, *TP53* mutations in IBD-associated colorectal adenocarcinoma are an early event and typically found in not only precancerous neoplasms but also the non-neoplastic colonic mucosa [31–33]. In fact, identical mutations in *TP53* were previously reported to be detected within matched non-neoplastic and dysplastic colorectal specimens from the same IBD patient, supporting the concept of *field cancerization* in the development of IBD-associated colorectal adenocarcinoma [32]. Field cancerization refers to one or more colonic crypts or fields of the colon that become genomically unstable and predisposed to subsequent neoplastic transformation [34–36]. Based on our findings, we suspect that SEC is the morphologic manifestation of a colonic *field* in patients with IBD, but has not been previously recognized by prior publications [32]. In this study, half of the SEC specimens without neoplasia harbored *TP53* mutations, and the prevalence of *TP53* alterations increased with the grade of dysplasia. Moreover, the identification of *TP53* missense mutations in SEC that are preserved in colorectal dysplasia and adenocarcinoma from the same patient indicates a clonal relationship between SEC and IBD-associated colorectal neoplasia.

In addition to *TP53* mutations, the molecular pathogenesis of IBD-associated colorectal adenocarcinoma involves the acquisition of copy number alterations [31,37,38]. Copy number alterations begin to accrue during the transition from low-grade dysplasia to high-grade dysplasia [31]. Interestingly, the overall burden of chromosomal losses and gains between high-grade dysplasia and adenocarcinoma is equivalent and suggests stabilization of an altered genome upon malignant transformation. Analogous sequencing results were seen among advanced neoplasia specimens from patients with SEC. In contrast to SEC without neoplasia and specimens with low-grade dysplasia, deletions in *TP53*, *RNF43*, and *SMAD4* were restricted to high-grade dysplasia and adenocarcinoma and had a similar prevalence for both neoplastic groups. Therefore, our findings would support that SEC is genetically related not only to IBD-associated colorectal neoplasia but also a precursor lesion that follows a similar molecular progression model as that reported for colorectal adenocarcinomas arising in patients with IBD.

Although the data presented here and prior clinical data support SEC as an IBD-associated precursor lesion, the differential diagnosis of serrated epithelium within SEC revolves around serrated colorectal polyps, especially hyperplastic polyps or sessile serrated adenomas/SSLs [39]. It is therefore understandable that many investigators have suggested that SEC should be categorized within the spectrum of sporadic serrated colorectal polyps but encountered within a background of IBD [16,18]. Serrated colorectal polyps that lack dysplasia are associated with a low risk of progression to carcinoma and, consequently, do not necessarily justify increased colonoscopic surveillance [17]. Hence, determining whether SEC as defined herein represents a discrete pathologic entity is clinically important and the impetus for this study. The macroscopic and microscopic features of SEC are distinct from those associated with serrated colorectal polyps. SEC is a subtle nodularity in the mucosa that is typically nonpolypoid, and although enhanced endoscopy techniques have improved the detection of SEC and other IBD-associated colorectal lesions, SEC may easily be overlooked by the unsuspecting gastroenterologist [12,39]. Histologically, SEC differs from serrated colorectal polyps on the basis of irregular serrations and different crypt architecture. Finally, the goblet cell–rich epithelium of SEC contrasts with most IBD-associated serrated colorectal polyps, which are often characterized by a microvesicular cytoplasm and indistinguishable from hyperplastic polyps [17,18].

Our genomic comparative analysis between serrated colorectal polyps and SEC further reinforces the dissimilarity between these two precursor lesions. Activating mutations in either *BRAF* or *KRAS* have been reported in 83% of serrated colorectal polyps without neoplasia [17]. In comparison, only 20% of SEC specimens without neoplasia in our series harbored a *KRAS* mutation. However, the AFs for mutant *KRAS* were appreciably lower than those for mutant *TP53*. Thus, it is plausible that the *KRAS* mutation within these two specimens is derived not from SEC, but another adjoining nonpolypoid to nodular precursor lesion, such as an SSL-like/SL-NOS. SSL-like/SL-NOS lesions within our cohort had overlapping morphologic features with SEC, but did not fulfill all three histologic requirements associated with SEC: disorganized crypt architecture, irregular serrations, and a goblet cell–rich epithelium. The premise that SEC specimens without neoplasia within this study are distinct from SSL-like/SL-NOS specimens is supported by the lack of *KRAS* mutations among SEC-associated neoplastic specimens. In addition, 91% of SSL-

like/SL-NOS specimens without neoplasia harbored recurrent mutations in *KRAS* or *BRAF*. Considering the genomic similarities between SSL-like/SL-NOS and serrated colorectal polyps, these IBD-associated precursors are likely one and the same and differ from SEC defined by using strict morphologic criteria. Similarly, traditional serrated adenoma–like lesions have also been reported in patients with IBD and are presumably analogous to their sporadic counterparts [18,40].

Although our data highlight the distinctive nature of SEC as a precursor lesion to IBD-associated colorectal adenocarcinoma, appropriate clinical surveillance and management for patients with SEC remains unclear. Some investigators have chosen to manage SEC as equivalent to IBD-associated lesions that are classified as *indefinite for dysplasia*. In simplistic terms, the diagnosis of indefinite for dysplasia includes all mucosal changes for which it is not possible to determine whether the alterations are inflammatory/regenerative or constitute genuine neoplastic lesions. Interestingly, recent outcome studies on patients with long-standing IBD after surveillance for indefinite for dysplasia have shown a clinical course that is superimposable on that for patients with IBD and low-grade dysplasia [41,42]. Based on follow-up data reported by Parian et al. [12], albeit imperfect, SEC would appear to merit intensified colonoscopic surveillance. The 2015 SCENIC consensus statement (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) recommends endoscopic removal of all visible polypoid lesions rather than definitive treatment by colectomy, and this would seem reasonable for visible SEC [11]. However, considering the likelihood of progression of isolated SEC without dysplasia/neoplasia remains unclear, it is difficult to suggest surveillance intervals based on available data, but as noted previously, the identification of SEC would seem to merit a closer follow-up interval than nondysplastic colonic mucosa alone.

It is worth noting that there are a few limitations to our study. It is retrospective in design, and although it represents the largest series of SEC, associated dysplasia, and uninvolved colonic mucosa to be molecularly evaluated, the patient cohort size was relatively small. Furthermore, targeted next-generation sequencing was limited to known genes frequently associated with gastrointestinal tract and hepatopancreatobiliary malignancies, and a complete assessment of the entire genome of SEC and the corresponding neoplasia was not performed [24,43]. However, whole-genome sequencing and whole-exome sequencing studies can be challenging with mucosal biopsies owing to limited amounts of lesional DNA and contaminating normal DNA. The minimum depth of coverage for these sequencing methodologies can vary, with a median range of 30× to 150× [44]. Therefore, the detection of genomic mutations with a low mutant AF and copy number alterations by whole-genome sequencing and whole-exome sequencing is unlikely. In comparison, the minimum depth of coverage for targeted next-generation sequencing performed herein was at least 1000× for each genomic region. Another limitation of this study is the lack of an orthogonal method to confirm genomic alterations, such as those involving *TP53* or *APC/CTNNB1*. Previous reports have found immunohistochemistry for p53 to be a reasonable surrogate for *TP53* mutational analysis in colorectal neoplasia. But, equivocal staining patterns for p53 can occur and are not infrequent [45]. In addition, considering the low *TP53* mutant AFs detected in SEC, these alterations are likely to be subclonal, and thus, p53

immunohistochemistry is expected to be inconclusive. Owing to scant nature of SEC and, in most cases, associated dysplasia, the corresponding tissue sections were exhausted in obtaining sufficient DNA for mutational analysis. Thus, we were unable to perform tandem p53 immunolabeling in the studied cases, but in our anecdotal experience, no aberrant expression for p53 has been detected. Interestingly, Galandiuk et al. [32] found the presence of *TP53* alterations in patients with Crohn disease did not correlate with aberrant nuclear accumulation of p53. Regardless, the targeted next-generation sequencing panel used within the study has been previously published and both internally and externally validated for gastrointestinal and pancreatobiliary neoplasms [24]. Finally, while SEC is not only grossly, microscopically, and molecularly distinct from SSL-like/SL-NOS lesions found in patients with IBD, the relationship between SEC and other forms of nonconventional dysplasia, such as hypermucinous dysplasia, terminal epithelial differentiation/crypt cell dysplasia (TED/CCD), and serrated dysplasia, remains to be determined [18]. Nevertheless, p53 appears to play a major role in the development of hypermucinous dysplasia and TED/CCD, whereas both p53 and β-catenin have been implicated in serrated dysplasia [46].

5. Conclusion

In summary, the presence of recurrent *TP53* alterations and the progressive accumulation of not only mutations but also gene deletions in *TP53* strongly supports SEC as a precursor lesion to IBD-associated colorectal adenocarcinoma. Consequently, based on our findings and those of Parian et al. [12], the identification of SEC warrants intensified colonoscopic surveillance for patients with long-standing IBD. However, considering the serrated nature of these lesions, SEC can be easily mistaken for hyperplastic polyps and sessile serrated adenomas, but SEC is both histologically and molecularly distinct from sporadic serrated colorectal polyps. It is therefore important for the practicing pathologist to recognize the key microscopic findings of SEC and differentiate these lesions from conventional serrated polyps occurring in the background of IBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Mrs. Kate Smith for outstanding administrative assistance.

Funding/Support:

This study was supported in part by the Pittsburgh Liver Research Center (NIH/NIDDK P30DK120531) at the University of Pittsburgh (to A.D.S.).

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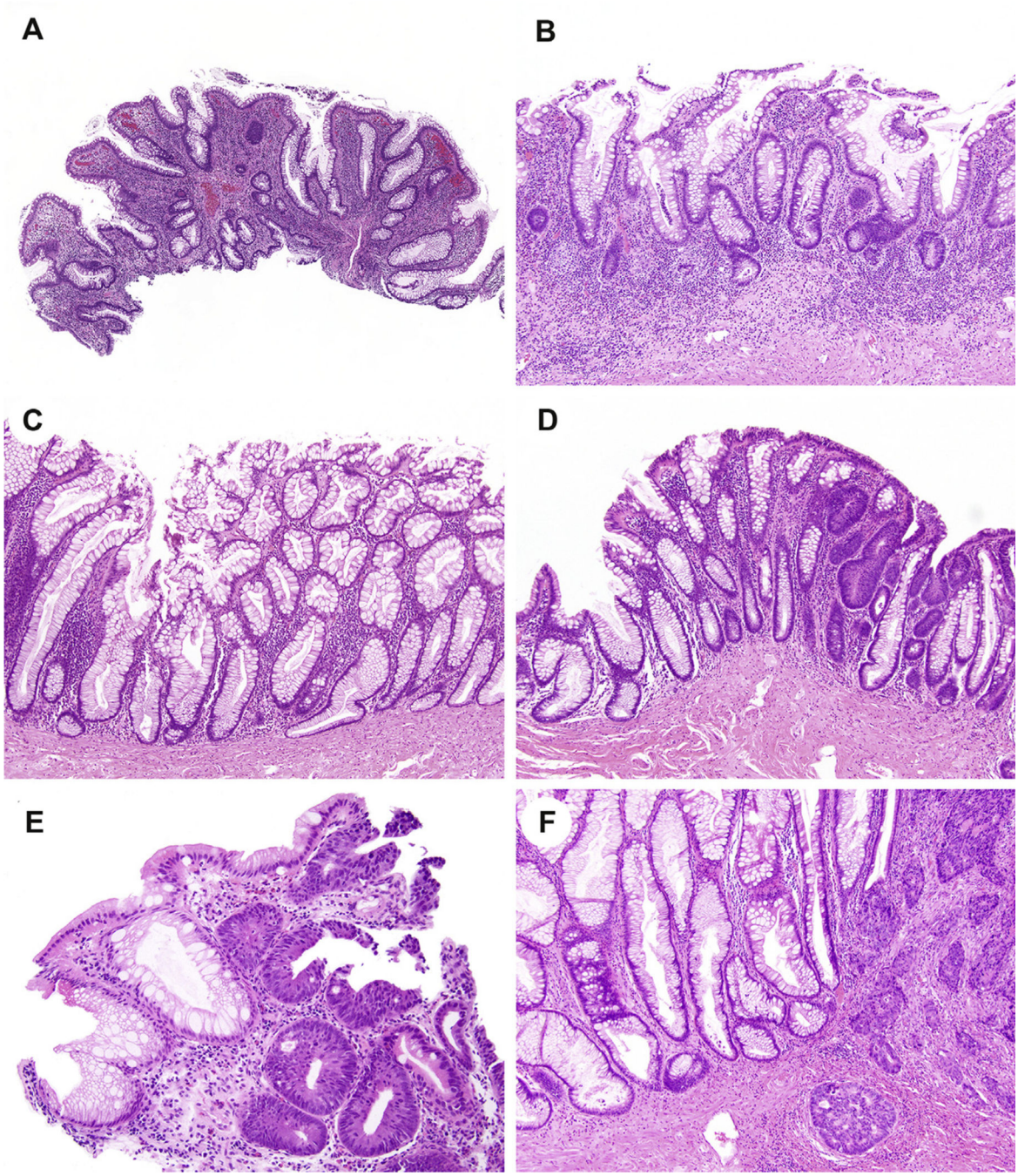

Fig. 1.

Serrated epithelial change (SEC) is microscopically characterized by a strikingly distorted architecture with crypts exhibiting loss of orientation and loss of their perpendicular arrangement to the muscularis mucosae (A). For a subset of cases, the crypts of SEC do not touch the muscularis mucosae and are separated by a layer of chronic inflammation (B). In addition, the serrated epithelium is present throughout the lesion, but irregular, unlike sessile serrated adenomas/lesions and hyperplastic polyps, and is rich in goblet cells. In this particular example, a *boot-shaped* crypt akin to sessile serrated adenomas/lesions

is present but differs by exhibiting subtle serrated and other cytologic differences (C). Additional pathologic findings seen in association with SEC include low-grade dysplasia (D), high-grade dysplasia (E), and invasive adenocarcinoma (F).

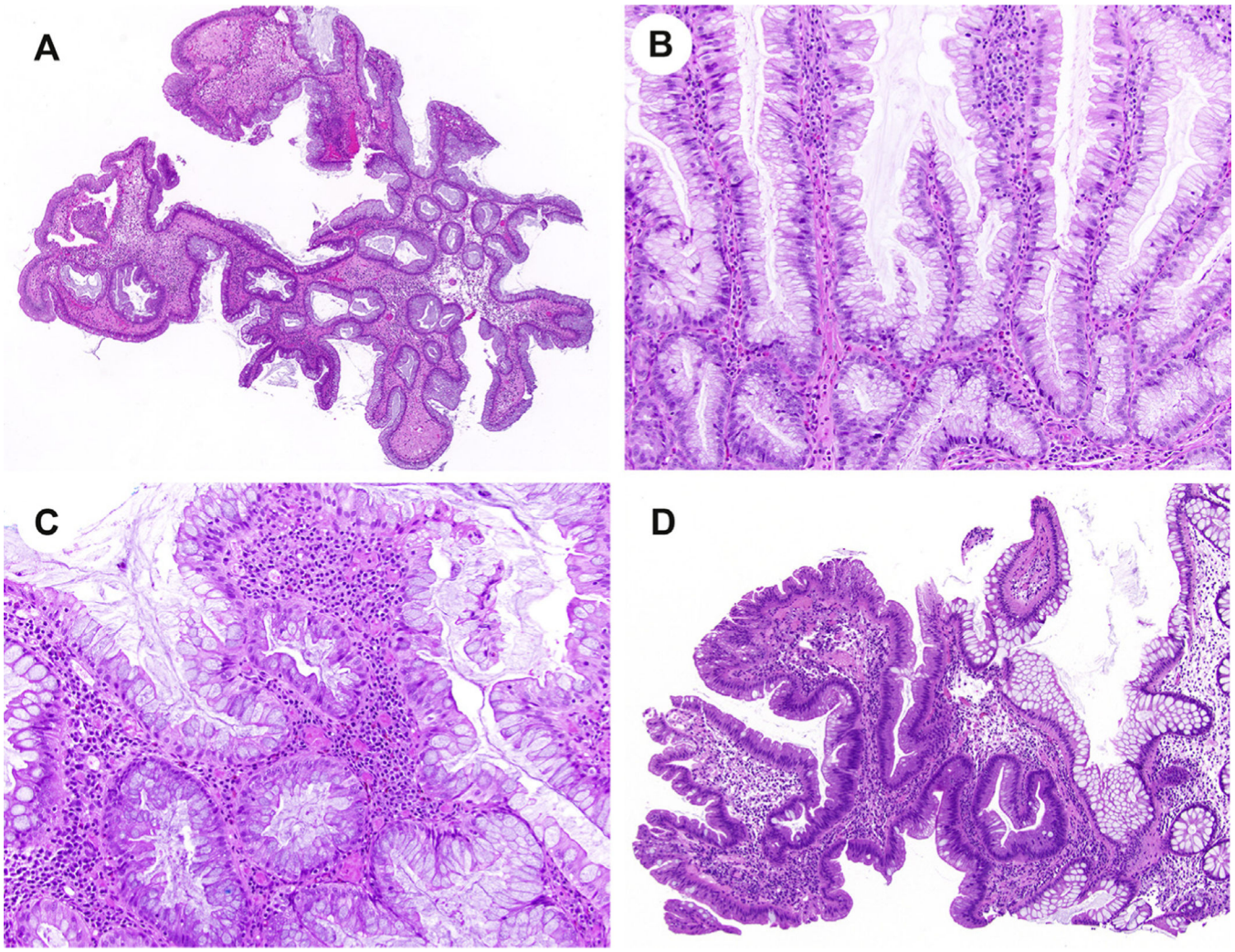

Fig. 2.

Sessile serrated lesion (SSL)–like and serrated lesion, not otherwise specified (SL-NOS), lesions can mimic an SEC owing to their serrated histologic findings. However, SSL-like/SL-NOS lesions show notable differences and do not exhibit all SEC-associated microscopic features. In contrast to SEC, SSL-like/SL-NOS can be villous or bullous in architecture (A) and exhibit serrations that are more prominent at either the mucosal surface (B) or base than throughout the lesion. In addition, a goblet cell–rich epithelium is typically absent in SSL-like/SL-NOS (C), but adjacent low-grade dysplasia can be seen in association (D). SEC, serrated epithelial change.

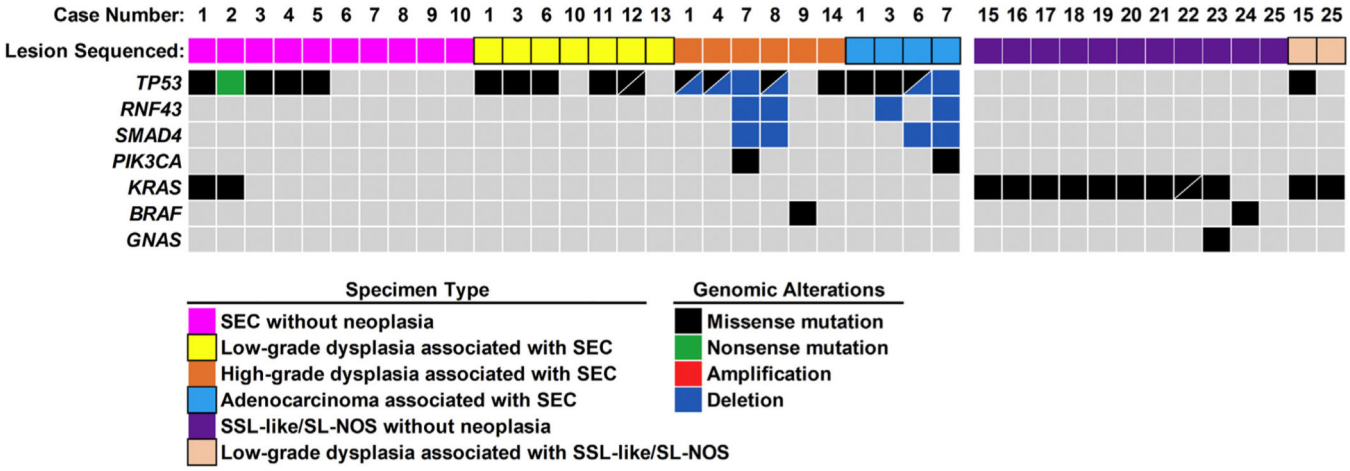

Fig. 3.

Summary of detected genomic alterations in SEC, SSL-like/SL-NOS, and associated dysplasia. The most prevalent genomic alterations in SEC and associated dysplasia occurred in *TP53*, whereas SSL-like/SL-NOS and associated dysplasia predominantly harbored *KRAS* missense mutations. SEC, serrated epithelial change; SSL, sessile serrated lesion; SL-NOS, serrated lesion, not otherwise specified.

Table 1

The clinicopathological features of 14 patients with serrated epithelial change (SEC).

Case number	Gender	Age (years) at presentation	Type of colitis	Duration of colitis	Location of serrated epithelial change	Synchronous or metachronous neoplasia	Type(s) of associated neoplasia[a]
1	M	28	Ulcerative colitis	7 years	Transverse colon	Synchronous	LGD, HGD, AdenoCA, and metastatic AdenoCA
2	M	42	Ulcerative colitis	14 years	Descending colon	No	N/A
3	F	85	Ulcerative colitis	10 years	Descending colon	Synchronous	LGD and AdenoCA
4	F	53	Crohn disease	30 years	Rectosigmoid colon	Metachronous	HGD
5	M	49	Crohn disease	20 years	Sigmoid colon	No	N/A
6	F	59	Crohn disease	38 years	Rectum	Synchronous	LGD, HGD, and AdenoCA
7	M	58	Ulcerative colitis	17 years	Rectum	Synchronous	HGD and AdenoCA
8	M	53	Ulcerative colitis	15 years	Descending colon	Synchronous	HGD
9	F	68	Ulcerative colitis	15 years	Transverse colon	Synchronous	HGD
10	M	24	Crohn disease	1 month	Transverse colon	Synchronous	LGD
11	M	65	Ulcerative colitis	30 years	Transverse colon	Synchronous	LGD
12	M	79	Ulcerative colitis	Unknown	Sigmoid colon	Synchronous	LGD
13	M	42	Ulcerative colitis	14 years	Distal sigmoid colon	Synchronous	LGD
14	M	59	Ulcerative colitis	13 years	Rectum	Synchronous	HGD

Abbreviations: AdenoCA, adenocarcinoma; F, female; HGD, high-grade dysplasia; LGD, low-grade dysplasia; M, male; N/A, not applicable.

[a]Neoplasia found in association with SEC.

Table 2

Clinicopathological features of 11 patients with a sessile serrated lesion (SSL)–like and serrated lesion, not otherwise specified (SL-NOS).

Case number	Gender	Age (years) at presentation	Type of colitis	Duration of colitis	Location of the serrated epithelial lesion	Synchronous or metachronous neoplasia	Type(s) of associated neoplasia[a]
15	M	65	Ulcerative colitis	57 years	Rectum	Synchronous	LGD
16	M	61	Ulcerative colitis	42 years	Sigmoid colon	No	N/A
17	M	61	Ulcerative colitis	42 years	Cecum	No	N/A
18	M	59	Ulcerative colitis	25 years	Rectum	No	N/A
19	F	47	Crohn disease	23 years	Ascending colon	No	N/A
20	M	46	Ulcerative colitis	14 years	Rectum	No	N/A
21	M	69	Ulcerative colitis	29 years	Rectum	No	N/A
22	F	46	Ulcerative colitis	33 years	Rectum	No	N/A
23	M	64	Ulcerative colitis	16 years	Rectum	No	N/A
24	M	42	Crohn disease	10 years	Ascending colon	No	N/A
25	M	41	Ulcerative colitis	19 years	Sigmoid colon	Metachronous	LGD

Abbreviations: F, female; LGD, low-grade dysplasia; M, male; N/A, not applicable.

[a]Neoplasia found in association with SSL-like/SL-NOS.