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ARTICLE

Nonconventional dysplasia in patients with inflammatory bowel disease and colorectal carcinoma: a multicenter clinicopathologic study

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Abstract

Several types of nonconventional dysplasia have been recently described in inflammatory bowel disease (IBD). However, strict morphologic criteria are lacking, and their clinicopathologic features (including potential association with conventional dysplasia and/or colorectal cancer [CRC]) are poorly understood. A total of 106 dysplastic or serrated lesions in 58 IBD patients with CRC were retrospectively identified from five institutions. Thirty-six cases of nonconventional dysplasia were identified in 26 (45%) of the 58 patients and occurred with similar frequency in men and women (58% and 42%, respectively), with a mean age of 54 years (range: 24–73) and a long history of IBD (mean: 17 years, range: 2–43). Six morphologic patterns were recognized. Hypermucinous dysplasia ($n = 15$; 42%) presented as either a 'pure type' ($n = 5$; 14%) or a 'mixed type' with either conventional or another nonconventional subtype ($n = 10$; 28%). Serrated lesions, as a group, were equally common ($n = 15$; 42%) and included three variants: traditional serrated adenoma-like ($n = 10$; 28%), sessile serrated lesion-like ($n = 1$; 3%), and serrated lesion, not otherwise specified ($n = 4$; 11%). Dysplastic lesions with increased Paneth cell differentiation ($n = 4$; 11%) and goblet cell deficient dysplasia ($n = 2$; 6%) were rare. Twelve (46%) of the 26 patients had only nonconventional dysplasia, whereas the remaining 14 patients (54%) had both nonconventional and conventional dysplasias. Nonconventional dysplasia was most often graded as low-grade dysplasia (81%), which was less common in conventional dysplasia (37%) ($p = 0.003$). When present alone, nonconventional dysplasia was predominantly found in the left colon (81%, $p = 0.006$) as a polypoid or raised lesion (75%, $p < 0.001$) compared with when it occurred simultaneously with conventional dysplasia (35% and 50%, respectively). When both nonconventional and conventional dysplasias occurred simultaneously, they were found in the same colonic segment in all but 3 patients (79%). Nonconventional dysplasia was also commonly detected in the same colonic segment as CRC or immediately adjacent to the CRC at a rate (85%) similar to conventional dysplasia (96%). CRC occurring in patients with only nonconventional dysplasia was more likely to be high-grade (poorly differentiated; 36%) than CRC that occurred in association with conventional dysplasia (10%) ($p = 0.026$). In conclusion, nonconventional dysplasia is common in IBD patients with CRC. It appears to develop in the same field of carcinomatous development, and it is not uncommonly associated with conventional dysplasia.

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Introduction

Patients with inflammatory bowel disease (IBD) are at high risk for developing dysplasia and colorectal cancer (CRC) [1–5]. The early detection and treatment of dysplasia forms the main strategy to reduce mortality from CRC in IBD patients [6–9]. Since 1983, the grading system proposed by Riddell and associates for IBD-related dysplasia has been widely used to guide management of patients with dysplasia [10]. In this system, dysplasia is graded as either low-grade (LGD) or high-grade dysplasia (HGD) based on the degree of cytologic and/or architectural atypia. LGD is defined as having mild to moderate cytologic atypia with limited architectural changes, whereas HGD demonstrates more severe cytologic and/or architectural changes. Recently, SCENIC guidelines emphasize another feature of dysplasia, namely whether it is endoscopically visible or invisible [11]. Although visible (polypoid or raised) dysplasia can be managed with endoscopic resection [12–15], invisible (flat) dysplasia may necessitate colectomy [16–20].

Most of the literature on dysplasia refers to conventional (or intestinal type) dysplasia, the most well-recognized form of dysplasia. However, other patterns of dysplasia can occur (albeit mostly described in abstract form), and these are referred to as nonconventional dysplasia, of which hypermucinous dysplasia has received the most attention [21–23]. Nonconventional dysplasia includes at least six subtypes, including (1) hypermucinous; (2) goblet cell deficient (GCD); (3) terminal epithelial differentiation (TED; also known as crypt cell dysplasia [CCD]); (4) traditional serrated adenoma (TSA)-like; (5) sessile serrated lesion (SSL)-like; and (6) serrated lesion, not otherwise specified (NOS). As in conventional dysplasia, p53 appears to play a major role in the development of hypermucinous dysplasia and TED/CCD, whereas combined alterations of p53 and β-catenin are common in serrated lesions [22]. It is worth noting that TED/CCD shares similar morphologic features with the recently described "crypt cell atypia (CCA)", except that dysplastic cells should not involve the mucosal surface in CCA [24]. CCA has been defined as having mild enlargement and hyperchromasia of slightly irregular, but mostly non-stratified nuclei limited to the crypt base without surface involvement.

A good level of diagnostic agreement among gastrointestinal (GI) pathologists has been reported in the categorization of nonconventional dysplasia, with the highest agreement for GCD (92% agreement); intermediate for hypermucinous, SSL-like, and TED/CCD (≥60% agreement); and lowest for TSA-like (<50% agreement) [21]. However, strict morphologic criteria are lacking, and the clinicopathologic features of nonconventional dysplasia, including potential association with conventional dysplasia and/or CRC, are poorly understood. Thus, we aimed to further define the morphologic features of nonconventional dysplasia in a cohort of IBD patients with CRC, and to determine the clinicopathologic characteristics of these patterns, including their association with conventional dysplasia and/or CRC.

Materials and methods

Patients and data collection

Fifty-eight patients with IBD-related CRC were identified from five institutions (Table 1). Six of the co-authors

Table 1 Characteristics of IBD patients with CRC

	Entire cohort ($n = 58$ patients)
Mean age, years (range)	55 (24–80)
Gender (%)	37 males (64%)
Ethnicity (%)	52 Caucasians (90%)
Type of IBD (%)	
Ulcerative colitis	41 (71%)
Crohn's disease	15 (26%)
Indeterminate	2 (3%)
IBD duration, years (range)	17 (0–53)
PSC (%)	4 yes (7%)
	Characteristics of CRC ($n = 73$, 58 patients)
Mean size, cm (range)	3.4 (0.1–10)
Degree of differentiation (%)	
Low-grade	63 (86%)
High-grade	10 (14%)
Depth of invasion (%)	
Intramucosal (pTis)	6 (8%)
Submucosa (pT1)	13 (18%)
Muscularis propria (pT2)	18 (25%)
Subserosa (pT3)	32 (44%)
Serosa (pT4)	4 (5%)
Lymphovascular invasion (%)	17 yes (23%)
Lymph node metastasis (%)	25 yes (34%)
Location of CRC (%)	
Left colon	39 (53%)
Transverse colon	13 (18%)
Right colon	21 (29%)
Multifocal CRC (%)	12 patients (21%)
Histologic subtype of CRC (%)	
Tubuloglandular	2 (3%)
Mucinous features	30 (41%)
Signet-ring cell features	5 (7%)
Both mucinous and signet-ring cell features	2 (3%)

retrospectively reviewed all available preoperative biopsies and CRC resection specimens to identify dysplastic or serrated lesions from their cohort and subtyped them as: conventional or nonconventional dysplasia. Conventional dysplasia included tubular adenoma (TA)-like, tubulovillous adenoma (TVA)-like, and villous adenoma (VA)-like. Nonconventional dysplasia included hypermucinous, GCD, dysplasia with increased Paneth cell differentiation (DPD), TSA-like, SSL-like, and serrated lesion NOS (Table 2). Notably, we did not find obvious cases of TED/CCD in our cohort. Detailed histologic descriptions of nonconventional subtypes with illustrative pictures were provided to each GI pathologist prior to the classification. The participating pathologists submitted representative images of their nonconventional dysplastic cases to one GI pathologist (WTC) to ensure uniform classification of nonconventional subtype.

Hypermucinous dysplasia was defined as a tubulovillous/villous lesion with prominent mucinous differentiation representing >50% of the lesion (Fig. 1). DPD was coined to describe lesions showing a tubular growth of dysplastic crypts lined by mostly elongated, hyperchromatic nuclei and, in some cases, reduced goblet cells; however, while goblet cells may be reduced, they are not absent or nearly absent. Increased Paneth cell differentiation (beyond what is present in background mucosa) was always present and involved at least two contiguous crypts in two different foci (Fig. 2a, b). GCD dysplasia also showed a tubular growth of dysplastic crypts but was characterized by a complete or near-complete absence of goblet cells (Fig. 2c, d). In GCD dysplasia, scattered Paneth cells may be present in the lesion and in adjacent mucosa, but not in multiple clusters of dysplastic crypts as seen in DPD. To distinguish from metaplastic or reactive changes, unequivocal histologic evidence of dysplasia (i.e., lack of surface maturation and/or severe cytologic/architectural atypia) needed to be present in DPD and GCD dysplasia. Serrated lesions were subclassified into TSA-like, SSL-like, or

Table 2 Characteristics of dysplasia occurring in patients with only nonconventional dysplasia (NCD), only conventional dysplasia (CD), or both

	NCD only ($n = 16$, 12 patients)	CD only ($n = 51$, 32 patients)	Both NCD ($n = 20$) and CD ($n = 19$) (14 patients)	P values
Mean age, years (range)	54 (38–72)	57 (34–80)	55 (24–73)	0.531
Gender (%)	8 males (67%)	22 males (69%)	7 males (50%)	0.464
Ethnicity (%)	10 Caucasians (83%)	28 Caucasians (88%)	14 Caucasians (100%)	–
Type of IBD (%)	8 ulcerative colitis (67%)	23 ulcerative colitis (72%)	11 ulcerative colitis (79%)	0.791
IBD duration, years (range)	20 (10–38)	17 (0–53)	15 (2–43)	0.065
PSC (%)	2 yes (17%)	2 yes (6%)	0 yes (0%)	–
Multifocal dysplasia (%)	2 patients (17%)	13 patients (41%)	0 patients (0%)	–
Type of dysplasia (%)				–
Nonconventional dysplasia				
Hypermucinous	7 (44%)		8 (21%)	
DPD	3 (19%)		1 (3%)	
GCD	0 (0%)		2 (5%)	
TSA-like	3 (19%)		7 (18%)	
SSL-like	1 (6%)		0 (0%)	
Serrated lesion NOS	2 (13%)		2 (5%)	
Conventional dysplasia				
TA-like		37 (73%)	14 (36%)	
TVA-like		12 (24%)	4 (10%)	
VA-like		2 (4%)	1 (3%)	
Grade of dysplasia (%)	14 LGD (88%)	20 LGD (39%)	21 LGD (54%)	0.003
Location of dysplasia (%)				0.006
Left colon	13 (81%)	30 (59%)	14 (36%)	
Transverse colon	0 (0%)	8 (16%)	9 (23%)	
Right colon	2 (13%)	13 (25%)	15 (38%)	
Entire colon	0 (0%)	0 (0%)	1 (3%)	
Unknown	1 (6%)	0 (0%)	0 (0%)	
Endoscopic appearance (%)	12 polypoid/raised (75%)	46 polypoid/raised (90%)	18 polypoid/raised (46%)	< 0.001

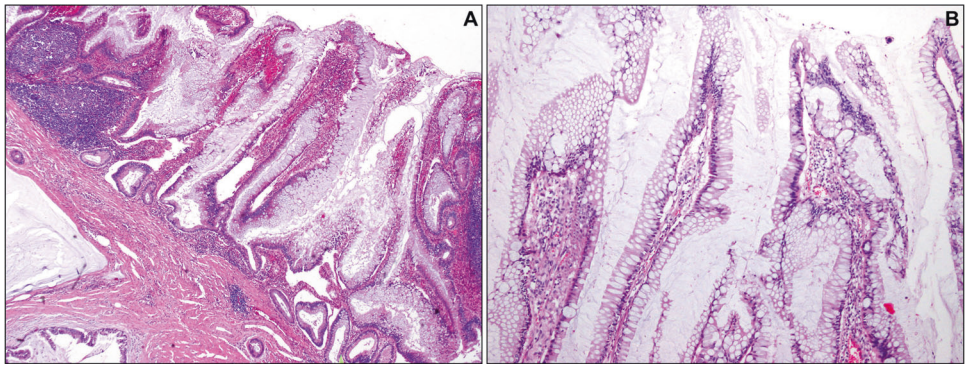

Fig. 1 Hypermucinous dysplasia. a Low- (H&E, 10×) and **b** medium-power views (H&E, 20×) of hypermucinous dysplasia. It shows a tubulovillous/villous architecture with mild nuclear atypia and prominent mucinous differentiation. The degree of atypia seems to decrease towards the surface of the villi. CRC with mucinous features is present in Part A

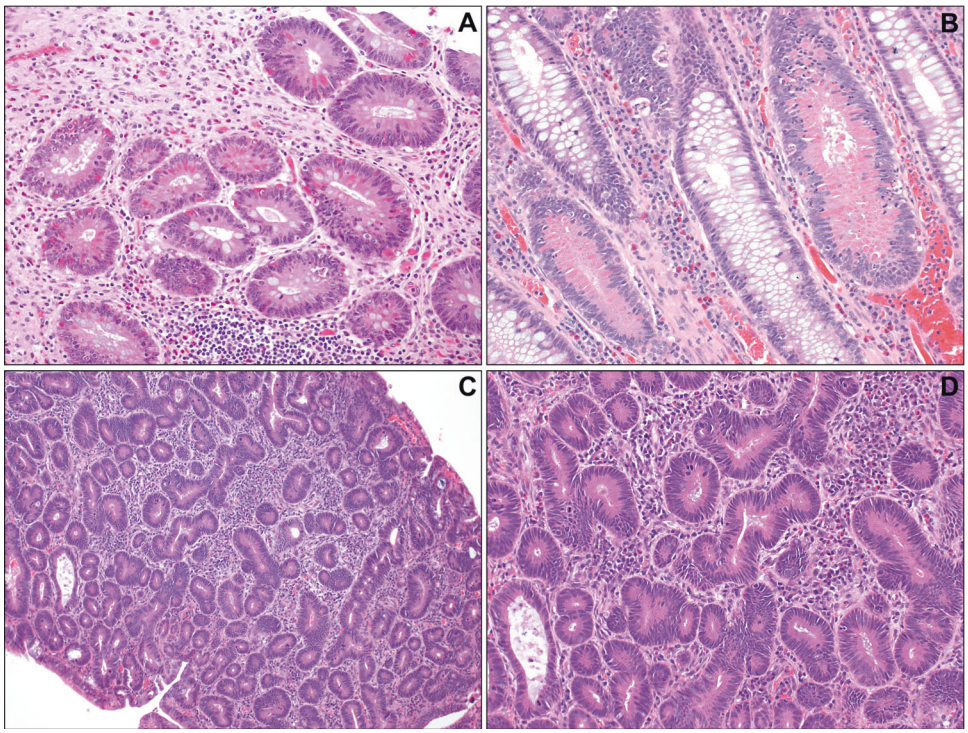

Fig. 2 DPD and GCD dysplasia. a, **b** Medium-power views (H&E, 20×) of two different DPD cases. Characteristic features include elongated, hyperchromatic nuclei and increased Paneth cell differentiation present in clusters of crypts. Despite some loss, goblet cells are easily identified. **c** Low- (H&E, 10×) and **d** medium-power views (H&E, 20×) of GCD dysplasia. It is characterized by a complete or near-complete absence of goblet cells. No obvious Paneth cells are present

serrated lesion NOS based on previously published criteria for TSA [25–30] and SSL [25, 27, 28, 30, 31]. TSA-like lesions demonstrated a villiform growth pattern lined by elongated nuclei with intensely eosinophilic cytoplasm and ectopic crypts, creating a serrated profile (Fig. 3a, b). SSL-like lesions showed pronounced serration and/or dilation at the crypt base and surface, including dilated L- or inverted T-shaped crypts at the interface with muscularis mucosa (Fig. 3c, d). Serrated lesions without definite features of TSA or SSL were classified as serrated lesion NOS (Fig. 4). To be categorized as a specific subtype of serrated lesion, a serrated architecture should form the predominant feature representing >50% of the lesion. Serrated lesions may harbor dysplasia, which may be confined to the lower portion or involve the entire thickness of the mucosa. For each nonconventional subtype, LGD was defined as having uniform, elongated, crowded, and hyperchromatic nuclei that are confined to the basal aspect of crypts and surface epithelial cells, whereas HGD showed more severe cytologic (i.e., enlarged, rounded nuclei, pleomorphism, and loss of nuclear polarity) and/or architectural atypia (such as cribriform growth).

For each case, additional pertinent data were retrieved, including clinical information (such as age, gender, ethnicity, IBD subtype and duration, and the presence of primary sclerosing cholangitis [PSC]) and endoscopic features (such as location and appearance). Clinicopathologic features of associated CRC (including size, pathologic grade and stage [pT], location, histologic subtype, and the presence of

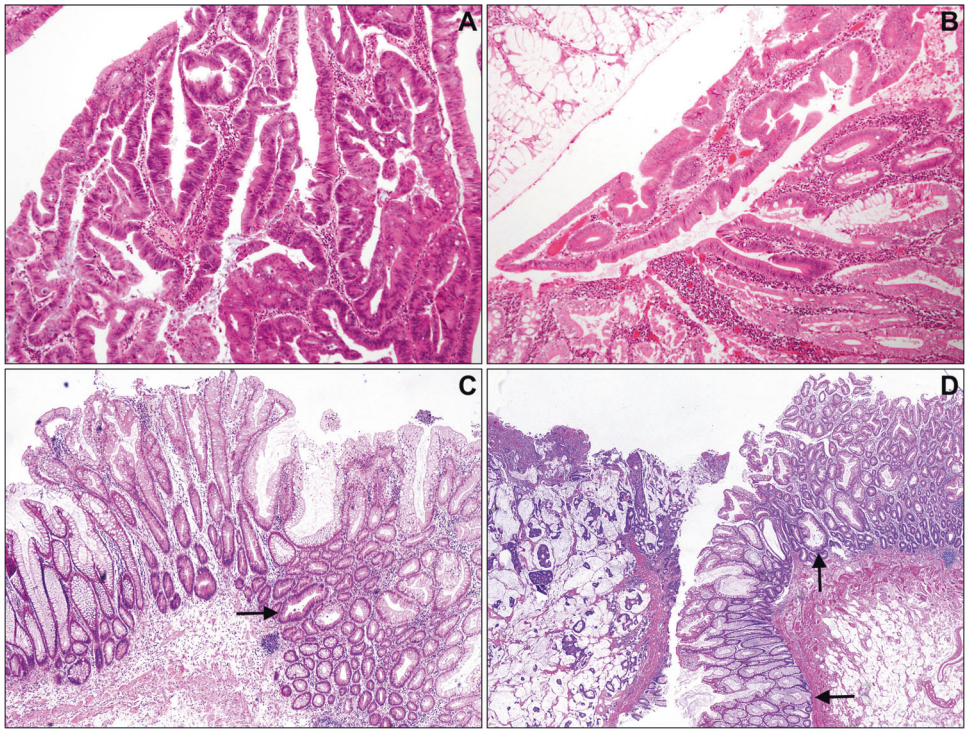

Fig. 3 TSA-like and SSL-like lesions. a TSA-like lesion represents a tubulovillous/villous lesion (with epithelial serration) lined by elongated nuclei with intensely eosinophilic cytoplasm and ectopic crypts (H&E, 20×). **b** Another example of TSA-like lesion with a focus of hypermucinous dysplasia (on the top left corner) (H&E, 10×). **c**, **d** SSL-like lesion demonstrates prominent serration and dilation at the crypt base and surface, including dilated L-shaped crypts at the interface with muscularis mucosa (**d**) (H&E, 2×, arrows). While the upper portion shows more mature cells, low-grade dysplastic crypts are present in the deeper part of the mucosa (**c**) (H&E, 10×, arrow). Mucinous adenocarcinoma is present in Part D

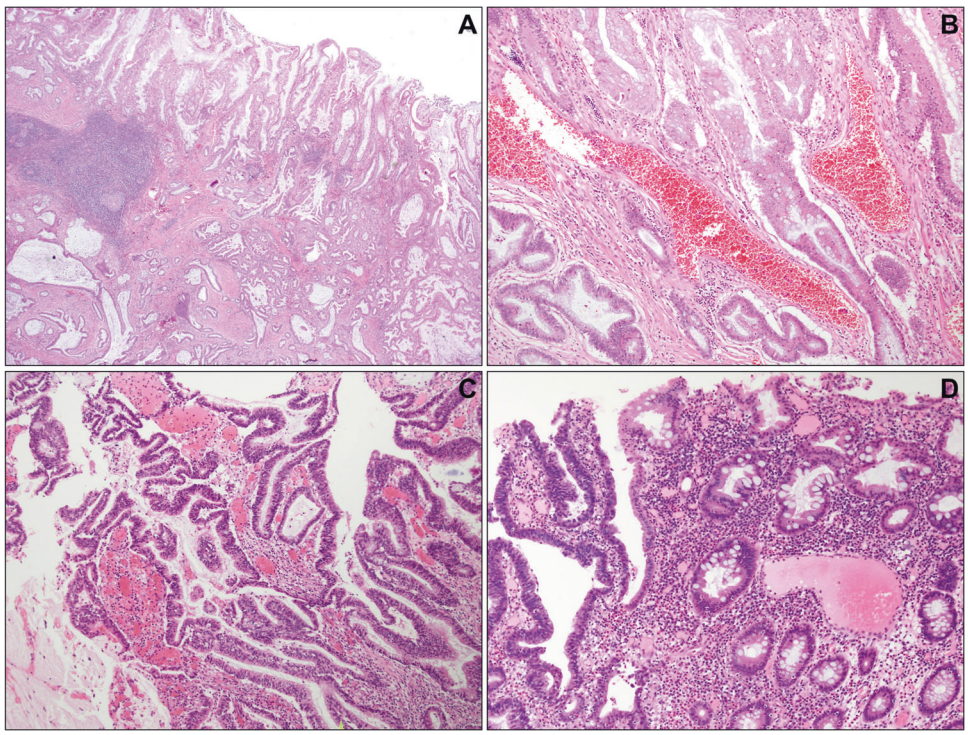

Fig. 4 Serrated lesion NOS. a Low- (H&E, 10×) and **b** medium-power views (H&E, 20×) of serrated lesion NOS. It shows a complex serrated architecture without definite features of TSA or SSL. Despite having minimal nuclear atypia, it is associated with CRC, which showed a similar nuclear morphology. **c**, **d** Medium-power views (H&E, 20×) of another serrated lesion NOS with LGD. Although the majority of the lesion is lined by hyperchromatic, crowded, pseudostratified nuclei, 'HP-like' changes with no nuclear atypia are noted in adjacent mucosa (**d**)

lymphovascular invasion [LVI], lymph node [LN] metastasis, and multifocality) were also recorded. The Institutional Review Board for human subjects research at the University of California, San Francisco (UCSF) Medical Center approved the study (IRB # 16-21034).

Statistical analysis

For descriptive purposes, continuous data were summarized by mean, and categorical data were summarized by percentage. The Pearson's chi-squared test was used to

Table 3 Characteristics of CRC occurring in patients with only nonconventional dysplasia (NCD), only conventional dysplasia (CD), or both

	Only NCD ($n = 14$, 12 patients)	Only CD ($n = 41$, 32 patients)	Both NCD and CD ($n = 18$, 14 patients)	*P* values
Mean size, cm (range)	3.3 (0.3–9.5)	3.5 (0.1–10)	3.0 (0.8-8.5)	0.308
Degree of differentiation (%)				0.026
Low-grade	9 (64%)	37 (90%)	17 (94%)	
High-grade	5 (36%)	4 (10%)	1 (6%)	
Depth of invasion (%)				0.470
Intramucosal (pTis)	1 (7%)	5 (12%)	0 (0%)	
Submucosa (pT1)	2 (14%)	9 (22%)	2 (11%)	
Muscularis propria (pT2)	3 (21%)	9 (22%)	6 (33%)	
Subserosa (pT3)	6 (43%)	16 (39%)	9 (50%)	
Serosa (pT4)	2 (14%)	2 (5%)	1 (6%)	
Lymphovascular invasion (%)	4 yes (29%)	10 yes (24%)	3 yes (17%)	0.709
Lymph node metastasis (%)	4 yes (29%)	15 yes (37%)	6 yes (33%)	0.858
Location of CRC (%)				0.134
Left colon	9 (64%)	24 (59%)	6 (33%)	
Transverse colon	1 (7%)	7 (17%)	5 (28%)	
Right colon	4 (29%)	10 (24%)	7 (39%)	
Multifocal CRC (%)	2 patients (17%)	7 patients (22%)	3 patients (21%)	0.928
Histologic subtype of CRC (%)				
Tubuloglandular	0 (0%)	0 (0%)	2 (11%)	–
Mucinous features	3 (21%)	15 (37%)	12 (67%)	0.024
Signet-ring cell features	3 (21%)	2 (5%)	0 (0%)	0.063
Both mucinous and signet-ring cell features	1 (7%)	1 (2%)	0 (0%)	0.417

compare the clinicopathologic features of dysplasia or CRC occurring in patients with only nonconventional dysplasia, only conventional dysplasia, or both (Table 2 and 3).

Results

Clinicopathologic features of IBD patients with CRC

Table 1 shows demographic and clinicopathologic characteristics of our cohort. The patients included 37 (64%) men and 21 (36%) women with a mean age of 55 years (range: 24–80). The majority of patients had a long history of IBD (mean: 17 years). However, 11 patients had colitis for fewer than 5 years with 2 patients having colitis for <1 year. Forty-one patients (71%) had ulcerative colitis, 15 (26%) had Crohn's disease, and the colitis in 2 (3%) was indeterminate. Four patients (7%) also had PSC. Most patients ($n = 46$; 79%) had a single primary CRC, and the most frequently affected segment was the left colon (53%). The mean tumor size was 3.4 cm (range: 0.1–10), and most cases (86%) were low-grade (well to moderately differentiated). Thirty (41%) of the 73 CRC cases had varying degrees of mucinous features, and 11 (15%) of them were classified as mucinous adenocarcinoma (composed of pools of extracellular mucin accounting for >50% of the lesion). Five cases (7%) showed signet-ring cell features; 3 cases (4%) were categorized as signet-ring carcinoma (i.e., >50% of the tumor cells having prominent intracytoplasmic mucin), while the remaining 2 cases (3%) had a minor component of signet-ring cells (<50%). Two cases (3%) had a small component of both mucinous and signet-ring cell features. Only 2 cases (3%) were tubuloglandular adenocarcinoma (defined as extremely well differentiated adenocarcinoma composed of small to medium sized glands with round or tubular profiles and absence or paucity of desmoplastic reaction). Many cases showed a deeply invasive tumor (49% were pT3 or pT4), and 34% had LN metastases (clinical stage 3).

Characteristics of dysplasia

A total of 106 dysplastic or serrated lesions from the 58 patients were identified. The majority of the lesions ($n = 76$; 72%) presented as a polypoid or raised lesion, while the remaining 30 lesions were found as an endoscopically and/or grossly visible flat lesion (Table 2). Among the 30 flat

lesions, 14 lesions (47%) represented nonconventional dysplasia. Of the 106 lesions, 90 (85%) were found in the same colonic segment as CRC or immediately adjacent to the CRC. Sixteen lesions were found away from CRC, including 8 TA-like, 1 VA-like, 3 hypermucinous, 3 TSA-like, and 1 serrated lesion NOS. Among these 16 lesions, 10 lesions were found in the adjacent colonic segment of CRC. Only six lesions were identified at least two colonic segments away from CRC, including 1 TA-like, 1 VA-like, 2 hypermucinous, 1 TSA-like, and 1 serrated lesion NOS. Of the 58 patients, 26 (45%) had nonconventional dysplasia (Table 2). Of the 26 patients with nonconventional dysplasia, 12 (46%) had only nonconventional dysplasia (accounting for 16 lesions), whereas 14 patients (54%) had both nonconventional (20 lesions) and conventional dysplasias (19 lesions). When present alone, nonconventional dysplasia was more likely to be found in the left colon (81%, $p = 0.006$) as a polypoid or raised lesion (75%, $p < 0.001$) compared with when it occurred simultaneously with conventional dysplasia (7 [35%] and 10 [50%] of 20, respectively). When nonconventional and conventional dysplasias occurred simultaneously, they frequently presented in the same colonic segment (11 of the 14 patients, 79%). No significant difference was noted in the other features of dysplasia, including patient age ($p = 0.531$) and gender ($p = 0.464$), as well as IBD subtype ($p = 0.791$) and duration ($p = 0.065$).

The most common subtype of nonconventional dysplasia was hypermucinous dysplasia ($n = 15$; 42%), either as a pure type ($n = 5$; 14%) or mixed with other dysplastic subtypes ($n = 10$; 28%). The mixed dysplastic lesions maintained a prominent hypermucinous component representing >50% of the lesion, and the second component included 4 conventional dysplasias, 3 TSA-like lesions, and 3 serrated lesions NOS. Serrated lesions were also common when considered together ($n = 15$; 42%) and included 10 TSA-like lesions, 1 SSL-like lesion, and 4 serrated lesions NOS. DPD ($n = 4$; 11%) and GCD ($n = 2$; 6%) dysplasia were relatively uncommon. Nonconventional dysplasia was more likely to be low-grade (29 of 36, 81%) than conventional dysplasia (26 of 70, 37%) ($p = 0.003$).

Characteristics of colorectal carcinomas

CRC occurring in patients with only nonconventional dysplasia was more likely to be high-grade (poorly differentiated; 36%) than CRC in patients with conventional dysplasia (10%) ($p = 0.026$) (Table 3). Signet-ring cell features appeared more common in CRC patients with only nonconventional dysplasia (21%) than in those with conventional dysplasia (5%), but this difference did not reach statistical significance in the present sample size ($p = 0.063$). However, mucinous features were more frequently associated with CRC occurring in patients with conventional dysplasia (67%) (vs. 21% for CRC in patients with only nonconventional dysplasia; $p = 0.024$). No significant difference was noted in the other characteristics of CRC, including size ($p = 0.308$), pathologic stage ($p = 0.470$), location in the colon ($p = 0.134$), presence of LVI ($p = 0.709$), LN metastasis ($p = 0.858$), or multifocality ($p = 0.928$).

Discussion

Conventional (or intestinal type) dysplasia is the most well-recognized form of dysplasia, and the identification and grading of dysplasia in IBD is the cornerstone of management of these patients. More recently, in addition to conventional dysplasia, several morphologic variants of dysplasia have been described [21–23], which are less familiar to pathologists. However, beyond the establishment of some morphologic criteria of nonconventional dysplasia, there has been limited research into the clinicopathologic features of these variants, including potential association with conventional dysplasia and/or CRC. In this study, we found that nonconventional dysplasia is common in IBD patients with CRC, detected in 45% of our cohort. In addition, nonconventional dysplasia was found in the same colonic segment as CRC or immediately adjacent to the CRC at a rate (85%) similar to conventional dysplasia (96%). Despite the fact that nonconventional dysplasia was more likely to be low-grade, it was more frequently associated with high-grade (poorly differentiated) CRC compared with conventional dysplasia-associated CRC. Overall, these findings suggest that nonconventional dysplasia carries at least a similar CRC risk as conventional dysplasia. This argument is further supported by the fact that nonconventional and conventional dysplastic lesions were frequently found in the same colonic segment (79%) when they were detected simultaneously.

A major challenge in studying nonconventional dysplasia is the limited literature on their morphologic features, making them less familiar to pathologists who may overlook some of these dysplastic lesions as benign, reactive, or conventional dysplasia. In this study, we used specific histologic definitions to characterize these nonconventional lesions (Table 4). Hypermucinous dysplasia demonstrates a tubulovillous/villous architecture with tall mucinous cells representing >50% of the lesion (Fig. 1). It typically shows low-grade dysplastic features affecting the crypts with mild nuclear enlargement and hyperchromasia, and elongated, slightly irregular nuclei. Notably, the degree of atypia tends to decrease towards the surface of the lesion. It can present as either a pure type or a mixed type (with either conventional dysplasia or another nonconventional subtype);

however, to be categorized as the mixed type, the hypermucinous component should represent >50% of the lesion. DPD shows a tubular growth pattern with dysplastic crypts lined by mostly elongated, hyperchromatic nuclei as well as increased Paneth cell differentiation involving at least two contiguous crypts in two different foci (beyond what is present in background mucosa) (Fig. 2a, b). Although some loss of goblet cells is expected, goblet cells should not be absent or nearly absent. It is important to note that DPD appears to be different from the previously reported TED/CCD. While DPD shows mostly elongated, hyperchromatic nuclei and always demonstrates increased Paneth cell differentiation, TED/CCD is characterized by mostly round-to-oval, nonstratified nuclei with occasional Paneth cell differentiation. GCD dysplasia is similar to DPD but demonstrates complete or near-complete absence of goblet cells (Fig. 2c, d). Scattered Paneth cells may be present in the lesion and in adjacent mucosa, but not in multiple clusters of dysplastic crypts as seen in DPD. Since metaplastic (i.e., Paneth cell metaplasia) and reactive changes can mimic DPD and GCD dysplasia, respectively, it is important to note that a diagnosis of DPD or GCD dysplasia requires unequivocal histologic evidence of dysplasia demonstrating a distinct lack of surface maturation and/or severe cytologic/architectural atypia. As for serrated lesions, TSA-like lesions have a tubulovillous/villous architecture with serrated villi lined by tall columnar cells with elongated nuclei and intensely eosinophilic cytoplasm. Characteristic ectopic crypts are noted as well (Fig. 3a, b). SSL-like lesions are marked by prominent serration and/or dilation at the crypt base and surface. The presence of dilated L- or inverted T-shaped crypts is diagnostic (Fig. 3c, d). Serrated lesions without definite features of TSA or SSL should be categorized as serrated lesion NOS (Fig. 4). All serrated lesions should exhibit a prominent serrated profile representing >50% of the lesion. They may have dysplasia, which may be confined to the lower portion or involve the entire thickness of the mucosa.

One of the challenges in this area of IBD-related dysplasia is the confusion surrounding serrated lesions in IBD. Endoscopically visible TSA-like and SSL-like lesions in IBD patients may represent IBD-related lesions, but they might also be sporadic serrated polyps. In fact, IBD-associated serrated lesions are known to share similar clinical and molecular features with their sporadic counterparts, although their natural history is largely unknown [32–36]. However, in our cohort, we identified 4 additional serrated lesions NOS without definite features of TSA and SSL, which demonstrated a complex serrated architecture and evidence of dysplasia throughout the entire thickness of the mucosa (Fig. 4). For instance, despite having minimal nuclear atypia, one case was associated with CRC (which showed a similar nuclear morphology) and thus considered dysplastic (Fig. 4a, b). Another case showed LGD, but 'hyperplastic polyp (HP)-like' changes without any nuclear atypia were noted in adjacent mucosa (Fig. 4c, d). Interestingly, in the 1983 grading system proposed for IBD-related dysplasia, Riddell et al. noted that serrated lesions with 'HP-like' features can present with a complete spectrum of epithelial changes ranging from negative to indefinite to dysplastic, and that dysplasia in serrated lesions is more often confined to the lower portion of the mucosa, while the upper part shows more mature cells and a serrated pattern [10]. It is also noteworthy that serrated lesions, including serrated lesions NOS and TSA-like lesions, can present as a minor component of hypermucinous dysplasia (Fig. 3b). Since superficial biopsies and/or sampling issues (i.e., biopsying adjacent mucosa or a minor component of the main lesion) may prevent the evaluation of the entire/main lesion, we recommend that the terms 'TSA-like,' 'SSL-like,' or 'serrated lesion NOS' be used to describe serrated lesions detected in IBD patients, especially for endoscopically visible serrated lesions found in segments of colon with evidence of chronic colitis. For endoscopically invisible lesions, the differential diagnosis in this setting includes 'serrated epithelial change (SEC),' which is a term used for epithelial serration without dysplasia in nonpolypoid random colonic biopsies in IBD patients [31, 37–39]. SEC in IBD may represent a distinct entity from endoscopically visible serrated lesions, as a small subset of SEC cases demonstrated aneuploidy, whereas aneuploidy was not detected in SSLs (with or without dysplasia) or HPs regardless of IBD status [39].

In our study, the majority of nonconventional dysplastic cases (85%) were found in the same colonic segment as CRC or immediately adjacent to the CRC, further supporting their dysplastic nature. All (100%) of the DPD, GCD, and SSL-like lesions, 12 (80%) of the 15 hypermucinous dysplasia, 7 (70%) of the 10 TSA-like lesions, and 3 (75%) of the 4 serrated lesions NOS were identified in the same colonic segment as CRC or immediately adjacent to the CRC. More interestingly, despite what could be constituted as a lower rate of malignant transformation (to either HGD or CRC) in nonconventional dysplasia (7 of 36, 19%) than in conventional dysplasia (44 of 70, 63%) ($p = 0.003$), nonconventional dysplasia seems to have CRC (more often high-grade or poorly differentiated; $p = 0.026$) arising in it or near to the dysplasia, at a rate (85%) similar to conventional dysplasia (96%). This is consistent with the previous report that compared with conventional (or intestinal type) HGD, hypermucinous dysplasia (despite its low-grade appearance) has twice the frequency of *KRAS* mutation, which is one of the first alterations to occur in the colorectal adenoma-carcinoma sequence [23]. This is further supported by our preliminary findings that the rate of aneuploidy detected by DNA flow cytometry is significantly

Table 4 Morphologic criteria of nonconventional subtypes

	Hypermucinous type	Intestinal type		Crypt cell type	Serrated type		
	Hypermucinous	DPD	GCD	CCA/D [24]	TSA-like	SSL-like	Serrated lesion NOS
Architecture	Tubulovillous/villous	Tubular	Tubular	Flat	Tubulovillous/ villous with serration	Tubular with serration	Tubular with serration
Defining features	Tall mucinous cells with typically mildly elongated, hyperchromatic nuclei Hypermucinous component should represent >50% of the lesion	Intestinal type cells with mostly elongated, hyperchromatic nuclei Increased Paneth cell differentiation involving at least two contiguous crypts in two different foci (beyond what is present in background mucosa)	Intestinal type cells with mostly elongated, hyperchromatic nuclei Complete or near-complete absence of goblet cells	Mostly round-to-oval, non-stratified nuclei Atypia can be limited to the crypt base without obvious surface involvement	Columnar cells with mostly elongated nuclei, intensely eosinophilic cytoplasm, and ectopic crypts TSA-like component should represent >50% of the lesion	Prominent serration and dilation at the crypt base and surface, including dilated L- or inverted T-shaped crypts at the interface with muscularis mucosa SSL-like component should represent >50% of the lesion	Often complex serration but without definite features of TSA or SSL Serrated lesion NOS component should represent >50% of the lesion
Other features	Degree of atypia tends to decrease from the crypts to the surface of the villi	Some loss of goblet cells allowed, but no complete or near-complete absence of goblet cells	Scattered Paneth cells allowed, but not in multiple clusters of dysplastic crypts as seen in DPD Similar degree of Paneth cell differentiation is present in the lesion and in adjacent mucosa	Some loss of goblet cells allowed, but no complete or near-complete absence of goblet cells Occasional Paneth cells may be seen, but similar degree of Paneth cell differentiation is present in the lesion and in adjacent mucosa		May show dysplasia, which may be confined to the lower portion or involve the entire thickness of the mucosa	May show dysplasia, which may be confined to the lower portion or involve the entire thickness of the mucosa 'HP-like' changes may be present in adjacent mucosa or represent the entire lesion

higher in low-grade hypermucinous (80%) and GCD (25%) dysplasias than in low-grade DPD (10%) or conventional dysplasia (8%), and that HGD is more likely to be associated with hypermucinous (43%) and GCD dysplasias (40%) than DPD (11%) or conventional dysplasia (12%) (unpublished results).

In conclusion, at least six morphologic patterns of nonconventional dysplasia can be detected in IBD patients with CRC, and of these, hypermucinous dysplasia is the most common. Nonconventional dysplasia can be present by itself or together with conventional forms of dysplasia. Despite its low-grade histology, nonconventional dysplasia is detected in the same colonic segment as CRC or immediately adjacent to the CRC at a rate similar to conventional dysplasia, and greater than a third of CRCs arising in association with nonconventional dysplasia are high-grade (poorly differentiated). Additional studies with larger number of cases may allow for a more precise determination of the natural history and CRC risk of the various subtypes of nonconventional dysplasia.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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