Journal of Crohn's and Colitis, 2022, 98–108
https://doi.org/10.1093/ecco-jcc/jjab120
Advance Access publication July 7, 2021
Original Article

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Hypermucinous, Goblet Cell-Deficient and Crypt Cell Dysplasias in Inflammatory Bowel Disease are Often Associated with Flat/Invisible Endoscopic Appearance and Advanced Neoplasia on Follow-Up

Won-Tak Choi,[a] Marcela Salomao,[b] Lei Zhao,[c] Lindsay Alpert,[d] Namrata Setia,[d] Xiaoyan Liao,[e] Michael G. Drage,[e] Maria Westerhoff,[f] Jerome Cheng,[f] Gregory Y. Lauwers,[g] Huaibin Mabel Ko[h]

[a]University of California at San Francisco, Department of Pathology, San Francisco, CA, USA [b]Mayo Clinic, Department of Pathology, Scottsdale, AZ, USA [c]Brigham and Women's Hospital, Department of Pathology, Boston, MA, USA [d]University of Chicago, Department of Pathology, Chicago, IL, USA [e]University of Rochester, Department of Pathology, Rochester, NY, USA [f]University of Michigan, Department of Pathology, Ann Arbor, MI, USA [g]H. Lee Moffitt Cancer Center, Department of Pathology, Tampa, FL, USA [h]Icahn School of Medicine at Mount Sinai, Department of Pathology, New York, NY, USA

Corresponding author: Won-Tak Choi, MD, PhD, University of California at San Francisco, Department of Pathology, 505 Parnassus Avenue, M552, Box 0102, San Francisco, CA 94143, USA. Tel: 415-353-9533; Fax: 415-353-1200; Email: Won-Tak.Choi@ucsf.edu

Abstract

Background and Aims: Several different types of non-conventional dysplasia have been recently described in inflammatory bowel disease [IBD]. Hypermucinous, goblet cell-deficient and crypt cell dysplasias have received most attention, but there is limited information regarding their clinicopathological features and clinical outcomes.

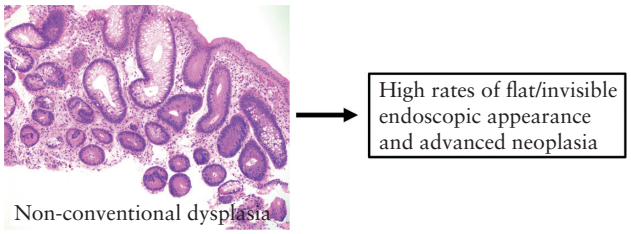
Methods: A total of 126 cases of hypermucinous [n = 55], goblet cell-deficient [n = 26] and crypt cell [n = 45] dysplasias from 97 IBD patients were collected from seven different institutions and analysed.

Results: The cohort included 62 [64%] men and 35 [36%] women with a mean age of 49 years [range: 20–78]. The majority of affected patients had longstanding IBD [mean duration: 18 years]. Nineteen [20%] patients had a concurrent history of primary sclerosing cholangitis. As a group, non-conventional dysplasia was predominantly found in patients with ulcerative colitis [UC] [n = 68; 70%] and occurred in the left colon [n = 80; 63%]; however, hypermucinous dysplasia [57%] was the least frequently associated with UC compared with goblet cell-deficient [74%] and crypt cell [89%] dysplasias [p = 0.016]. Fifty [52%] patients had a history of conventional dysplasia, detected in the same colonic segment as non-conventional dysplasia at a rate of 33%. Goblet cell-deficient dysplasia [74%] was more frequently associated with conventional dysplasia than hypermucinous [43%] and crypt cell [48%] dysplasias [p = 0.044]. While hypermucinous dysplasia often had a polypoid appearance [58%], crypt cell [96%] and goblet cell-deficient [65%] dysplasias were more likely to present as flat/invisible lesions [p < 0.001]. Most lesions were low-grade [87%] at diagnosis, but goblet cell-deficient dysplasia [31%] more often showed high-grade

dysplasia [HGD] compared with hypermucinous [15%] and crypt cell [0%] dysplasias [$p = 0.003$]. Hypermucinous dysplasia usually demonstrated a tubulovillous/villous architecture [76%], whereas goblet cell-deficient dysplasia was predominantly tubular [92%]. A flat architecture was exclusively associated with crypt cell dysplasia [100%] [$p < 0.001$]. Immunohistochemical stain results for p53 were available for 33 lesions; 14 [42%] showed strong [3+] and patchy [10–50%] to diffuse [>50%] nuclear overexpression or null staining pattern, including four [33%] of 12 hypermucinous, two [29%] of seven goblet cell-deficient and eight [57%] of 14 crypt cell dysplastic lesions [$p = 0.726$]. Follow-up biopsies or resections were available for 92 low-grade lesions from 71 patients; 55 [60%] lesions, including 19 [49%] of 39 hypermucinous, 10 [59%] of 17 goblet cell-deficient and 26 [72%] of 36 crypt cell dysplastic lesions [$p = 0.116$], were associated with subsequent detection of HGD [$n = 34$; 37%] or adenocarcinoma [$n = 21$; 23%] at the site of previous biopsy or in the same colonic segment within a mean follow-up time of 12 months [range: <1–73].

Conclusions: Hypermucinous, goblet cell-deficient and crypt cell dysplasias have distinct clinicopathological features but appear to have a similar high risk of association with advanced neoplasia [HGD or adenocarcinoma]. More than half of the lesions [66%] presented as flat/invisible dysplasia, suggesting that IBD patients may benefit from random biopsy sampling in addition to targeted biopsies. Although not uncommonly associated with conventional dysplasia, non-conventional dysplasia may be the only dysplastic subtype identified in IBD patients. Therefore, it is important to recognize these non-conventional subtypes and recommend complete removal and/or careful examination and follow-up.

Graphical Abstract



Key Words: Dysplasia; inflammatory bowel disease; non-conventional

1. Introduction

Patients with inflammatory bowel disease [IBD] are at an increased risk of developing dysplasia and/or colorectal cancer [CRC].[1,2] IBD-related dysplasia is categorized into either low-grade [LGD] or high-grade dysplasia [HGD],[3] but the recent SCENIC [Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations] guidelines emphasize another feature of dysplasia, namely whether it is endoscopically visible or invisible, to guide its clinical management.[4] Under the SCENIC guidelines, while endoscopic resection is appropriate to treat polypoid/visible dysplasia, making it unnecessary to distinguish IBD-related dysplasia from a sporadic adenoma from a therapeutic standpoint, colectomy is often recommended to manage flat/invisible dysplasia, especially for flat/invisible HGD or multifocal LGD, due to its strong association with advanced neoplasia [HGD or CRC].[5–8]

Indeed, there is some evidence that flat/invisible dysplasia in IBD may have different molecular features when compared with polypoid/visible dysplasia.[8–10] For instance, flat/invisible dysplasia has a higher rate of aneuploidy [41% for flat/invisible LGD and 93% for flat/invisible HGD][8] than IBD-related polypoid LGD [8%] or sporadic adenomas [9%].[9] Similarly, using next-generation sequencing, Wanders *et al.* reported that IBD-related dysplastic lesions that are often flat/invisible have more DNA copy number alterations [average number of gains and losses of 4.3 and 3.2, respectively] than sporadic adenomas [1.5 and 0.5, respectively].[10] Overall, these findings indicate that flat/invisible dysplasia is more genetically unstable than IBD-related polypoid dysplasia or sporadic adenomas, possibly explaining its frequent association with advanced neoplasia in IBD patients. In support of this hypothesis, we also demonstrated that the presence of aneuploidy is a significant predictor of advanced neoplasia in the setting of flat/invisible LGD with univariate and multivariate hazard ratios of 5.3 [$p = 0.006$] and 4.5 [$p = 0.040$], respectively.[8]

Adding to this complexity, several different histological patterns of non-conventional dysplasia in IBD have been recently described that are morphologically distinct from conventional [intestinal-type] dysplasia.[9,11–13] At least seven subtypes have been reported, including [1] hypermucinous dysplasia; [2] goblet cell-deficient dysplasia; [3] crypt cell dysplasia [also known as dysplasia with terminal epithelial differentiation]; [4] dysplasia with increased Paneth cell differentiation; [5] sessile serrated lesion-like dysplasia; [6] traditional serrated adenoma-like dysplasia; and [7] serrated dysplasia, not otherwise specified.[9,11–13] Of these, hypermucinous, goblet cell-deficient and crypt cell dysplasias have received more attention, but there is limited information regarding their clinicopathological

features and clinical outcomes, in part due to the rarity of these subtypes and the likelihood that they are under-recognized.

In this regard, we recently reported that there is a higher risk of harbouring advanced neoplasia in patients with non-conventional dysplasia [38%] than in those with IBD-related conventional dysplasia [19%] on follow-up [$p < 0.001$].[9,12] This higher association with advanced neoplasia was particularly noted in crypt cell [93%], hypermucinous [57%] and goblet cell-deficient [40%] dysplasias. Also, the rate of aneuploidy was significantly higher in low-grade non-conventional dysplasia [46%], in particular crypt cell [100%], hypermucinous [80%] and goblet cell-deficient [25%] dysplasias, than in low-grade polypoid conventional dysplasia [8%; $p = 0.002$] or sporadic adenomas [9%; $p = 0.037$].[9,12] Furthermore, as a group [including all seven non-conventional subtypes], non-conventional dysplasia was more likely to present as a flat/invisible lesion [41% vs 18% of conventional dysplasia; $p < 0.001$].[9] However, these previous studies were limited by the small numbers of cases from a single institution. Therefore, to validate these findings and to further characterize the clinicopathological features of non-conventional dysplasia, in particular hypermucinous, goblet cell-deficient and crypt cell dysplasias, we report a multicentre clinicopathological analysis of 126 additional cases of hypermucinous [$n = 55$], goblet cell-deficient [$n = 26$] and crypt cell [$n = 45$] dysplasias collected from seven different institutions.

2. Materials and Methods

2.1. Patients and data collection

A total of 126 cases of non-conventional dysplasia, including 55 hypermucinous, 26 goblet cell-deficient and 45 crypt cell dysplasias, from 97 IBD patients were collected from seven different institutions [Tables 1–3]. Since the terms 'hypermucinous', 'goblet cell-deficient' and 'crypt cell' dysplasias are not routinely used in clinical practice, participating gastrointestinal [GI] pathologists were asked to search their database using alternative terms to describe these changes: 'indefinite for dysplasia' for hypermucinous, goblet cell-deficient or crypt cell dysplasia; 'hypermucinous', 'mucinous', 'tubulovillous' or 'villous' for hypermucinous dysplasia; 'goblet cell' for goblet cell-deficient dysplasia; and 'crypt atypia', 'glandular atypia' or 'epithelial atypia' for crypt cell dysplasia.

Previously published detailed morphological descriptions of each subtype were provided to the GI pathologists.[9,11–13] The pathologists reviewed their cases to identify the recently described features of these subtypes and submitted representative images of their cases to one GI pathologist [W.T.C.] for central review to ensure uniform classification for each subtype. If there was disagreement in the classification, histological grade or other pathological characteristics, consensus diagnosis was made by the participating pathologist and the central reviewer. In brief, hypermucinous dysplasia often shows a tubulovillous/villous architecture lined by tall, prominent mucinous cells representing >50% of the lesion, with typically mild nuclear atypia [Figure 1]. Goblet cell-deficient dysplasia predominantly shows a tubular growth of dysplastic crypts with mildly elongated, crowded and hyperchromatic nuclei but is characterized by a complete or near-complete absence of goblet cells, often leading to intensely eosinophilic cytoplasm [Figure 2]. Crypt cell dysplasia demonstrates crypts lined by cells with mostly round-to-oval or slightly irregular to elongated, hyperchromatic nuclei with mild nuclear enlargement [Figure 3]. Nuclear crowding is typically limited to the crypt base without surface involvement or significant architectural atypia, and the degree of atypia does not represent unequivocal evidence of HGD. To avoid confusion with regenerative/reactive changes, significant neutrophilic inflammation and/or ulceration should be absent in crypt cell dysplasia. For all three subtypes, in addition to the distinctive morphological features described for each subtype, LGD is defined as having mild nuclear atypia typically involving both crypts and surface epithelial cells, but may show only involvement of the crypts [i.e. crypt cell dysplasia]. HGD demonstrates more severe cytological [i.e. enlarged, rounder nuclei and loss of nuclear polarity] and/or architectural atypia [i.e. cribriform formation] [Figures 1C, D, and 2D]. Of note, an objective grading criterion for crypt cell dysplasia has yet to be developed, but crypt cell dysplasia probably represents at least LGD based on the presence of aneuploidy, p53 positivity, and development of HGD or CRC on follow-up.[12]

For each case, pertinent clinical information (including patient age, gender, and ethnicity, presence of primary sclerosing cholangitis [PSC] and conventional dysplasia, and IBD subtype, duration and extent), endoscopic/gross features [including lesion location,

Table 1. Characteristics of IBD patients with non-conventional dysplasia

	Overall [$n = 126$, 97 patients]	Hypermucinous [$n = 55$, 47 patients]	Goblet cell-deficient [$n = 26$, 23 patients]	Crypt cell [$n = 45$, 27 patients]	p value
Mean age, years [range]	49 [20–78]	50 [20–77]	51 [25–78]	47 [24–78]	0.648
Male gender, n [%]	62 [64%]	30 [64%]	15 [65%]	17 [63%]	0.986
Caucasian ethnicity, n [%]	90 [93%]	44 [94%]	22 [96%]	24 [89%]	0.624
IBD subtype, n [%]	68 UC [70%] 25 CD [26%] 4 IND [4%]	27 UC [57%] 16 CD [34%] 4 IND [9%]	17 UC [74%] 6 CD [26%] 0 IND [0%]	24 UC [89%] 3 CD [11%] 0 IND [0%]	0.016
Mean IBD duration, years [range]	18 [<1–49]	21 [3–49]	16 [<1–33]	14 [7–29]	0.320
Extent of colitis, n [%]	86 Pancolitis [89%] 11 Left-sided [11%]	42 Pancolitis [89%] 5 Left-sided [11%]	21 Pancolitis [91%] 2 Left-sided [9%]	23 Pancolitis [85%] 4 Left-sided [15%]	0.776
PSC, n [%]	19 [20%]	10 [21%]	3 [13%]	6 [22%]	0.661
History of conventional dysplasia, n [%]	32 Same segment [33%] 18 Different segment [19%] 47 No [48%]	11 Same segment [23%] 9 Different segment [19%] 27 No [57%]	14 Same segment [61%] 3 Different segment [13%] 6 No [26%]	7 Same segment [26%] 6 Different segment [22%] 14 No [52%]	0.044

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IND, indeterminate colitis; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

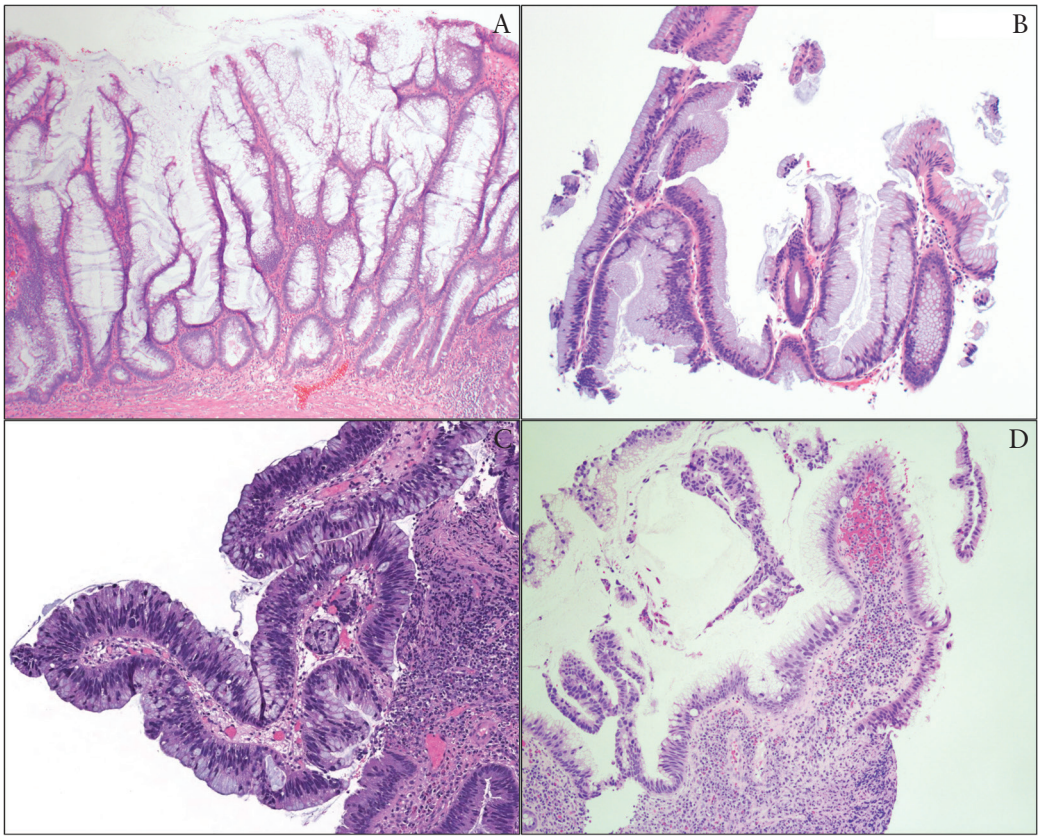


Figure 1. Hypermucinous dysplasia. [A] Hypermucinous dysplasia demonstrates tall, prominent mucinous cells. Cytological atypia is typically more prominent in the lower portion of crypts, and the degree of atypia tends to decrease towards the surface epithelium due to prominent mucinous differentiation. [B] Anther case of hypermucinous dysplasia shows low-grade nuclear atypia characterized by mildly elongated, hyperchromatic nuclei. [C, D] Two different cases of hypermucinous dysplasia demonstrate a tubulovillous architecture with areas of severe nuclear atypia.

size and endoscopic/gross appearance, as well as multifocality], and pathological characteristics [including histological grade and architecture, and p53 immunohistochemical stain results] were collected by reviewing electronic medical records, endoscopic notes, pathology reports and glass slides [Tables 1–3]. Dysplasia was classified as invisible only when it was described as a random biopsy in endoscopic reports and/or grossly normal in resections. If available, all follow-up biopsies and/or resections of each lesion at the site of previous biopsy or in the same colonic segment were reviewed for the occurrence of HGD or adenocarcinoma. The intensity of p53 staining was graded as weak [1+], moderate [2+] or strong [3+], whereas the extent of staining was graded as negative/wild type [<10%], patchy [10–50%] or diffuse [>50%].[12] The null staining pattern was defined as the complete absence of p53 staining in dysplastic cells. To highlight distinctive features of non-conventional dysplasia, we compared the clinicopathological features of non-conventional dysplastic lesions in the current series to those of previously published 239 IBD-related conventional dysplastic lesions from 149 IBD patients identified at the University of California, San Francisco [UCSF] Medical Center.[9] The Institutional Review Board for human subjects research at the UCSF Medical Center approved the study [IRB # 16-21034].

2.2. Statistical analysis

Pearson's chi-squared test was utilized for all analyses [Tables 1–3] with a p value <0.05 considered statistically significant.

3. Results

3.1. Clinicopathological features of the entire cohort

The cohort included 126 cases of non-conventional dysplasia from 97 IBD patients. The patients included 62 [64%] men and 35 [36%] women with a mean age of 49 years [range: 20–78] [Table 1]. Sixty-eight [70%] patients had ulcerative colitis [UC], 25 [26%] had Crohn's disease [CD] and four [4%] had indeterminate colitis. Most patients had a long history of IBD [mean duration: 18 years, range: <1–49] with pancolitis [89%]; however, one patient had colitis for less than 5 years, and another patient had a diagnosis of colitis for less than 1 year. PSC was common [n = 19; 20%]. Forty-seven [48%] patients were diagnosed with non-conventional dysplasia only, whereas the remaining 50 [52%] patients had both non-conventional and conventional dysplasias, more commonly in the same colonic segment [n = 32; 33%]. All lesions were found in segments of colon with histological and/or endoscopic evidence of chronic and/or active colitis. The majority of the lesions were found in endoscopic biopsies [n = 112; 89%], whereas the remaining 14 [11%] lesions were identified in surgical resections.

Of the 126 non-conventional dysplastic lesions, 69 [55%] were endoscopically/grossly invisible, and 14 [11%] were endoscopically/grossly visible but flat in appearance [i.e. scar, stricture, plaque] [Table 2]. The remaining 43 [34%] lesions had a polypoid appearance. The visible lesions tended to be large with a mean size of 2.3 cm [range: 0.2–20]. There was a predilection for the left colon

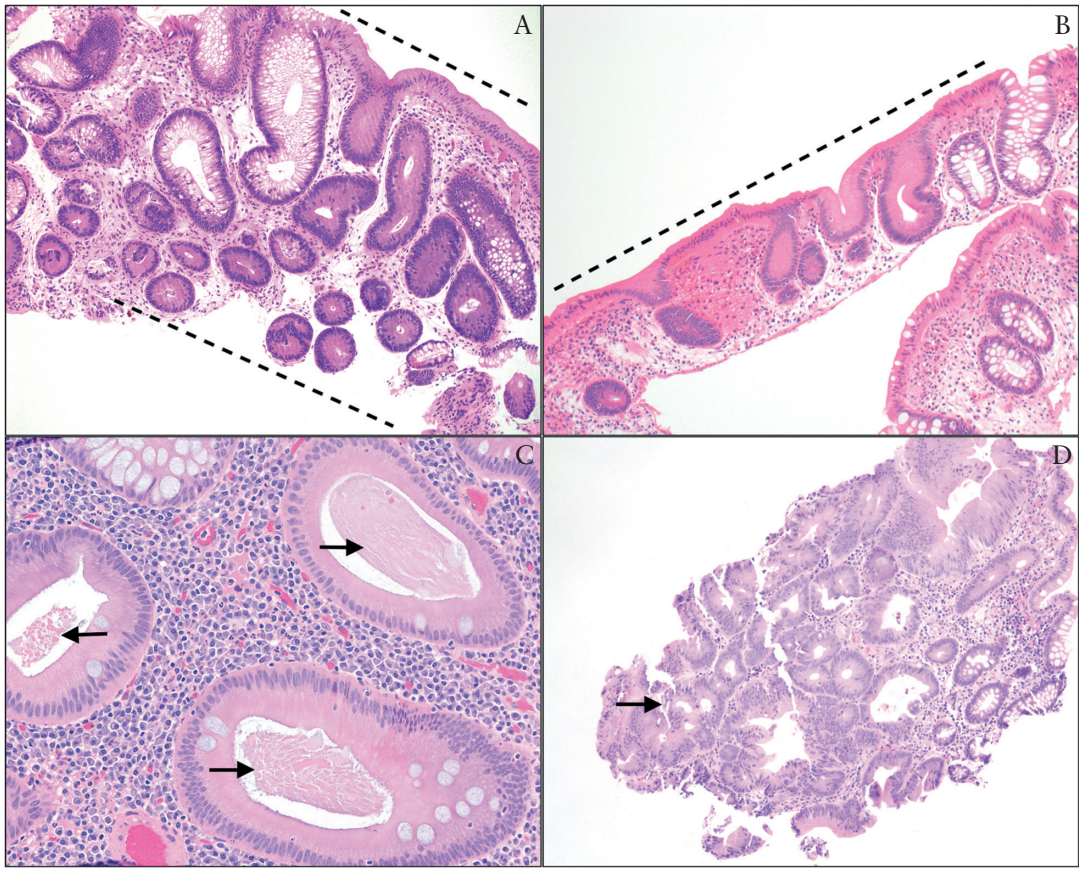


Figure 2. Goblet cell-deficient dysplasia. [A, B] Goblet cell-deficient dysplasia is defined by a complete or near-complete absence of goblet cells. There is a sharp transition from normal crypts to dysplastic crypts with mildly elongated, crowded nuclei and a complete absence of goblet cells, leading to intensely eosinophilic cytoplasm [dotted lines]. [C] Eosinophilic luminal secretion is often seen in goblet cell-deficient dysplasia [arrows]. [D] Goblet cell-deficient dysplasia shows high-grade architectural atypia, including cribriform growth [arrow].

[*n* = 80; 63%], followed by the right colon [*n* = 27; 21%] and transverse colon [*n* = 19; 15%]. Fourteen [14%] patients had multifocal lesions of the same non-conventional subtype, which were found in the same colonic segment in six [43%] patients. Microscopically, most lesions were low-grade [*n* = 110; 87%] with either tubular [*n* = 37; 29%] or tubulovillous/villous architecture [*n* = 44; 35%]. Immunohistochemical stain results for p53 were available for 33 lesions, of which 14 [42%] showed strong [3+] and patchy [10–50%] to diffuse [>50%] nuclear overexpression or null staining pattern [Figure 4]. Of note, the mean number of biopsy samples obtained during each colonoscopy when non-conventional dysplasia was first diagnosed was 5.7 [range: 1–19].

Follow-up biopsies or resections were available for 92 low-grade lesions from 71 patients; 55 [60%] lesions were correlated with subsequent detection of HGD [*n* = 34; 37%] or adenocarcinoma [*n* = 21; 23%] at the site of previous biopsy or in the same colonic segment within a mean follow-up time of 12 months [range: <1–73]. In the remaining 37 [40%] lesions, there was either persistent LGD [*n* = 27; 29%] or no evidence of dysplasia [*n* = 10; 11%] within a mean follow-up time of 13 months [range: <1–44]. Using only adenocarcinoma as the outcome, 21 [23%] lesions were associated with subsequent detection of adenocarcinoma within a mean follow-up time of 9 months [range: <1–37]. For outcome analysis per patient, 37 [52%] of the 71 patients were diagnosed with HGD [*n* = 19; 27%] or adenocarcinoma [*n* = 18; 25%] on follow-up. Six [6%] patients also had a history of synchronous [*n* = 3], metachronous [*n* = 1] or previous [*n* = 2] adenocarcinoma in a different colonic segment away from non-conventional dysplasia. Among the 47 patients who were diagnosed with non-conventional dysplasia only, 33 [70%] patients had follow-up biopsies or resections for 46 low-grade lesions. Twenty-five [54%] lesions were correlated with subsequent detection of HGD [*n* = 15; 33%] or adenocarcinoma [*n* = 10; 22%] at the site of previous biopsy or in the same colonic segment within a mean follow-up time of 13 months [range: <1–47].

3.2. Clinicopathological features of non-conventional dysplasia

The most common subtype identified in our cohort was hypermucinous dysplasia [*n* = 55; 44%], followed by crypt cell [*n* = 45; 36%] and goblet cell-deficient [*n* = 26; 21%] dysplasias. All three subtypes were more commonly found in UC patients [89% for crypt cell, 74% for goblet cell-deficient and 57% for hypermucinous]; however, hypermucinous dysplasia [57%] was less frequently associated with UC than goblet cell-deficient [74%] and crypt cell [89%] dysplasias [*p* = 0.016] [Table 1]. One patient with colitis for less than 5 years had hypermucinous dysplasia, while another patient with colitis for less than 1 year had goblet cell-deficient dysplasia. Goblet cell-deficient dysplasia [74%] was more likely to be detected in association with conventional dysplasia than hypermucinous [43%] and crypt cell [48%] dysplasias [*p* = 0.044]. Nineteen [20%] lesions were found in PSC patients, including 10 [21%] of the 55 hypermucinous,

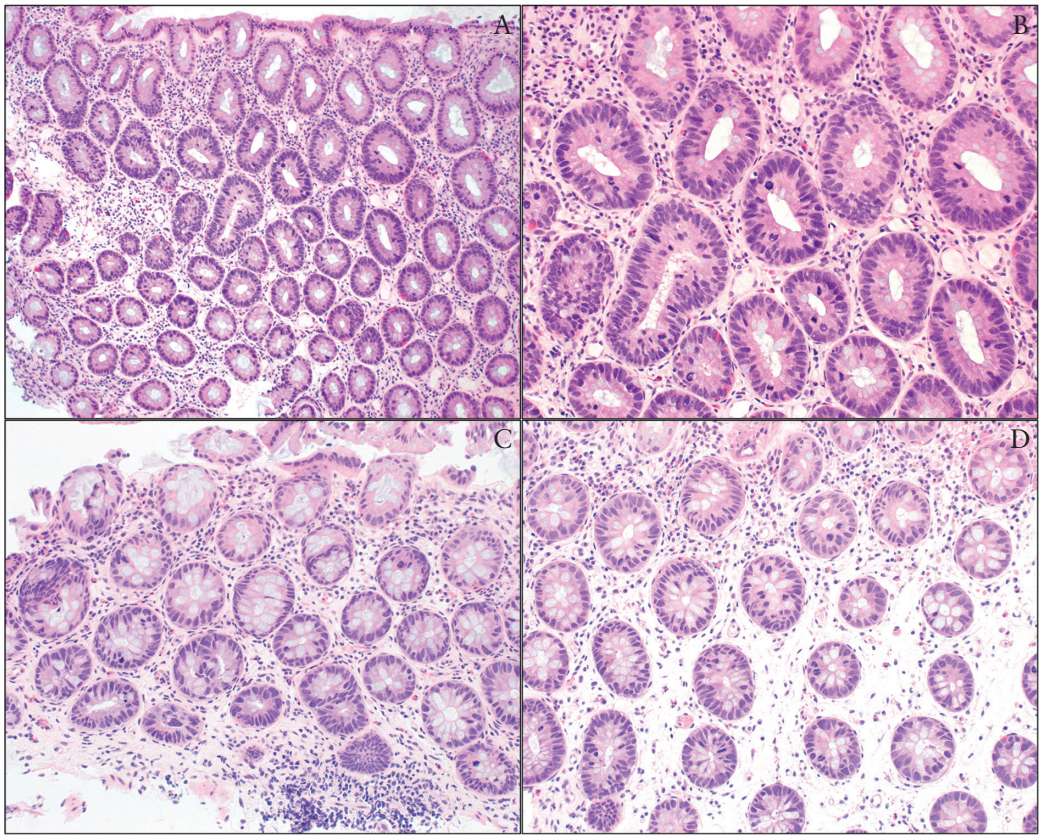


Figure 3. Crypt cell dysplasia. [A, B] Crypt cell dysplasia shows slightly elongated nuclei with mild nuclear enlargement, crowding, and hyperchromasia limited to the crypt base. High-power view [B] demonstrates increased mitoses and mucin depletion. There is no significant architectural atypia or active inflammation. [C, D] Another case of crypt cell dysplasia demonstrates crypts lined by cells with mostly round-to-oval or slightly irregular, hyperchromatic nuclei with mild nuclear enlargement and crowding, limited to the crypt base without surface involvement. Increased mitoses are present in D.

Table 2. Clinicopathological features of non-conventional dysplasia

	Overall [*n* = 126, 97 patients]	Hypermucinous [*n* = 55, 47 patients]	Goblet cell-deficient [*n* = 26, 23 patients]	Crypt cell [*n* = 45, 27 patients]	*p* value
Location, *n* [%]	27 Right [21%] 80 Left [63%] 19 Transverse [15%]	10 Right [18%] 35 Left [64%] 10 Transverse [18%]	8 Right [31%] 13 Left [50%] 5 Transverse [19%]	9 Right [20%] 32 Left [71%] 4 Transverse [9%]	0.205
Endoscopic/gross appearance, *n* [%]	43 Polypoid [34%] 14 Flat [11%] 69 Invisible [55%]	32 Polypoid [58%] 8 Flat [15%] 15 Invisible [27%]	9 Polypoid [35%] 3 Flat [12%] 14 invisible [54%]	2 Polypoid [4%] 3 Flat [7%] 40 Invisible [89%]	<0.001
Mean size, cm [range]	2.3 [0.2–20]	2.5 [0.2–20]	1.7 [0.3–7]	Not applicable	0.612
Histological grade at diagnosis, *n* [%]	110 LGD [87%] 16 HGD [13%]	47 LGD [85%] 8 HGD [15%]	18 LGD [69%] 8 HGD [31%]	45 LGD [100%] 0 HGD [0%]	0.003
Histological architecture, *n* [%]	37 Tubular [29%] 43 Tubulovillous [34%] 1 Villous [1%] 45 Flat [36%]	13 Tubular [24%] 41 Tubulovillous [75%] 1 Villous [2%] 0 Flat [0%]	24 Tubular [92%] 2 Tubulovillous [8%] 0 Villous [0%] 0 Flat [0%]	0 Tubular [0%] 0 Tubulovillous [0%] 0 Villous [0%] 45 Flat [100%]	<0.001
Multifocality, *n* [%]	14 [14%]	7 [15%]	2 [9%]	5 [19%]	0.611
p53 stain results [%]	19/33 Wild type [58%] 14/33 Positive or null [42%]	8/12 Wild type [67%] 4/12 Positive or null [33%]	5/7 Wild type [71%] 2/7 Positive or null [29%]	6/14 Wild type [43%] 8/14 Positive or null [57%]	0.726
Outcomes, *n* [%]	27/92 LGD [29%] 34/92 HGD [37%] 21/92 CRC [23%] 10/92 Negative [11%]	15/39 LGD [38%] 9/39 HGD [23%] 10/39 CRC [26%] 5/39 Negative [13%]	7/17 LGD [41%] 4/17 HGD [24%] 6/17 CRC [35%] 0/17 Negative [0%]	5/36 LGD [14%] 21/36 HGD [58%] 5/36 CRC [14%] 5/36 Negative [14%]	0.116
CRC in a different colonic segment, *n* [%]	6 [6%]	3 [6%]	0 [0%]	3 [11%]	0.624

Abbreviations: CRC, colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

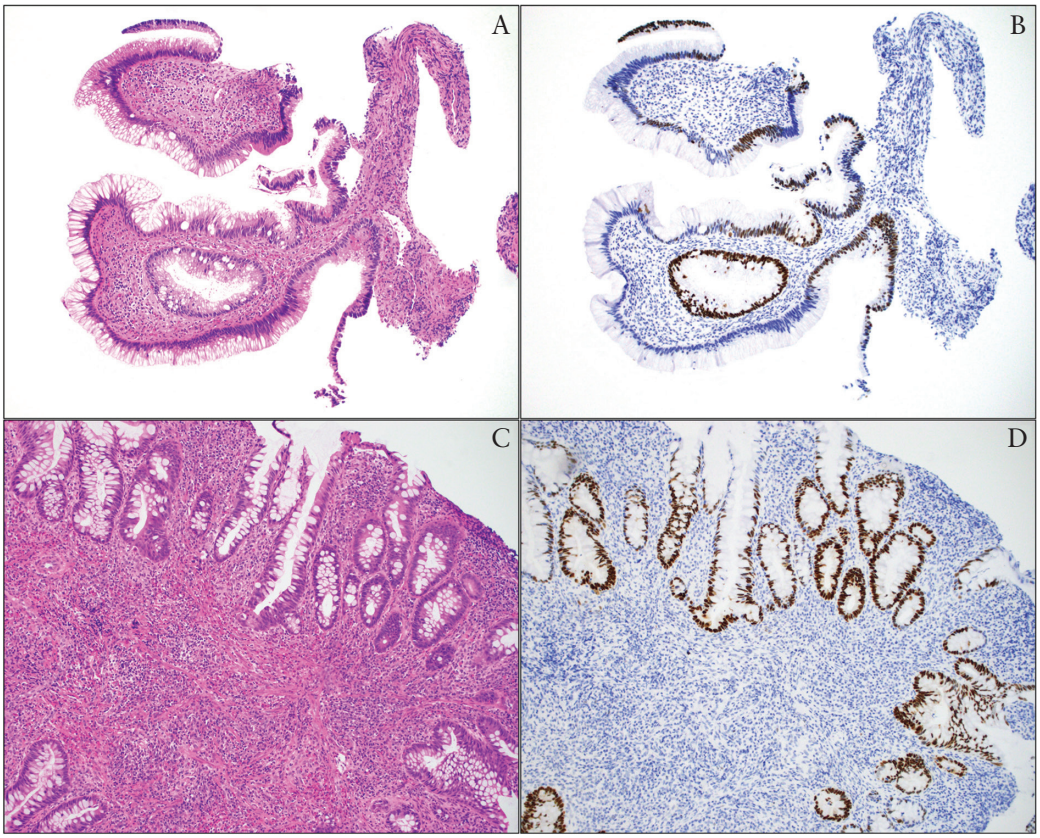


Figure 4. Positive p53 nuclear overexpression in hypermucinous and crypt cell dysplasias. [A, B] Hypermucinous dysplasia shows tall, prominent mucinous cells with areas of low-grade nuclear features. There is strong [3+] and patchy [10–50%] nuclear staining for p53. [C, D] Crypt cell dysplasia demonstrates slightly elongated, irregular nuclei with mild nuclear enlargement, crowding, and hyperchromasia limited to the crypt base. The lesion shows strong [3+] and diffuse [>50%] nuclear immunoexpression of p53.

three [13%] of the 26 goblet cell-deficient and six [22%] of the 45 crypt cell dysplastic lesions [$p = 0.661$].

While hypermucinous dysplasia commonly had a polypoid appearance [58%], crypt cell [96%] and goblet cell-deficient [65%] dysplastic lesions more frequently presented as flat/invisible dysplasia [$p < 0.001$] [Table 2]. When endoscopically/grossly visible, hypermucinous and goblet cell-deficient dysplasias were large lesions with similar mean sizes of 2.5 cm [range: 0.2–20] and 1.7 cm [range: 0.3–7], respectively [$p = 0.612$]. Hypermucinous dysplasia often demonstrated a tubulovillous/villous architecture [76%], whereas goblet cell-deficient dysplasia predominantly showed a tubular growth pattern [92%]. Crypt cell dysplasia exclusively demonstrated a flat architecture [100%] [$p < 0.001$]. At diagnosis, goblet cell-deficient dysplasia [31%] more often showed HGD than hypermucinous [15%] and crypt cell [0%] dysplasias [$p = 0.003$]. Seven [15%] of 47 hypermucinous, two [9%] of 23 goblet cell-deficient and five [19%] of 27 crypt cell dysplasia patients had multifocal lesions of the same non-conventional subtype [$p = 0.611$]. Of the 33 lesions with p53 staining results, four [33%] of 12 hypermucinous, two [29%] of seven goblet cell-deficient and eight [57%] of 14 crypt cell dysplastic lesions showed strong [3+] and patchy [10–50%] to diffuse [>50%] nuclear overexpression or null staining pattern [$p = 0.726$] [Figure 4]. There was no significant difference in the other features, including patient age, gender, ethnicity, IBD duration and extent, presence of PSC, and lesion location [$p > 0.05$] [Tables 1 and 2]. Of note, the mean number of biopsy samples obtained during each colonoscopy when hypermucinous, goblet cell-deficient or crypt cell dysplasia was first diagnosed was 5.3 [range: 1–13], 5.5 [range: 2–19] or 6.5 [range: 2–13], respectively.

Of the 92 low-grade lesions from the 71 patients with follow-up data, 19 [49%] of 39 hypermucinous, 10 [59%] of 17 goblet cell-deficient and 26 [72%] of 36 crypt cell dysplastic lesions were associated with subsequent detection of HGD [$n = 34$; 37%] or adenocarcinoma [$n = 21$; 23%] at the site of previous biopsy or in the same colonic segment within a mean follow-up time of 12 months [range: <1–73] [$p = 0.116$] [Table 2]. For outcome analysis per patient, 16 [47%] of 34 hypermucinous, eight [53%] of 15 goblet cell-deficient and 13 [59%] of 22 crypt cell dysplasia patients were diagnosed with HGD [$n = 19$; 27%] or adenocarcinoma [$n = 18$; 25%] on follow-up. The left colon [$n = 11$; 52%] was most frequently involved by adenocarcinoma, followed by the transverse colon [$n = 6$; 29%] and right colon [$n = 4$; 19%]. The mean size of the 21 adenocarcinomas was 2.9 cm [range: 0.2–8], and all but two [90%] were low-grade [well to moderately differentiated]. Eleven [52%] adenocarcinomas were deeply invasive [pT3 or pT4], and eight [38%] had lymph node metastases. Six [29%] of the 21 adenocarcinomas were classified as mucinous adenocarcinoma, five [83%] of which were associated with hypermucinous dysplasia and one [17%] of which was found in a patient with crypt cell dysplasia. Three [14%] adenocarcinomas were diagnosed as tubuloglandular adenocarcinoma, two [67%] of which were found in patients with crypt cell dysplasia and one [33%] of which was detected in a patient with hypermucinous dysplasia.

Table 3. Clinicopathological features of non-conventional vs conventional dysplasia

	Non-conventional dysplasia [n = 126, 97 patients]	Conventional dysplasia [n = 239, 149 patients][9]	p value
Mean age, years [range]	49 [20–78]	55 [21–78]	0.012
Male gender, n [%]	62 [64%]	92 [62%]	0.731
Caucasian ethnicity, n [%]	90 [93%]	133 [89%]	0.354
IBD subtype, n [%]	68 UC [70%] 25 CD [26%] 4 IND [4%]	112 UC [75%] 36 CD [24%] 1 IND [1%]	0.381
Mean IBD duration, years [range]	18 [<1–49]	17 [<1–52]	0.537
PSC, n [%]	19 [20%]	13 [9%]	0.013
Location, n [%]	27 Right [21%] 80 Left [63%] 19 Transverse [15%]	72 Right [30%] 119 Left [50%] 46 Transverse [19%] 2 Unknown [1%]	0.012
Endoscopic/gross appearance, n [%]	43 Polypoid [34%] 14 Flat [11%] 69 Invisible [55%]	196 Polypoid [82%] 7 Flat [3%] 36 Invisible [15%]	<0.001
Mean size, cm [range]	2.3 [0.2–20]	1.3 [0.1–6]	0.280
Histological grade at diagnosis, n [%]	110 LGD [87%] 16 HGD [13%]	200 LGD [84%] 39 HGD [16%]	0.358
Histological architecture, n [%]	37 Tubular [29%] 43 Tubulovillous [34%] 1 Villous [1%] 45 Flat [36%]	183 Tubular [77%] 54 Tubulovillous [23%] 2 Villous [1%]	<0.001
Outcomes, n [%]	27/92 LGD [29%] 34/92 HGD [37%] 21/92 CRC [23%] 10/92 Negative [11%]	61/68 LGD [90%] 1/68 HGD [1%] 6/68 CRC [9%]	<0.001

Abbreviations: CD, Crohn's disease; CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IND, indeterminate colitis; LGD, low-grade dysplasia; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

3.3. Comparison between non-conventional and conventional dysplasias

We recently reported the clinicopathological features of 239 IBD-related conventional dysplastic lesions from 149 IBD patients, which were used to underscore the distinctive features of non-conventional dysplasia [Table 3].[9] The patients with non-conventional dysplasia were younger [mean: 49 years, range: 20–78] than those with conventional dysplasia [mean: 55 years, range: 21–78] [p = 0.012]. They were also more likely to have a concurrent history of PSC [20%] than those with conventional dysplasia [9%] [p = 0.013]. Although HGD was uncommon in either non-conventional [13%] or conventional [16%] dysplasia at diagnosis [p = 0.358], non-conventional dysplasia [60%] was more often associated with HGD or adenocarcinoma than conventional dysplasia [10%] on follow-up [p < 0.001]. Furthermore, non-conventional dysplasia more frequently presented as flat/invisible dysplasia [66%; p < 0.001] in the left colon [63%; p = 0.012] than conventional dysplasia [18% and 50%, respectively]. When endoscopically/grossly visible, non-conventional dysplasia [mean: 2.3 cm, range: 0.2–20] was larger than conventional dysplasia [mean: 1.3 cm, range: 0.1–6], but this did not reach statistical significance [p = 0.280]. Tubular architecture was more common in conventional dysplasia [77%] than in non-conventional dysplasia [29%] [p < 0.001]. No significant difference was noted in the other features, including patient gender and ethnicity, as well as IBD subtype and duration [p > 0.05].

4. Discussion

Although different morphological patterns of non-conventional dysplasia have been recently described in IBD,[9,11–13] there has been limited research into their clinicopathological features and clinical outcomes, in part due to the rarity of these subtypes and the likelihood that they are under-recognized. If certain subtypes [such as hypermucinous, goblet cell-deficient and crypt cell dysplasias] more frequently present as flat/invisible lesions and develop advanced neoplasia on follow-up, this could potentially help identify patients who may benefit from increased colonoscopic surveillance with random biopsy sampling or even preventive colectomy. In this regard, we note that of the 126 non-conventional dysplastic lesions, 83 [66%] were endoscopically/grossly invisible [n = 69; 55%] or flat [n = 14; 11%] [vs 18% for conventional dysplasia; p < 0.001], and that the risk of harbouring HGD or adenocarcinoma on follow-up was greater in patients with non-conventional dysplasia [60%] than in those with conventional dysplasia [10%] [p < 0.001] [Table 3]. Also, PSC, a well-known risk factor for CRC, was more frequently associated with non-conventional dysplasia [20% vs 9% for conventional dysplasia] [p = 0.013]. Overall, these results support that hypermucinous, crypt cell and goblet cell-deficient dysplasias are high-risk markers for advanced neoplasia. This is further supported by our recent finding that crypt cell [100%], hypermucinous [80%] and goblet cell-deficient [25%] dysplasias have higher rates of aneuploidy than IBD-related polypoid conventional dysplasia [8%; p = 0.002] or sporadic adenomas [9%; p = 0.037].[9,12] Of note, the finding of aneuploidy is extremely rare in non-dysplastic IBD mucosa, as we previously reported that only two [4%] of 45 IBD biopsies without dysplasia showed a distinct aneuploid population.[8] In another study, all 30 non-dysplastic biopsies from 30 IBD patients showed normal DNA content.[14]

There is increasing evidence that hypermucinous dysplasia is a high-risk marker for advanced neoplasia. First, hypermucinous dysplasia was the most common non-conventional subtype [42%]

found in a cohort of IBD patients with CRC.[11] Second, despite its rather low-grade morphology, hypermucinous dysplasia has been shown to share similar molecular features with conventional HGD. For instance, Anderson *et al*. reported that hypermucinous dysplasia, even without cytological atypia, has a higher rate of *KRAS* mutations [61%] than conventional LGD [4%; $p < 0.001$] or HGD [29%; $p > 0.05$].[15] Similarly, we recently demonstrated that the frequency of aneuploidy is significantly higher in low-grade hypermucinous dysplasia [80%] than in low-grade polypoid conventional dysplasia [8%] or sporadic adenomas [9%] [$p < 0.001$].[9] Third, in the current study, we note that 19 [49%] of the 39 low-grade hypermucinous dysplastic lesions with follow-up data were correlated with subsequent detection of HGD [$n = 9$; 23%] or adenocarcinoma [$n = 10$; 26%] at the site of previous biopsy or in the same colonic segment within a mean follow-up time of 11 months [range: <1–44] [Table 2]. Although the finding of advanced neoplasia within a year after the index biopsy is likely to represent missed HGD or adenocarcinoma [rather than true neoplastic 'progression'], it remains a possibility that hypermucinous dysplasia represents at least a high-risk low-grade lesion, if not already HGD, as noted above. Interestingly, five [50%] of the 10 adenocarcinomas were classified as mucinous adenocarcinoma, raising the possibility that hypermucinous dysplasia may be a precursor lesion for mucinous adenocarcinoma in IBD patients. In another study, we reported that four [57%] of seven hypermucinous dysplastic lesions were associated with HGD or CRC on follow-up.[15] Finally, while hypermucinous dysplasia not uncommonly presented as flat/invisible dysplasia [42%] in contrast to conventional dysplasia [18%] [$p < 0.001$], when endoscopically/grossly visible, it was large, with a mean size of 2.5 cm [Tables 2 and 3].

Similar to hypermucinous dysplasia, goblet cell-deficient dysplasia may be considered as another high-risk lesion for subsequent detection of HGD or CRC. In support of this, we note that 10 [59%] of the 17 low-grade goblet cell-deficient dysplastic lesions with follow-up data were associated with subsequent detection of HGD [$n = 4$; 24%] or adenocarcinoma [$n = 6$; 35%] at the site of previous biopsy or in the same colonic segment within a mean follow-up time of 13 months [range: <1–47] [Table 2]. These findings are consistent with the previous results that four [40%] of 10 goblet cell-deficient dysplastic lesions were associated with HGD or CRC on follow-up, and that low-grade goblet cell-deficient dysplasia has a higher rate of aneuploidy [25%] than low-grade polypoid conventional dysplasia [8%] or sporadic adenomas [9%].[9] Other investigators have also commented on the high rates of *TP53* [44%], *KRAS* [22%] and *PIK3CA* [56%] mutations in goblet cell-deficient dysplasia.[16] Furthermore, goblet cell-deficient dysplasia more frequently presented as flat/invisible dysplasia [65%] than conventional dysplasia [18%] [$p < 0.001$] [Tables 2 and 3].

The current study confirms the previous finding that crypt cell dysplasia is a high-risk marker for advanced neoplasia.[9,12] We previously demonstrated that all 14 crypt cell dysplastic lesions from seven IBD patients presented as flat/invisible lesions and showed aneuploidy, and that six [86%] of the seven patients developed HGD [$n = 4$] or CRC [$n = 2$] in the same colonic segment within a mean follow-up time of 27 months. These results are in agreement with the current series in which the vast majority of crypt cell dysplastic lesions presented as flat/invisible lesions [96%], and that 26 [72%] of the 36 low-grade lesions with follow-up data were correlated with subsequent detection of HGD [$n = 21$; 58%] or adenocarcinoma [$n = 5$; 14%] at the site of previous biopsy or in the same colonic segment within a mean follow-up time of 16 months [range: <1–73] [Table 2]. In fact, the high rate of aneuploidy in crypt cell dysplasia is consistent with our previous finding that aneuploidy is a frequent event in flat/invisible dysplasia [41% for flat/invisible LGD and 93% for flat/invisible HGD],[8] suggesting that crypt cell dysplasia is at least LGD, if not already HGD. The dysplastic nature of crypt cell dysplasia is further supported by the recent molecular finding that *TP53* [43%] and *KRAS* [14%] mutations are common in crypt cell dysplasia.[16]

Although diagnostic agreement for each non-conventional subtype has been previously reported to be very good with four or more GI pathologists in agreement in 92% of goblet cell-deficient and ≥60% of hypermucinous and crypt cell dysplasia cases,[17] it may be difficult to diagnose and/or grade some of these lesions, in particular crypt cell dysplasia, in a consistent manner based on morphology alone. In fact, we previously reported a poor interobserver agreement in the diagnosis and grading of crypt cell dysplasia among seven GI pathologists.[12] Even though the majority of pathologists recognized the atypical morphology of crypt cell dysplasia and diagnosed as indefinite for dysplasia, LGD or HGD in 83% of their readings, the diagnosis of indefinite for dysplasia was made in 50% rather than either LGD [13%] or HGD [19%]. As such, we recommend that pathologists use the diagnostic term 'crypt cell atypia' to describe similar changes if a definite diagnosis of dysplasia cannot be made with certainty on histological grounds, and suggest the need for increased endoscopic surveillance [i.e. a repeat colonoscopy within 3–6 months]. If cytological atypia is accompanied by significant neutrophilic inflammation and/or ulceration, a diagnosis of indefinite for dysplasia may be more appropriate.

The detection of IBD-related dysplasia has traditionally relied on extensive random biopsies as well as targeted biopsies of visible lesions.[5,18,19] However, a recent randomized controlled trial demonstrated that targeted biopsies detect similar proportions of dysplasia as random biopsies,[20] which makes sense considering that the vast majority of IBD-related dysplasia is endoscopically visible.[19,21,22] In this regard, we note that 66% of non-conventional dysplastic lesions were endoscopically/grossly invisible or flat, suggesting that performing only targeted biopsies in IBD patients [as advocated by some authors[4,19,20]] may miss some of these high-risk lesions, and thus, IBD patients may benefit from random biopsy sampling in addition to targeted biopsies. Also, it is worth noting that 47 [48%] of the 97 patients were diagnosed with non-conventional dysplasia only. Of the remaining 50 [52%] patients who had both non-conventional and conventional dysplasias, 18 [19%] had non-conventional dysplasia in a different colonic segment away from conventional dysplasia [Table 1]. Hypermucinous [57%] and crypt cell [52%] dysplasias were less likely to be associated with conventional dysplasia than goblet cell-deficient dysplasia [26%] [$p = 0.044$]. Overall, these findings suggest that although not uncommonly associated with conventional dysplasia, non-conventional dysplasia may be the only dysplastic subtype identified in IBD patients.

There are some potential limitations to our study. First, pathologists do not routinely use the terms hypermucinous, goblet cell-deficient and crypt cell dysplasias, which makes it difficult to identify these cases retrospectively. Although our method of identifying these cases could have introduced potential bias, it is important to stress that these non-conventional subtypes appear to be rare. In our recent retrospective analysis of all dysplastic [$n = 417$] and serrated [$n = 148$] lesions from 264 IBD patients seen at UCSF, we identified only 14 crypt cell, 10 goblet cell-deficient and seven hypermucinous dysplastic lesions, but demonstrated that advanced neoplasia was more likely to be associated with crypt cell [$n = 13$;

93%], hypermucinous [n = 4; 57%] and goblet cell-deficient [n = 4; 40%] dysplasias than conventional dysplasia [19%] on follow-up [$p < 0.001$].[9] Our proposed standardized definitions of these non-conventional subtypes may allow for identification of more cases, so that future prospective studies can precisely determine their risk for advanced neoplasia. Second, one may argue that more than half of the 97 patients [n = 50; 52%] had conventional dysplasia in addition to non-conventional dysplasia, suggesting that there may be some confounding effects of conventional dysplasia on our outcome results. However, we note that the follow-up analysis of each non-conventional subtype is based on the occurrence of advanced neoplasia at the site of previous biopsy or in the same colonic segment where non-conventional dysplasia had been initially diagnosed. Also, 47 [48%] of the 97 patients had non-conventional dysplasia only, and among the 50 patients with both conventional and non-conventional dysplasias, 18 [19%] patients had conventional dysplasia in a different colonic segment away from non-conventional dysplasia. Overall, 65 [67%] of the 97 patients had non-conventional dysplasia either as the only dysplastic subtype or in a different colonic segment away from conventional dysplasia. Furthermore, among the patients who were diagnosed with non-conventional dysplasia only, 54% of the lesions were correlated with subsequent detection of advanced neoplasia, which is similar to the rate of advanced neoplasia in our entire cohort [60%]. Finally, although the finding of advanced neoplasia within a year after the index biopsy may suggest that some advanced lesions were already there at the initial colonoscopy [rather than true neoplastic progression], this does not conflict with one of our main findings that a seemingly low-grade lesion, but with histological features of hypermucinous, goblet cell-deficient or crypt cell dysplasia, is often associated with advanced neoplasia and may require at least a careful follow-up to ensure that there is no unsampled HGD or adenocarcinoma. Yet, it remains a possibility that these non-conventional subtypes may already represent HGD, even in the absence of classic high-grade histological features [i.e. severe cytological and/or architectural atypia].

In conclusion, hypermucinous, goblet cell-deficient and crypt cell dysplasias appear to have a higher malignant potential than conventional dysplasia or sporadic adenomas. More than half of the lesions presented as flat/invisible dysplasia and developed advanced neoplasia on follow-up. These results are further supported by the previous finding that these lesions often have molecular alterations characteristic of conventional HGD [i.e. higher rates of aneuploidy and/or *KRAS* mutations]. Thus, it is important for pathologists to recognize these non-conventional subtypes to ensure complete removal and/or careful follow-up. A larger, prospective study may be helpful to further validate these findings.

Funding

This work was supported by the UCSF Department of Pathology.

Conflict of Interest

None declared.

Author Contributions

W.T.C. contributed to the study concept and design, analysis and interpretation of data, and drafting of the manuscript. M.S., L.Z., L.A., N.S., X.L., M.G.D., M.W., J.C., G.Y.L., and H.M.K. contributed to the study design, analysis and interpretation of data, and critical review of the manuscript.

Data Availability Statement

The data underlying this article are available in the article.

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