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Nonconventional dysplasia in ulcerative colitis: a clinicopathological study of 694 patients

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Abstract

Background Ulcerative colitis (UC) carries an increased risk of colorectal carcinoma (CRC) through the inflammation–dysplasia–carcinoma sequence. Recently, several nonconventional dysplastic subtypes have been recognized, often lacking classical features and posing diagnostic challenges.

Method This retrospective study evaluated dysplasia frequency and patterns in UC patients using archival colonoscopic biopsy specimens from the Pathology Laboratory at Ain Shams University Hospitals between 2020 and 2024.

Results A total of 694 patients with histologically confirmed UC were included. For each patient, 1 representative colonoscopic biopsy was evaluated: the most recent biopsy from the most distal colonic site when multiple biopsies were available. This specimen was reviewed histologically, regardless of whether dysplasia had previously or concurrently been diagnosed at another site. Based on this standardized approach, 203 of the 694 patients (29.3%) were found to have dysplasia, including 88 patients (43.3%) with conventional dysplasia and 115 patients (56.7%) with nonconventional dysplasia. The most common nonconventional subtype was dysplasia with increased Paneth cell differentiation (48.7%), followed by hypermucinous dysplasia (19.1%), crypt cell dysplasia (18.3%), goblet cell-deficient dysplasia (11.3%), and serrated dysplasia variants (2.6%). Over 87% of nonconventional dysplastic lesions presented endoscopically with flat/invisible appearance; however, serrated dysplasia subtypes represented an exception, as all serrated lesions in our cohort were polypoid. Patients with nonconventional dysplasia were significantly younger (median 29.5 vs. 35 years for conventional dysplasia, P=0.015).

Conclusions Nonconventional dysplasia is frequent in UC, and often presents endoscopically with flat/invisible appearance. Pathologists should recognize and report these subtypes to improve surveillance accuracy.

Keywords Ulcerative colitis, dysplasia, nonconventional dysplasia

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Conflict of Interest: None

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease (IBD). Globally, UC has an estimated incidence of 9-20 patients per 100,000 persons per year, and a prevalence ranging from 156 to 291 per 100,000 [1]. In Egypt, the reported prevalence of UC remains low, probably because of underdiagnosis and limited awareness, although recent data suggest a rising incidence curve [2].

One of the most serious complications of UC is the development of colorectal carcinoma (CRC), which accounts for approximately 15% of UC-related deaths [3]. Patients with UC face a 2-3-fold higher risk of CRC compared with the general population [4,5]. This malignant transformation usually follows the classic inflammation–dysplasia–neoplasia sequence, where chronic inflammation drives genetic and epigenetic alterations in

the colonic epithelium. In support of this, dysplasia is identified in 75-90% of IBD-associated CRC patients. Although IBD-associated CRC is often conceptualized within the inflammation–dysplasia–neoplasia sequence, dysplasia is not unique to IBD and can also be observed in sporadic CRC. Moreover, mortality is higher in IBD-associated CRC, highlighting the importance of endoscopic surveillance [5,6].

Given that dysplasia is the earliest histologically detectable precursor to cancer, it has become the cornerstone of UC surveillance protocols and an active area of investigation. While conventional dysplasia is well recognized, emerging evidence highlights the presence of nonconventional dysplastic subtypes, which may lack classical features and thereby evade early detection [7-9]. These nonconventional subtypes pose a diagnostic challenge and may represent an underappreciated step in colorectal carcinogenesis.

Choi *et al* proposed a classification system for subtypes of nonconventional dysplasia, identifying distinct histomorphologic patterns, including hypermucinous dysplasia (HMD), dysplasia with increased Paneth cell differentiation (DPD), goblet cell-deficient (GCD), crypt cell dysplasia (CCD), sessile serrated lesion (SSL)-like and traditional serrated adenoma (TSA)-like dysplasia, and serrated dysplasia not otherwise specified (NOS). According to Choi *et al*, these subtypes may be present in approximately half of patients with IBD-associated CRC, suggesting their potential role in malignancy progression [9].

Subsequent studies demonstrated that these dysplastic variants often exhibit specific molecular alterations, such as aneuploidy, *KRAS* mutations and p53 abnormalities [9-13]. These findings indicate that nonconventional dysplasia represents not only a histological challenge, but also a potential precursor of HGD or CRC.

A review of the literature reveals that most existing studies on nonconventional dysplasia in IBD patients have focused on specimens from patients with established CRC [7,9,10,14]. Furthermore, data concerning the frequency and characteristics of these lesions within the Egyptian population are lacking. To date, however, no studies have investigated these dysplastic subtypes in the context of colonoscopic surveillance biopsies from the Egyptian population, representing a significant gap in the global understanding of UC-related neoplastic progression in underrepresented regions.

The aim of this study was to identify and evaluate the clinicopathological features of nonconventional dysplastic subtypes in UC patients by applying the morphological criteria proposed by Choi *et al* [9] to archival colonoscopic biopsy specimens retrieved from the Surgical Pathology Unit at Ain Shams University Hospitals. By focusing on endoscopic surveillance material rather than post-colectomy specimens, our study provides practical insights into the early histological identification of nonconventional dysplasia in routine practice.

Patients and methods

This retrospective study included all available UC patients diagnosed in the Pathology Laboratory at ASU Hospitals from January 2020 to December 2024. A total of 694 UC patients were included, with 1 representative colonoscopic biopsy retrieved per patient for histopathological evaluation, to ensure standardized histopathologic assessment. Therefore, the analyzed specimen may not fully reflect the overall dysplasia burden or the complete distribution of dysplastic subtypes throughout the colon.

Patients were included based on a confirmed diagnosis of UC, which was established based on colonoscopic and histopathological criteria [15]. Exclusion criteria included the unavailability of clinical or endoscopic data. All patients included were anonymized and assigned serial study numbers to ensure patient confidentiality. Relevant demographic and clinical data were retrieved from patients' archived records. For each patient, 1 biopsy specimen was included. If multiple specimens were available for a given patient, only the most recent biopsy from the most distal colonic site was included in the analysis, regardless of whether dysplasia had been previously or concurrently diagnosed at another site. This approach was chosen to standardize sampling and avoid overrepresentation of individual patients with multiple biopsies.

For each patient, 1 representative hematoxylin and eosin (H&E) stained slide was retrieved from the archives and examined for histological activity and the presence of conventional and/or nonconventional dysplasia. Conventional dysplasia was classified as low-grade (LGD) or high-grade (HGD), according to the criteria established by Riddell *et al* [16]. Nonconventional dysplasia was classified according to the morphological criteria described by Choi *et al* [9]. Briefly, DPD is characterized by tubular architecture with Paneth cell differentiation present in at least 2 adjacent crypts in 2 different foci. HMD demonstrates villous or tubulovillous pattern with tall mucin-secreting cells constituting more than 50% of the lesion. CCD presents as a flat lesion with basal crypts lined by cells with round or oval nuclei without nuclear stratification, along with preservation of surface epithelial maturation and absence of surface involvement. GCD shows tubular growth with cells having elongated hyperchromatic nuclei and complete or near complete absence of goblet cells. TSA-like dysplasia exhibits tubulovillous or villous architecture with serrated pattern and lining cells with elongated nuclei and eosinophilic cytoplasm. SSL-like dysplasia demonstrates tubular architecture with serrated appearance and T-shaped crypts. Serrated NOS dysplasia reveals tubular architecture with serration, but lacks specific features of SSL or TSA. In all subtypes of nonconventional dysplasia, the lining crypts exhibit at least low-grade dysplastic changes. During the study's retrospective review, dysplastic lesions were re-evaluated and classified into conventional and nonconventional subtypes according to current morphologic criteria. Since routine diagnostic reports during the study period did not systematically apply this classification, the exact numbers of cases originally reported as nonconventional dysplasia could not be reliably determined. Several lesions categorized as nonconventional dysplasia in the present study had previously been reported simply as dysplasia without subtype designation.

All biopsies were independently reviewed by 2 pathologists (MIH and FME). In case of discrepancy regarding the type

or grade of dysplasia, a consensus diagnosis was reached by 2 senior pathologists (TEH and NAR). All reviewers were blinded to the patients' clinical features. Evaluation was performed using a stepwise dual-power microscopic approach. An initial low-power examination was performed to screen for overall mucosal architecture and to identify areas suspicious of dysplasia or specific nonconventional subtypes. This was followed by high-power magnification to confirm the morphological features and establish the final classification. (Fig. 1).

Statistical analysis

The collected data were revised, coded, and entered into IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA). Quantitative data are presented as means, standard deviations, and ranges for parametric variables, and as medians and interquartile ranges (IQRs) for nonparametric variables. Qualitative data are presented as numbers and percentages. The chi-square test and Fisher's exact test (when the expected count in any cell was less than 5) were applied to assess the relationships between different types of dysplasia and other clinicopathologic features. A P-value less than 0.05 was considered significant.

The Declaration of Helsinki's guidelines were followed in this retrospective cohort study. The study methodology was authorized by the Research Ethical Committee for scientific research at the Faculty of Medicine, Ain Shams University, with IRB number M S 639/2023.

Results

Demographic and clinicopathologic data

A total of 694 patients with histologically confirmed UC were included in the study. The patients' age ranged from 5-80 years, with a median of 31 years. There were 396 female patients (57.1%), and 298 male patients (42.9%). Bleeding per rectum was reported in 443 patients (63.8%). Among the total patients, 375 (54.0%) were newly diagnosed at the time of specimen submission, with no prior treatment history, whereas 319 patients (46.0%) were previously diagnosed with UC and were receiving treatment.

Overall dysplasia and its relationship with other clinicopathologic features

Among the 694 studied patients, dysplasia was identified in 203 patients (29.3%). Among these, 88 patients (43.3%) were classified as conventional dysplasia, whereas 115 (56.7%) exhibited nonconventional dysplasia. The median age among dysplastic patients was 31 years, with 140 patients (69%) aged

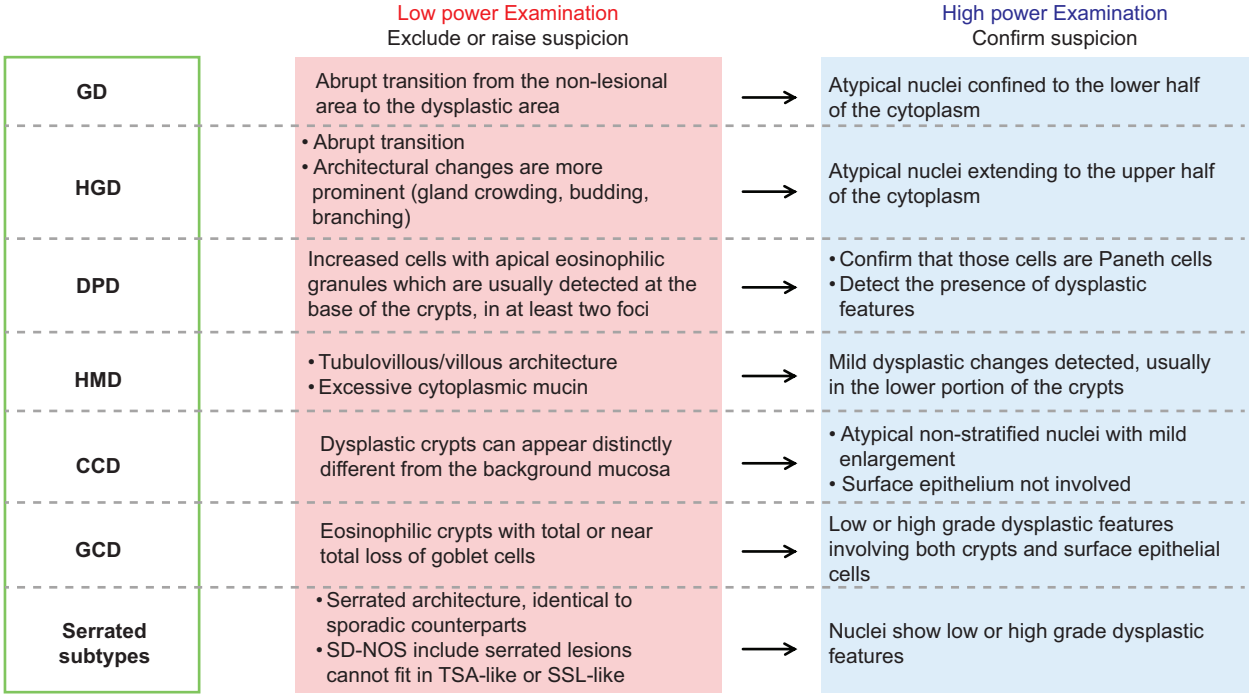

Figure 1 Stepwise dual-power approach for subclassification of conventional and nonconventional dysplasia in ulcerative colitis
SD-NOS, serrated dysplasia not otherwise specified; TSA, traditional serrated adenoma; SSL, sessile serrate lesion

40 years or younger and 63 (31%) older than 40 years. One hundred thirteen patients (55.7%) were female, and 90 (44.3%) were male. The frequency of dysplasia was significantly higher among previously diagnosed UC patients (52.7%) compared with newly diagnosed patients (47.3%) (P=0.03). However, no significant relationships were identified between dysplasia and other clinicopathological factors (Table 1).

Conventional dysplasia and its relationship with other clinicopathologic features

Patients with conventional dysplasia (n=88) ranged in age from 15-74 years, with a median age of 35 years. Fifty-five patients (62.5%) were younger than 40 years, while 33 (37.5%) were 40 years or older. In terms of sex, 50 patients (56.8%) were female and 38 (43.2%) were male. Eighty-one patients exhibited LGD, whereas 7 had HGD. The patients with HGD (median age 49 years) were significantly older than those with LGD (median age 33 years) (P=0.005). The majority of the LGD lesions presented with a flat/invisible endoscopic appearance (85.2%), in contrast to 42.9% of the HGD lesions (P=0.019). No significant relationships were identified between the grade of dysplasia and other clinicopathological features.

Nonconventional dysplasia and its relationship with other clinicopathologic features

Patients with nonconventional dysplasia (n=115) ranged in age from 19-68 years, with a median age of 29 years. Eighty-five patients (73.9%) were under the age of 40, and 30 (26.1%) were 40 years or older. Sixty-three patients (54.8%) were female, and 52 (45.2%) were male.

DPD (Fig. 2A) was the most prevalent nonconventional subtype and was identified in 56 patients (48.7%) in the nonconventional dysplasia group. The median age of DPD patients was 28 years. This subtype was more common among female patients (58.9%), and the majority (58.9%) were known patients with UC. Notably, all DPD lesions (100%) exhibited a flat/invisible endoscopic appearance.

HMD (Fig. 2B) was identified in 22 patients (19.1%), with a median age of 28 years. This subtype was slightly more prevalent in male patients (54.5%) and was most common in known UC patients (68.2%). On endoscopic examination, 11 HMD lesions (50%) appeared flat/invisible, whereas the remaining 11 (50%) presented as polypoid lesions.

CCD (Fig. 3) was identified in 21 patients (18.3%), with a median age of 37 years. Thirteen patients (61.9%) were under the age of 40, and 8 (38.1%) were aged 40 years or older. CCD was more frequently observed in female patients (57.1%), and was predominantly found in newly diagnosed UC patients (71.4%) without prior treatment history. On endoscopic evaluation, all CCD lesions (100%) had flat/invisible appearance.

GCD (Fig. 2C) was identified in 13 patients (11.3%), with a median age of 30 years. GCD was slightly more prevalent in male patients (53.8%), and was nearly equally distributed between known patients (46.2%) and newly diagnosed (53.8%) UC patients. Endoscopically, all GCD lesions presented with flat/invisible endoscopic appearance.

Serrated nonconventional dysplasia represented the least common group, identified in 3 (2.6%) of the nonconventional dysplasia patients. Only 1 case (0.9%) of TSA-like dysplasia was identified, and 2 patients (1.7%) were classified as serrated NOS. The median age of the affected patients was 26 years. The group had a male predominance (66.6%), and all were previously diagnosed with UC. Endoscopically, all

Table 1 Demographic and clinicopathologic characteristics of ulcerative colitis patients with and without dysplasia

Characteristics	Ulcerative colitis without dysplasia	Ulcerative colitis with dysplasia	Test value	P-value
	N=491	N=203		
Age (years)				
< 40	337 (68.6%)	140 (69%)	0.00	>0.99
≥ 40	154 (31.4%)	63 (31%)		
Sex				
Female	283 (57.6%)	113 (55.7%)	0.16	0.69
Male	208 (42.4%)	90 (44.3%)		
Known case				
No (index diagnosis)	279 (56.8%)	96 (47.3%)	4.88	0.03
Yes	212 (43.3%)	107 (52.7%)		
Bleeding per rectum				
No	169 (34.4%)	82 (40.4%)	1.97	0.16
Yes	322 (65.6%)	121 (59.6%)		
Histologic activity status				
Active	446 (90.8%)	188 (92.6%)	0.37	0.54
Quiescent	45 (9.2%)	15 (7.4%)		

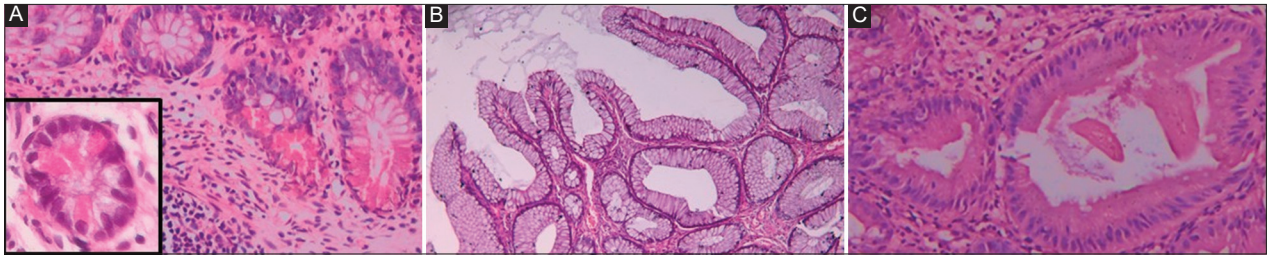

Figure 2 (A) Nonconventional increased Paneth cell differentiation dysplasia in a patient with ulcerative colitis, showing numerous Paneth cells located at the base of the crypts exhibiting characteristic apical eosinophilic cytoplasmic granules. (B) Polypoid nonconventional hypermucinous dysplasia in a patient with ulcerative colitis, exhibiting a tubulovillous architecture lined by cells showing prominent intracytoplasmic mucin. (C) Nonconventional goblet cell-deficient dysplasia in a patient with ulcerative colitis, showing nearly complete loss of goblet cells with low-grade nuclear dysplastic changes. (hematoxylin and eosin stain: A, C ×400, inset ×1000, B ×200)

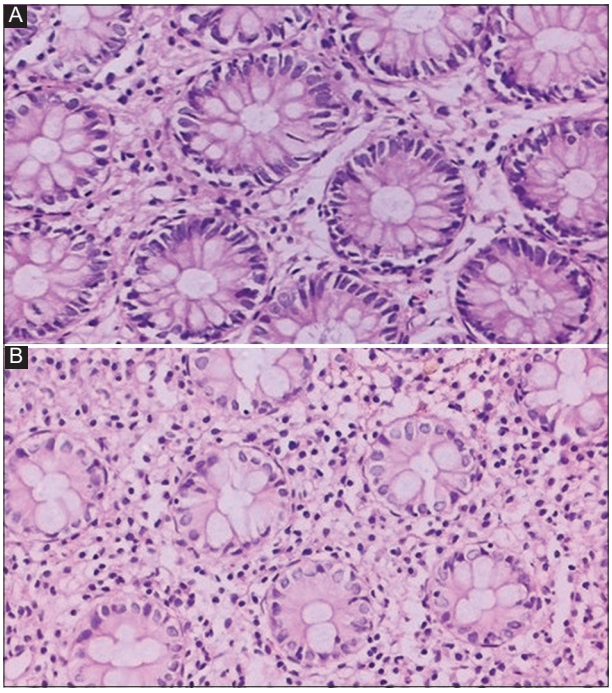

Figure 3 A case of ulcerative colitis with nonconventional crypt cell dysplasia: (A) dysplastic crypts exhibiting slightly elongated hyperchromatic nuclei, absence of nuclear stratification and preserved goblet cells; (B) adjacent non-dysplastic crypts from the same specimen, showing normal cytological features (hematoxylin and eosin stain, ×400)

were polypoid. Regarding the architecture, all the polypoid lesions exhibited a tubulovillous architecture.

A statistically significant association was identified between rectal bleeding, as a clinical symptom, and the presence of nonconventional dysplasia (P=0.014), indicating that nonconventional dysplasia was more frequently observed among UC patients presenting with rectal bleeding. No other significant associations were identified between nonconventional dysplasia and demographic or clinicopathological parameters.

Comparison between conventional dysplasia and nonconventional dysplasia

Among patients with nonconventional dysplasia, 101 (87.8%) presented with flat/invisible endoscopic appearance, while in 14 (12.2%) the lesions were polypoid. In contrast, among patients with conventional dysplasia, 72 (81.8%) presented with flat/invisible endoscopic appearance, and 16 patients (18.2%) with polypoid lesions. Patients with nonconventional dysplasia were significantly younger than those with conventional dysplasia (P=0.013). After stratification by age group, no significant association was found between dysplasia type and age category, as both conventional and nonconventional dysplasia patients were distributed across all age bins, without a dominant cluster (Table 2).

Discussion

The present study provides a comprehensive histopathological and clinicopathological evaluation of conventional and nonconventional dysplasia in a large cohort of UC patients undergoing colonoscopic surveillance. By systematically applying the recent morphologic criteria for nonconventional dysplasia to a large series of endoscopic biopsy specimens, this study expands existing biopsy-based literature and highlights the practical relevance of these entities in routine diagnostic practice.

We identified overall dysplasia in 29.3% of patients, which exceeds the range reported in several prior studies (6-21%) [17-19]. This higher frequency of overall dysplasia in our study is probably multifactorial. Importantly, earlier studies focused predominantly on conventional dysplasia, and did not assess nonconventional subtypes. Greater awareness and deliberate evaluation for nonconventional dysplasia in the present study probably contributed to the higher detection rate. Differences in the cohort composition and characteristics of the study population may also have contributed to these findings. Overall dysplasia was significantly more common in already

Table 2 Comparison between conventional dysplasia and nonconventional dysplasia in the studied ulcerative colitis patients

Characteristics	Conventional dysplasia	Nonconventional dysplasia	Test value	P-value
	N=88	No=115		
Age (years)				
< 40 years	55 (62.5%)	85 (73.9%)	2.52	0.11
≥ 40 years	33 (37.5%)	30 (26.1%)		
Sex				
Female	50 (56.8%)	63 (54.8%)	0.02	0.88
Male	38 (43.2%)	52 (45.2%)		
Known case				
No (index diagnosis)	43 (48.9%)	53 (46.1%)	0.06	0.8
Yes	45 (51.1%)	62 (53.9%)		
Bleeding per Rectum				
No	30 (34.1%)	52 (45.2%)	2.12	0.14
Yes	58 (65.9%)	63 (54.8%)		
Histologic activity status	82 (93.2%)	106 (92.2%)		
Active	6 (6.9%)	9 (7.8%)	0.00	>0.99
Quiescent				
Endoscopic appearance				
Flat/invisible	72 (81.8%)	101 (87.8%)	0.99	0.31
Polypoid	16 (18.2%)	14 (12.2%)		

known UC patients than in newly diagnosed patients, which is consistent with the well-established correlation between longer disease duration, cumulative inflammatory damage, and dysplasia development [5,20]. Similarly, patients with HGD were significantly older than those with LGD, supporting the same concept of cumulative inflammatory burden.

A key finding of this study is the substantial contribution of nonconventional dysplasia to the overall dysplasia burden in UC. Nonconventional dysplasia accounted for 56.7% of dysplasia patients in our cohort. Although prior studies have not consistently demonstrated a significantly higher overall frequency of nonconventional dysplasia compared with conventional dysplasia, several have highlighted that nonconventional features are common, particularly in flat/invisible, endoscopically subtle, or previously unrecognized lesions [9,10,21,22]. Our findings emphasize the importance of actively commenting on nonconventional dysplasia in daily practice pathology reports, especially given its frequent presentation as flat or endoscopically invisible lesions, as observed in our cohort and others [11,22].

Recognition of nonconventional dysplasia is clinically significant, as accumulating evidence suggests that certain subtypes are more frequently associated with HGD or CRC than conventional dysplasia [9,10]. These morphological features may be unfamiliar to many practicing pathologists. Therefore, these lesions, especially in patients with subtle cytologic atypia, may be underdiagnosed or misinterpreted as benign, reactive changes or conventional dysplasia [9,10,23,24].

Patients with nonconventional dysplasia demonstrated a significantly lower median age compared with those with conventional dysplasia (29.5 vs. 35 years, P=0.013). Although the age ranges overlapped (19-68 and 15-74 years, respectively), age analyzed as a continuous variable confirmed a statistically significant difference between the 2 groups. Similar observations have been reported by Nguyen *et al* and Choi *et al*, who also noted a lower median age in nonconventional dysplasia patients with overlapping age distributions between the groups [9,25].

Among nonconventional dysplasia subtypes, DPD was the most frequent in our cohort, accounting for 48.7% of nonconventional dysplasia patients. This finding is comparable to those of Lee *et al* and Nguyen *et al*, who also identified DPD as the most common nonconventional subtype in their cohort [10,25]. In contrast, DPD was relatively uncommon in the cohorts of Choi *et al* and Bahceci *et al*, which included IBD patients who developed CRC [9,21]. These observations are consistent with the prior classification of DPD as a low-risk nonconventional dysplasia subtype, which may explain its higher prevalence in general population cohorts and lower prevalence in IBD-associated CRC cohorts [9,10]. Following DPD, HMD and CCD represented 19.1% and 18.3% of nonconventional dysplasia patients in our cohort. These 2 subtypes are of clinical importance, as they have been reported to have higher frequencies of KRAS mutations and DNA aneuploidy compared with conventional LGD or sporadic adenomas, and are more frequently linked to HGD or CRC, despite often subtle or low-grade morphology [9,10]. Our findings underscore the need for heightened awareness of these subtypes, especially given the diagnostic challenges associated with detecting CCD.

GCD represented 11.3% of our nonconventional dysplasia patients, a frequency consistent with the biopsy cohorts of Nguyen *et al* [10,25]. However, Bahceci *et al* reported a higher percentage of GCD cases in their IBD-associated CRC cohort, supporting its classification as a relatively high-risk subtype [21]. As a group, serrated dysplasias were rare in our

cohort, representing only 2.6% of nonconventional dysplasia patients, in line with previously published data [21,25].

The recognition of high-risk subtypes (HMD, CCD, GCD) is becoming important, as they often present endoscopically as invisible lesions, which may contribute to under-recognition in routine biopsies, and show molecular changes such as aneuploidy, KRAS mutations, and p53 abnormalities, which are associated with a higher risk of progression to HGD or CRC compared with conventional dysplasia [10,12,13,22].

In conclusion, nonconventional dysplasia is frequent and clinically relevant in UC surveillance biopsies, comprising over half of dysplastic lesions and commonly, apart from serrated subtypes, presenting with flat/invisible endoscopic appearance. Accurate recognition of these subtypes, particularly in superficial endoscopic biopsies, can be challenging. Maintaining awareness of nonconventional dysplasia and applying our structured stepwise dual-power microscopic approach may serve as a practical framework to support routine microscopic evaluation and may help reduce the overlooking or misinterpreting these lesions as reparative changes, especially given the high-risk potential of certain subtypes, including HMD, GCD and CCD, despite their low-grade morphology. Incorporation of these entities into routine diagnostic practice and histopathological reporting of endoscopic biopsies of UC patients may improve clinicopathologic correlation and support more informed patient management decisions. Further studies on the molecular characteristics of the various subtypes of nonconventional dysplasia are in our research plan.

Summary Box

What is already known:

- Ulcerative colitis (UC) is associated with an increased risk of colorectal carcinoma (CRC) through the inflammation–dysplasia–neoplasia sequence
- Dysplasia is the earliest histologically detectable precursor and the cornerstone of surveillance strategies
- While conventional dysplasia is well recognized, nonconventional dysplastic subtypes are increasingly described, but remain underdiagnosed because of their subtle morphology

What the new findings are:

- This study provides data from a large Egyptian cohort
- Nonconventional dysplasia accounts for a substantial proportion of dysplastic lesions (56.7%)
- Dysplasia with increased Paneth cell differentiation is the most common subtype
- Most nonconventional dysplasia lesions present with flat/invisible endoscopic appearance

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