

Systematic Classification of Colonic Crypts with Architectural Distortions Inulcerative Colitis

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Abstract: In ulcerative colitis (UC) the colonic mucosa shows in addition to high number of inflammatory cells, crypts with architectural distortions (CAD). Here we classify the histologic repertoire and assess the frequency of CAD in UC. Five-hundred and sixteen histologic sections from 29 colectomy specimens with UC (24 having adenocarcinoma and five, high-grade dysplasia, HGD) were reviewed. CADs were subdivided into four groups: i) Crypts with fission distortions, ii) Crypts with length distortions, iii) Crypts with outlines distortions and iv) Crypts with axial polarity distortions. The most frequent CAD group had axial polarity distortions (33.4%), and the less frequent CAD group, outline distortions (21.1%) ($P < 0.05$). No apparent differences in frequency between groups were found in colectomies with HGD/carcinoma, or in colectomies performed for medically-refractory UC without HGD/carcinoma. Most mucosal areas, however, portrayed countless crypts with normal shapes (CNS) lined with normal epithelium, excepting 45 CNS: 28 showed in conclusive-suspected cellular changes (ISCC), and 17, HGD. In contrast, out of the 902 CAD present in the specimens, 343 (38.0%) displayed ISCC, 186 (20.6%) HGD, and the remaining 373 (41.4%) normal epithelium. Hence, out of the 203 crypts exhibiting HGD, 186 (91.6%) were CAD and the remaining 17 (8.4%) CNS ($P < 0.05$). Based on these findings it is suggested that the microscopic search for HGD in UC colectomy-specimens should preferentially be focused to mucosal areas exhibiting CAD. This view is validated by recent findings showing that p53 over expression (a biomarker of epithelial carcinogenesis) significantly correlated with architectural distortions of the crypts in UC.

Keywords: ulcerative colitis, colonic crypts, aberrations, histology, phenotypes

1. INTRODUCTION

The normal colonic mucosa is built of a single layer of epithelial cells with inward folds called crypts. Crypts replicate by symmetric fission, beginning at their base, and proceeding upwards until two identical, individual crypts are created [1]. Sections cut perpendicular to the surface epithelium show a characteristic appearance of “row of test tubes” due to tightly packed, parallel crypts, “resting” on the *muscularis mucosae*. A slight variation in the configuration of the crypts and in the space between the crypts may occur, but crypt branching is rare. This architecture is retained throughout the colon, except in in nominate grooves (cloverleaf-like crypts connecting to a single lumen) [1]. In ulcerative colitis (UC) the colonic mucosa shows, in addition to high numbers of inflammatory cells, distortions of crypt architecture [2]. These architectural distortions

usually persist despite regress of inflammation due to treatment. In some colitic patients however, architectural crypt irregularities enigmatically revert to normal after many years of disease, a setting referred to as with *restitutio ad integrum* [3, 4].

The architectural crypt irregularities in UC have received various descriptive terms such as architectural aberrations [5], architectural crypt distortion [6] ramification of the crypts [7] considerable branching at the base of the crypts [8], crypt bifurcations [9], and crypt architectural disarray [10], to name some. Nearly 30 years ago, Allen *et al.* used semi-automatic image analysis to assess the architectural features of colorectal mucosa in UC [11]. Discriminant analysis using the variables mean epithelial height and mean *lamina propria* area per unit length of *muscularis mucosae*, separated normal from UC.

Subsequently, Hamilton *et al.* applied morphometry and stereology, to evaluate the architectural characteristics of regenerative and of dysplastic colorectal mucosa in ulcerative colitis [12]. Using neural networks on a mosaic of pixelated images (without any image analysis or image segmentation) the authors concluded that quantitative histological analysis of mucosal abnormalities may be of use in the objective diagnosis of reactive and dysplastic change in patients with ulcerative colitis [12]. More recently, Ficsor *et al.* [13] reported architectonic irregularities in the colonic

2. MATERIAL AND METHODS

Archival histological sections from 35 colectomies in patients with UC were reviewed. Six out of the 35 colectomies were rejected from the study: four due to partial mucosal autolysis and the remaining two due to partial faded stainability. In the remaining 29 colectomies, 516 histological sections (mean 17.8, range 10-42 sections) were available for study. Sections were cut at 4 μ m thickness and stained with hematoxylin and eosin (H&E). Three colectomy-specimens performed because of severe UC refractory to clinical treatment (without carcinoma or HGD) [14] were included as controls.

CAD were subdivided into four groups: *i*) Crypt-fission distortions, *ii*) Crypt-length distortions, *iii*) Crypt-outline distortions, and *iv*) Crypt-axial polarity distortions (in relationship to the muscularis mucosae).

The epithelial lining in CAD displayed the following features:

- a) Normal epithelium,
- b) Inconclusive or suspected cellular changes (ISCC), ranging from cell regeneration to possibly low-grade dysplasia. CAD lined with ISCC were often seen in areas with chronic- active inflammation, with ulcerated mucosa or with severe chronic inflammation without acute inflammation,
- c) High-grade dysplasia (HGD, as define by Riddell *et al* [15].

Not with standing, the vast majority of the colonic crypts both in areas with or without chronic inflammation, exhibited normal shapes (CNS) lined with normal epithelium. However, some CNS were lined with inconclusive or suspected cellular changes (ISCC), and others with unequivocal high-grade dysplasia (HGD) [15].

mucosa by the aid of automated digital microscopy and advanced digital analysis. Shape-related morphological changes helped to distinguish between normal mucosa and UC. However, despite those studies, the systematic analysis of the spectrum of crypts with architectural distortions (CAD) in UC, has remained unattended.

The purpose of this communication was to classify and to assess the frequency of CAD found in a cohort of colectomy specimen from patients with UC.

Statistical analysis. The non-parametric Kruskal-Wallis test was applied, to compare difference between groups. Statistical significance was defined as $P < 0.05$.

This study was approved by the Ethical Committee of the Karolinska Institute No.2017/1657-32

3. RESULTS

3.1. Clinical Data

3.1.1. Gender

Twenty-two were males and the remaining seven, females

3.1.2. Age

The mean age at colectomy was 48.1 years (range 32-65 years)

3.1.3. No. of Years with UC Prior Surgery

The mean number of years with UC prior surgery was 20.7 (range 10-32 years).

3.2. Histological Findings

The histological examination of the 29 colectomy specimens revealed adenocarcinoma in 24 and high-grade dysplasia in the remaining five.

The histological evaluation also revealed a total of 902 CAD in the 29 colectomy specimens (mean 31.1 CAD/colectomy, range 22-48). Two or more histologic phenotypes were found in each group:

Group1. (Crypts with fission distortions) included asymmetric crypt fissions and cystic crypts (Figure 1)

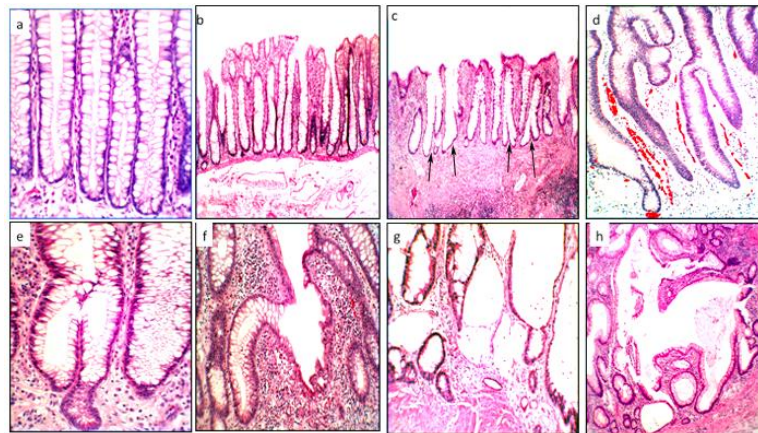


Figure1. Colonic crypts with fission distortions in ulcerative colitis **a:** Normal colonic mucosa (for comparison) showing tightly packed, parallel crypts “resting” on the muscularis mucosae, H&E x20, **b:** Colonic mucosa with mild chronic inflammation having parallel crypts resting on the muscularis mucosae, H&E x4, **c:** Colonic mucosa with expanded lamina propria due to severe chronic inflammation. Note colonic crypts with asymmetric fission at arrows H&E x4, **d:** Colonic crypts with asymmetric fission (one crypt seems to have “lost a shoe”, H&E x20), **f:** Colonic crypts with asymmetric fission (H&E x20), **g:** Colonic crypts with cystic dilations, (H&E x10), **h:** Colonic crypt with “deer-like” cystic dilatation (H&E x10).

Group2. (Crypts with length distortions), comprised hyperplastic crypts and atrophic crypts (Figure2)

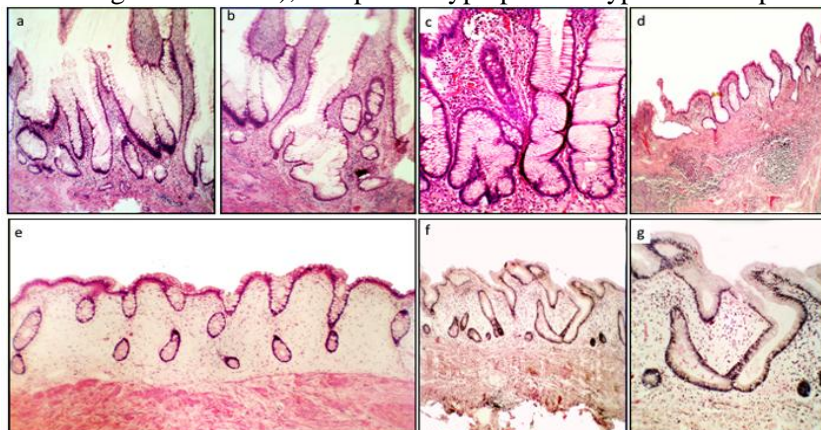


Figure2. Colonic crypts with length distortions in ulcerative colitis **a, b:** Hyperplastic colonic crypts with asymmetric fission (H&E x 4), **c:** Hyperplastic colonic crypts H&E x 4), **d-f:** Hypoplastic-atrophic colonic crypts (H&E x4), **g:** UC in remission with two “merging” atrophic crypts (H&E x 10).

Group3. (crypts with outline distortions) encompassed multi-lobate-scalloped crypts, and crypts with: *i*) serrated outlines, and *ii*) microtubular outlines (Figure 3), and

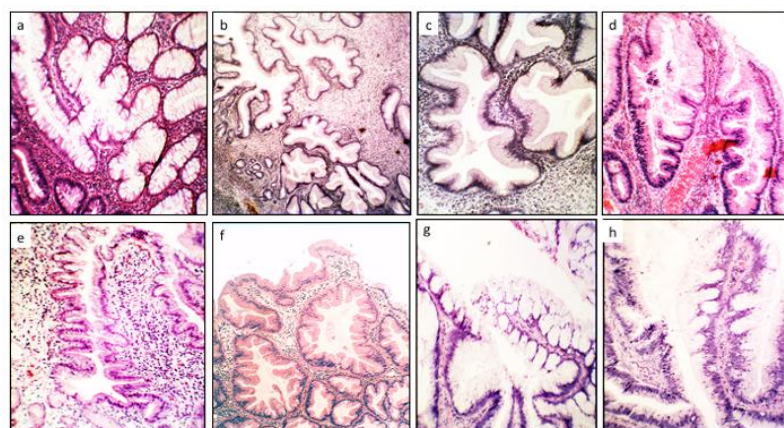


Figure3. Colonic crypts with outline distortions in ulcerative colitis **a:** Multi-lobate crypts (H&E x10), **b:** Crypts with scalloped architecture (H&E x4), **c:** Detail of **b** to highlight the scalloped architecture (H&E x20), **d-f:** Crypts with serrated architecture (H&E x10, x4 and x4, respectively.), **g-h:** Crypts with scallop (microtubular-like) architecture (H&E x4).

Group4. (Crypts with axial polarity distortions in relation to the *muscularis mucosae*), included meandering-serpentine crypts, inter

communicating crypts, ring-shaped crypts, inverted L shapes and horizontal ring-shaped crypts (Figure 4 and 5).

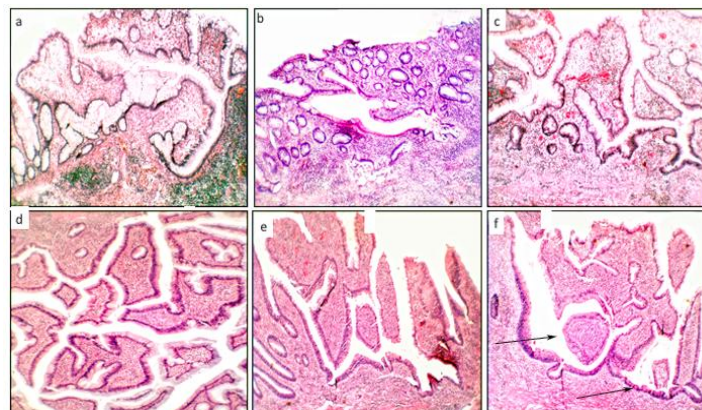


Figure4. Colonic crypts with axial polarity distortions in relation to the *muscularis mucosae* in ulcerative colitis **a-e:** Meandering-intercommunicating crypts, several with axial polarity distortions (H&E x4), **f:** Ring-shaped crypts, at arrows (H&E x4).

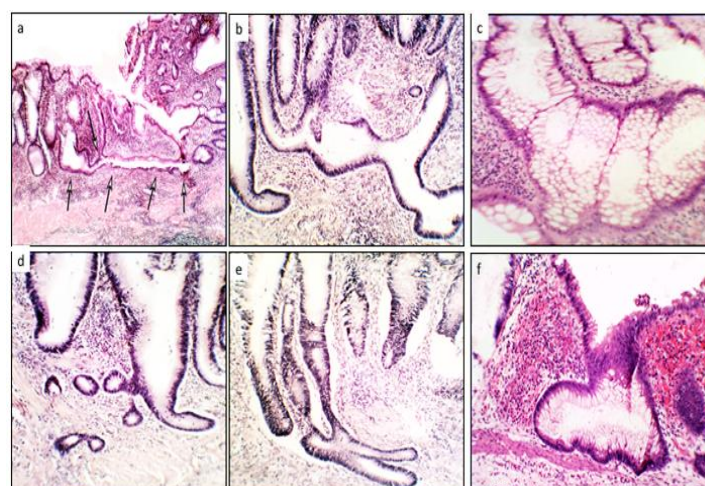


Figure5. Colonic crypts with axial polarity distortions in relation to the *muscularis mucosae* in ulcerative colitis **a:** Intercommunicating crypts with axial polarity distortions (at arrows, H&E x4), **b:** Long crypt parallel with the *muscularis mucosae* (H&E x10), **c:** Detail from another long horizontal crypt with “ring-accretions” (H&E x20), **d:** Horizontal epithelial “rings” at arrows (H&E, x10), **e:** Crypt with inverted L (showing fission distortion (H&E x10), **f:** “shoe-shaped” crypt found bordering regenerating ulcer (H&E, x20)

The most frequent CAD -groups (33.4%), portrayed crypt axial-polarity distortions (in relationship to the *muscular is mucosae*), and

the less frequent CAD-groups (18.7%), crypt-outline distortions (P< 0.05). (cfr. Table1).

Table1. The frequency of histologic groups of crypts with architectural distortions (CAD) found in 29 colectomy specimens in patients with ulcerative colitis having carcinoma (n=24), or high-grade dysplasia (n=5). Three additional colectomy specimens performed because of severe UC refractory to clinical treatment (without carcinoma or HGD) are also shown.

Groups with architectural crypt distortions(ACD)	29 colectomies* No. ACD (percent)	Three colectomies No. ACD (percent)
Distortions in crypt fission	242 (26.8%)	20 (28.6%)
Distortions in crypt length	190 (21.1%)	16 (22.9%)
Distortions in crypt outlines	169 (18.7%)	14 (20.0%)
Distortions in axial polarity of crypts (in relationship to the <i>muscularis mucosae</i>)	301 (33.4%)	20 (28.6%)
All	902 (100%)	70 (100%)

3.2.1. Epithelial Lining in CAD

Out of a total of 902 CAD, 373 (41.4%) had normal epithelial lining, 343 (38.0%) ISCA and

the remaining 186 (20.6%), HGD (Figure 6). CAD with normal epithelium/ISCA vs. HGD, $P < 0.05$.

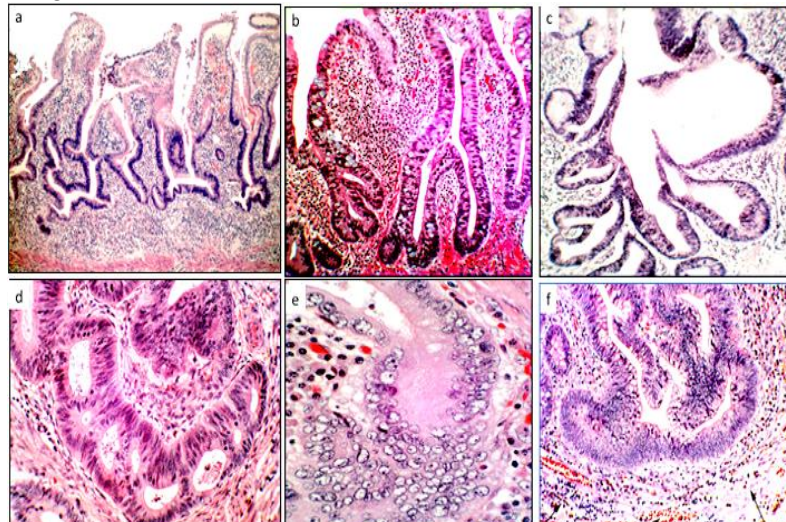


Figure 6. Colonic crypts with various phenotypes of architectural distortions having high-grade dysplasia in ulcerative colitis **a:** Note that the dysplasia includes the lower half of the crypts having severe architectural distortions (H&E, x4), **b:** Dysplasia in crypts with asymmetric fission (H&E x10), **c:** Dysplasia in a multi-lobate crypt with asymmetric fission (H&E x4), **d:** Dysplasia in agglutinated tubules in a row with axial polarity distortion (H&E x20), **e, f:** Detail of high-grade dysplasia in crypts with architectural distortions (H&E, x20).

Hence, out of the 203 colonic crypts with HGD 186 (91.6%) occurred in CAD and the remaining 17 (8.4%) in CNS ($P < 0.05$), inconclusive-suspected cellular changes (ISCC),

3.2.2. Epithelial Lining in CNS

The specimens had innumerable CNS lined with normal epithelium, in areas with or without inflammation. However, out of 45 CNS, 28 had ISCA and the remaining 17, HGD.

4. DISCUSSION

The systematic analysis of the spectrum of the colonic crypts with abnormal configurations, called CAD, was carried out in colectomy specimens with UC. The analysis revealed a high number of CAD exhibiting a wide gamut of architectural phenotypes. Rationally, crypts with or namentation distortions should had been generated by the chronic inflammation. And yet, large mucosal areas with chronic inflammation in the specimens had none to occasional CAD. In similarity with these findings, none to occasional CAD had been found in other colonic diseases with chronic inflammation such as diverticular disease-associated colitis [16], diversion colitis [17], lymphocytic colitis [18], radiation colitis [19], collagenous colitis [20], ischemic colitis [21], chronic colitis in Behçet’s disease [22] and non-specific ulcers of the colon [23]. A rational explanation for these findings

might be that CAD in UC were generated by factors other than ongoing chronic mucosal inflammation; one possible candidate might be an abnormal mucosal regeneration in areas with formerly mucosal denudation. In this context, CAD were recently found in mucosal areas bordering regenerating UC ulcers [14]. Why the process of mucosal regeneration severely alters the colonic crypts surrounding ulcers in colitic patients, remains enigmatic. Nevertheless, since chronic mucosal inflammation *per se* might not be crucial for the development of CAD [16-23], we are prone to speculate that the CAD found in the non-ulcerated colonic mucosa in UC could represent abnormal crypt regeneration in areas with formerly mucosal ulcerations in colitic patients [14].

The significance of ISCA, often found in CAD in UC, remains challenging. This since McKenna and Appel man [24] postulated that the category 'indefinite for dysplasia' is an honest recognition of the difficulties in distinguishing reactive or regenerative epithelium from low-grade dysplasia. Moreover, studying inter-observer variation between pathologists regarding the degree of dysplasia in UC, Eaden *et al.* [25] found total concordance of the 13 pathologists in only four of the 51 slides. Agreement was best for high-grade dysplasia. Based on those findings we opted for classifying crypts with regenerative, 'indefinite for dysplasia' or low-grade dysplasia [24] as with

inconclusive or suspected cellular changes (ISCC), and those with HGD (the histological phenotype less amenable to diagnostic disagreement)[25].

In conventional colonic adenomas, HGD initially develops at the luminal aspect of the crypts and progress downwards, towards the base of the crypts [26]. In UC, in contrast, dysplasia initially develops at the base of the crypts and progresses upwards, towards the luminal aspect of the crypts [27]. In CAD, we found normal epithelial lining in >40%, ISCC in 38% and HGD in >20%. The finding that HGD was often found in the lower aspect of the CADs, appears to be in concert with the “bottom-up” replacement concept, conveyed by up-growing dysplastic cells in UC [29]. Based on these considerations, it is not inconceivable that CAD might act as scaffolds at the time of “bottom-up” replacement by up-growing mutated dysplastic cells, a notion previously advanced in experimental animals [28]. The finding of serrated and micro tubular configurations with normal epithelial lining in CAD (cfr. Figure 3) supports the “dysplastic-replacement-of-the-crypts” concept, inasmuch as serrated adenomas and micro tubular adenomas do eventually evolve in patients with UC [29-33].

In a recent work, Popp *et al.* [34] found over expression of p53 -a tissue biomarker of epithelial carcinogenesis- in sections of UC patients. The authors found that architectural distortion significantly correlated with p53 over expression[34]. The results of Popp *et al.* [34] seem to be in concert with the present findings, inasmuch as HGD in UC mainly occurred in crypts with architectural distortions (here referred to as CAD).

It should be understood that innumerable CNS lined with normal epithelium were found in areas with and without inflammation, excepting for 45 CNS displaying ISCC or HGD.

While cellular descriptions and molecular signals that control cell proliferation and cell mutations during carcinogenesis in UC have received much attention [35-41] the signals that might be instrumental in choreographing morphogenesis [42] resulting in the “etching” of various CAD phenotypes in UC, have remained unexplored.

In closing, one possible practical implication of the present findings might be that the microscopic search for HGD in UC-colectomies

should primarily be focused to mucosal areas exhibiting CAD. This notion is validated by recent findings showing that p53 over expression (a biomarker of epithelial carcinogenesis) significantly correlated with architectural distortions of the crypts in UC [34]

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