Dysplastic Crypts in Asymmetric Branching in Ulcerative Colitis: A Preliminary Report

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Abstract. Aim: To report the detection of dysplastic crypts in asymmetric branching (DCAB) in biopsies from patients with ulcerative colitis (UC). Patients and Methods: One hundred consecutive endoscopic biopsies from patients with UC undergoing surveillance were reviewed. Results: Three biopsy/cases showed DCAB. The frequency of DCAB varied from two in one case, three in another case, and five in the remaining case. Conclusion: The final outcome of DCAB is to generate two or more dysplastic asymmetric offspring-crypts. Repeated DCAB offspring formation, together with new DCAB, would boost the pool of dysplastic crypts, resulting in an exponential expansion of the mucosal area occupied by dysplasia in UC.

The colorectal mucosa in patients with ulcerative colitis (UC) is subjected to recurring inflammatory insults followed by compensatory reparative processes. This inflammatory turmoil generates substantial epithelial alterations and triggers DNA methylation, crucial for the epigenetic long-term modulation of gene expression in UC-associated tumorigenesis (1). The appearance of epithelial dysplasia is the starting point in UC-associated malignant transformation. This fundamental notion is the base for surveillance programs in UC.

UC-associated dysplasia replaces the normal epithelium both in crypts displaying “test tube” shapes and in those with architectural distortions, which include branching crypts (2). Progression from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) may take several years, as demonstrated in endoscopic-biopsies in UC-patients undergoing surveillance (3). In 1984, we reported aneuploid cells lines in flow-cytometric DNA analysis of surveillance endoscopic-biopsies in a UC patient; subsequently this patient developed a colon carcinoma (4). The value of flow-cytometric DNA analysis in detecting aneuploid cells lines was subsequently confirmed by other authors (5). More recently, several molecular biomarkers were proposed for the early detection of colitis associated CRC (6); it was demonstrated that the molecular structure of the neoplastic epithelium in UC had been altered. Notwithstanding, the studies did not address the question: Which are the mechanisms whereby microscopic areas with UC-associated dysplasia, gradually attain larger dysplastic areas. The answer to this question is crucial for our understanding of the growth of colorectal dysplasia in UC-patients undergoing surveillance.

In previous work, we found crypts in asymmetric branching in colonic biopsies from patients with UC (7). Since such crypt phenotype does not occur in the normal colon mucosa, crypts in asymmetric branching were regarded as pathologic aberrations of cryptogenesis. Recently, while reviewing a new series of biopsies in patients with UC, we found cases with dysplastic crypts in asymmetric fission. The purpose of this communication is to describe and illustrate this previously unreported histologic parameter, in biopsies from patients with UC undergoing surveillance.

Patients and Methods

The material consists of 100 endoscopic biopsies with epithelial dysplasia in patients with UC undergoing surveillance. All patients were treated at the Klinikum Bayreuth, Fredrich-Alexander University, Erlangen-Nuremberg, Germany. A minimum of two endoscopic biopsies were taken from various colon segment and rectum. Biopsies were cut in 4 μm thick sections, stained with...
hematoxylin and eosin (H&E) and subsequently digitalized with a Hamamatsu Nanozoomer S360 digital scanner (Hamamatsu, Martins, Germany) and made them available online, to all authors. Ethical approval was obtained from the Ethics Committee of Friedrich-Alexander University, Erlangen-Nuremberg, Germany, for validation of the IBD-DCA score (ID number: 365_19 Bc).

**Results**

The 100 biopsies/cases displayed chronic mucosal inflammation and crypts with architectural distortions (2). Three biopsy/cases showed, in addition, dysplastic crypts in asymmetric branching (Figure 1). Dysplastic crypts in asymmetric fission were those exhibiting two or more back-to-back “ring-shaped” colorectal crypts varying in diameter and/or shape, apart from each other by the branching crest (7). The frequency of dysplastic branching crypts varied from two in one case, three in another case, and five dysplastic branching crypts in the remaining case.

**Discussion**

To keep constant the number of crypts in the normal colorectal mucosa in adults, crypts generate two daughter crypts by a process of symmetric crypt branching (8). In this preliminary communication, we detected in three UC-patients undergoing surveillance, dysplastic crypts in asymmetric branching. Rationally, dysplastic crypts in asymmetric branching will also generate at least, two asymmetric dysplastic daughter crypts (Figure 1A), thus increasing the pool of dysplastic crypts of various size and shapes usually found in UC-associated dysplasia. Succeeding waves of dysplastic daughter crypts and of occasional dysplastic crypts in asymmetric branching will exponentially boost the pool of offspring dysplastic crypts, resulting in a substantial expansion of the mucosal area occupied by UC-associated dysplasia.

Dulai et al. (9) postulated that the chronically inflamed mucosa produces a field of molecular changes that trigger histologic alterations leading to multiple dysplastic foci. Our findings offer an alternative view to the multiple dysplastic foci-theory of Dulai et al. (9).

It is reported that as a result of succeeding replications of dysplastic crypts in asymmetric branching, the size of a single microscopic mucosal area with UC-associated dysplasia will exponentially expand over time, snowballing thereby the development of a larger area with epithelial dysplasia. These dysplastic crypt-kinetic events in UC-patients might increase the risk for developing an invasive neoplasia. It is suggested that this previously unaddressed histological parameter is included in pathological descriptions of follow-up endoscopic biopsies in patients with UC-associated dysplasia.

![Figure 1. Example of dysplastic branching crypts in ulcerative colitis. A. Tri-foiled dysplastic crypt in asymmetric branching (H&E, original ×10), B and C: Dysplastic crypt in asymmetric branching. Arrows denoting asymmetric crypt lumen (H&E, original ×10), D, E and F: Other examples of crypts in asymmetric branching (H&E, original ×20).](image)
Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study

Authors’ Contributions

CAR responsible for concept and design, the review of the scanned sections, analysis and interpretation of data and wrote the original draft. CL-S and MV scanned sections with a Nanozoomer S360, making them available online to all authors for review. They also revised and finally approved the manuscript.

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