Chapter 2

Histologic Features with Predictive Value for Outcome of Patients with Ulcerative Colitis

Cristiana Popp and Radu Bogdan Mateescu

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Abstract

Ulcerative colitis is an inflammatory bowel disease with variable evolution, in which is difficult to establish patient's outcome. Histology is an important part of diagnosis of ulcerative colitis and has an increasing role in patients' management, since increasingly more histologic features with predictive value are being identified and validated. This chapter presents the most important histologic prognostic factors that should be included in histologic reports of patients with ulcerative colitis. Basal plasmacytosis and histologic healing are the most significant validated factors of prognosis in ulcerative colitis, while dysplasia is important since colorectal carcinoma is a severe complication of the disease.

Keywords: ulcerative colitis, predictive value, prognosis, histologic factors, basal plasmacytosis, dysplasia, histologic scores, histologic healing

1. Introduction

Inflammatory bowel diseases (IBD) are a group of chronic diseases with an unpredictable evolution, with repeated flare-ups and remissions. The most important inflammatory bowel diseases are ulcerative colitis and Crohn's disease.

One of the most difficult problems of management of patients with inflammatory bowel disease is the prognosis of these patients. This is an important issue for patients, since their life is involved; for medical specialists, who should choose the best therapeutical approach and surveillance schedule; for the health insurance system, which should tailor costs according to patient's needs and for the society, since patients with IBD are young and are facing a lifetime of partial disability and medical dependence.

This chapter aims to describe histologic features with prognostic significance in ulcerative colitis (UC). Usually, patients with UC undergo multiple colonoscopies with biopsies for diagnosis and surveillance. The European consensus on the histopathology of inflammatory

bowel disease recommends for diagnosis to harvest at least two biopsies from minimum five sites along the colon, including the rectum and the terminal ileum, and for surveillance four biopsies from every 10 cm of the colon [1]. Routinely reporting histologic features with prognosis values is an important component of management of these patients.

2. Histologic diagnosis of ulcerative colitis

Histologic diagnosis of UC requires examination of multiple colonic biopsies, including ones from the rectum and the terminal ileum, accompanied by clinical and endoscopical data [1].

Classical histologic features of untreated UC can be divided into three categories:

a. Inflammatory lesions: characteristic pattern is chronic active colitis with polymorphous inflammatory infiltrate in lamina propria and variable intraepithelial extension of neutrophils with or without ulcerations [2]. Activity is defined by the presence of neutrophils in lamina propria, in crypt epithelium (cryptitis) and inside crypt lumina (crypt abscesses) [3]. Chronicity is defined by lymphoplasmacytosis of lamina propria, with variable basal plasmacytosis instead of plasma cell gradient [2–4].

b. Architectural changes: including distortion of crypts' architecture, cryptic atrophy and villous aspect of superficial epithelium [1]. In normal large bowel mucosa, crypts are evenly distributed, parallel, with similar length (in accordance with the site of the biopsy). Architectural distortion in UC includes shortening and branching of crypts, separated by unequal spaces. Also, there is a variable hyperplasia of muscularis mucosa (especially in long-standing disease). Although architectural distortion is variable in time, it is found in all patients with UC, even during remission periods [5].

c. Cellular changes: including Paneth cell metaplasia, mucin depletion, regenerative epithelial changes and dysplastic epithelial changes. Paneth cells are normal in proximal colon, but finding them in the distal colon and in the rectum is a sign of repeated processes of ulceration repair and epithelial regeneration [6]. Although nonspecific, Paneth cell metaplasia is suggestive of a long-standing ulcerative colitis [7]. Paneth cells are involved in innate and acquired local immunity and can be modulators of inflammation and repair in UC [8]. Mucin depletion is the reduction of number of goblet cells and/or the decrease of the quantity of mucin in their cytoplasm [7]. It is not a diagnosis change, being correlated with inflammation and regeneration [7]. Dysplasia in UC is a late event and has a great significance for patients' outcome. It will be discussed later.

3. Histologic features with prognosis value in UC

Although prognosis is always an important challenge in management of chronic diseases, reporting prognosis factors in UC is, somehow, a new target for pathologists. There are three issues that should be accomplished for a histologic feature to become a used prognosis factor: validated predicting value, high intra- and interobserver agreement and wide applicability.

Multiple histologic and immunohistochemical features were proposed to be used in current practice, but only some are properly studied and validated. None of these features is reliable by itself; so, probably histologic prognosis factors will be better used in a composite score, including clinical, endoscopical and serologic features [9, 10].

Some of the most important histologic features involved in establishing prognosis in UC are as follows:

3.1. Basal plasmacytosis

Basal plasmacytosis (**Figure 1**) represents the presence of plasma cells in the lower part of the mucosa, between the base of the crypts and muscularis mucosae [11]. Rectal basal plasmacytosis is the most used microscopic lesion as prognosis factor, confirmed and validated by several studies [10–12]. Basal plasmacytosis is an early feature, frequently found in patients with UC, being used in diagnosis [12]. Its presence on rectal biopsies taken during remission has a strong value in predicting short-time relapse of the disease, especially if there is an increase of severity of basal plasmacytosis in asymptomatic patients [11, 13]. Although a recent study failed to demonstrate the value of basal plasmacytosis as prognosis factor [14], it is included in most recent ECCO-ESP European consensus on histopathology of inflammatory bowel disease as predictive of ensuing clinical relapse [1]. It fulfills all three conditions for a good predictive factor, because it was validated in some independent case series and cohort studies, has a very good reproducibility and a wide applicability, since it can be evaluated on routine histologic slides.

3.2. High number of eosinophils

The presence of eosinophils (**Figure 2**) is usually associated with basal plasmacytosis. Eosinophils are not simple effectors in UC but active players in inflammation and mucosal repair [12, 15].

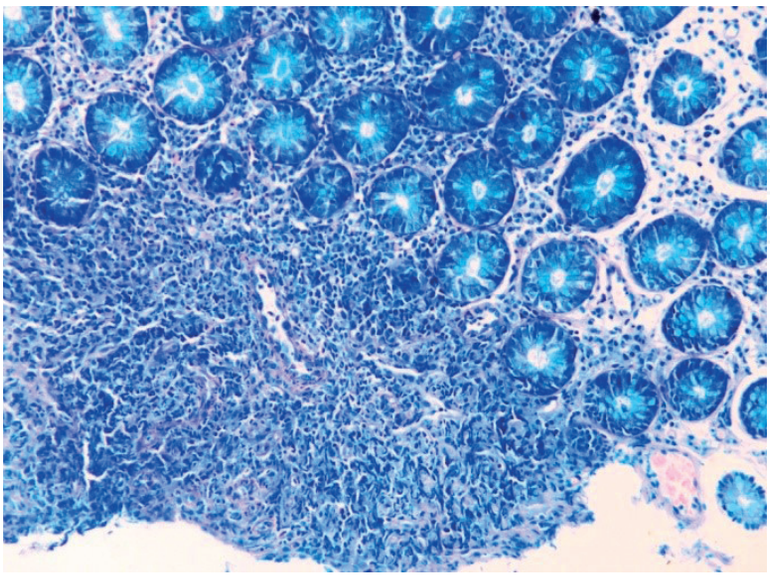

Figure 1. Basal plasmacytosis in a newly diagnosed patient with UC (Giemsa, 200×).

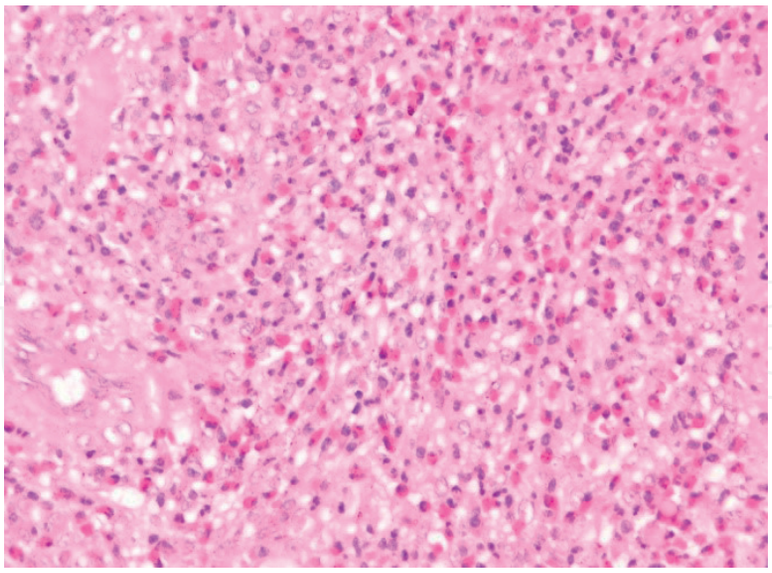

Figure 2. Numerous eosinophils in lamina propria in a patient with active UC. The area is in the immediate vicinity of an ulceration (hematoxylin & eosin, 100×).

Persistence of eosinophils in lamina propria after clinical remission indicates a high risk of relapse [1, 11], and some studies demonstrated that in quiescent phase of UC, remaining eosinophils are activated [16]. Their exact role is not fully understood, but they seem to be involved in plasma cell survival [12], to have proinflammatory and promotility effects [15] and to participate in normal and pathological repair of the mucosa [16]. Some studies demonstrated that high number of eosinophils is associated with a poor response to therapy [17], an increased incidence of relapse [18] and a high risk of extensive fibrosis and stenosis [12]. Reporting the number of eosinophils in UC patients can be done semi-quantitatively and this can be a good predictive factor if more studies will validate it.

3.3. Cryptitis and crypt abscesses

Cryptitis is the extension of neutrophils in the epithelium of crypts, while crypt abscesses are accumulations of neutrophils in the lumina of the crypts (**Figure 3**). They are, both, identified in active phase of UC [2]. They are predictive for an aggressive, refractory disease especially in older patients [19]. One study identified cryptitis in the majority of relapsing patients, while none of the non-relapsers had this feature on the initial biopsy [18]. The presence of cryptitis and crypt abscesses is a histologic feature with high reproducibility and wide applicability, but needs further studies to validate it as a valuable predictive factor.

3.4. Histologic activity

It is usually evaluated using a semi-quantitative score. The most frequently used in UC is Geboes score, which is a histologic scale including data about active inflammation and chronicity changes [20]. Although there are studies that validated Geboes score as a predictive marker in UC [10, 21], it is difficult to use in current practice because there are too many parameters to be quantified, some of them having a poor reproducibility. Also, interobserver

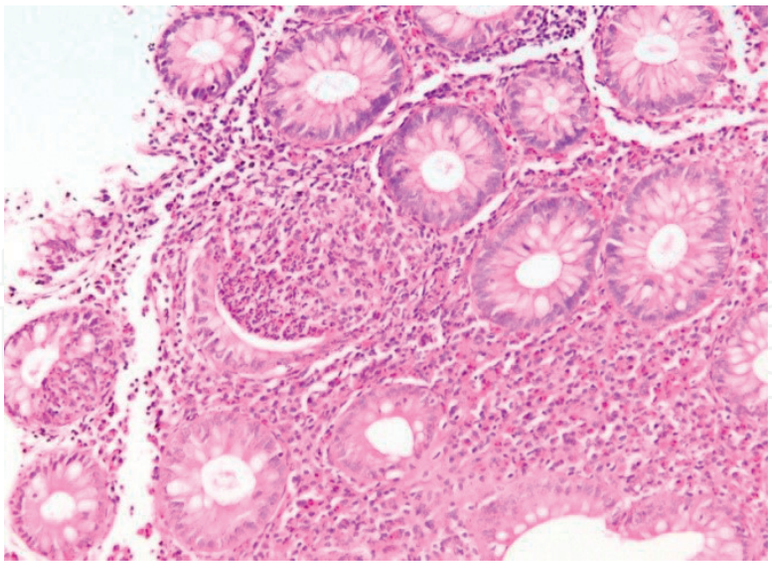

Figure 3. Cryptitis and cryptic abcess in a patient with active UC in the first relapse after initiating therapy (hematoxylin & eosin, 100×).

agreement varies among studies, being probably responsible for contradictory results. A Simplified Geboes Score is also available, being developed and validated with similar results as the original score [22].

Recently, some other promising scores for UC have been validated and used in current practice, the most prominent being Nancy and Robarts Indexes [23, 24]. They have a good reproducibility and a wider accessibility, but they still need validation as predictive tools for UC [25]. Nancy Index assesses, in a sequential form, the presence of ulceration, acute inflammatory infiltrate (presence of neutrophils and eosinophils in lamina propria and in epithelium) and chronic inflammatory infiltrate, using a semi-qualitative scale very easy to understand, which allows a great reproducibility [23]. All features have demonstrated their predictive value for relapse in different studies, so we have a good probability for Nancy Index to have an acceptable predictive value. It is recommended that Nancy Index be used in current practice; a fact that will ease further studies for validating this index [26]. Robarts Index is considered to be validated for UC diagnosis, but data are still lacking about its predictive value for UC outcome. Robarts score includes evaluation of: chronic inflammatory infiltrate, activity and the severity of erosions or ulceration [26]. Since it is more difficult to use, probably it is more suitable for clinical trials and research studies [27].

3.5. Architectural distortion

Distortion of crypt architecture (**Figure 4**) is usually present on colonic biopsies in patients with UC, even in cases with complete remission. It is the result of repeated episodes of inflammation, ulceration and repair and is the witness of mucosal remodeling. Architectural distortion includes shortening and branching of the crypts with inequality of inter-crypt distance [2]. Severe architectural distortion in a predictive factor for a short-time relapse in patients with clinical remission of UC [28]. Also, worsening of architectural distortion in

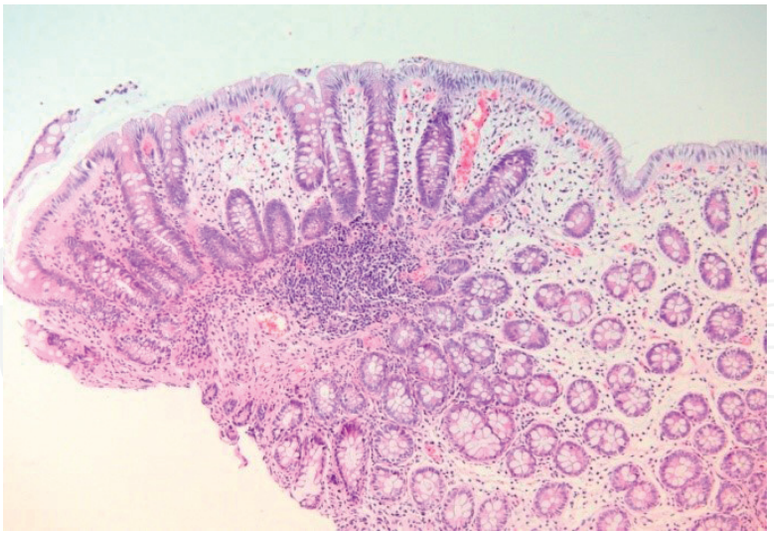

Figure 4. Architectural distortion of colonic mucosa in a patient with long-standing UC. Note an unequal distance between crypts and lack of crypt parallelism. Also, although there is no activity, some inflammation persists (hematoxylin & eosin, 40×).

patients with UC without an intervening acute inflammatory episode is usually a good predictor of evolution toward dysplasia, correlating with acquisition of mutations in epithelial cells [29].

3.6. Paneth cell metaplasia

Presence of Paneth cells (**Figure 5**) in the base of the crypts beyond splenic flexure is considered pathologic in UC. Their role and importance are still understudied. Paneth cell metaplasia

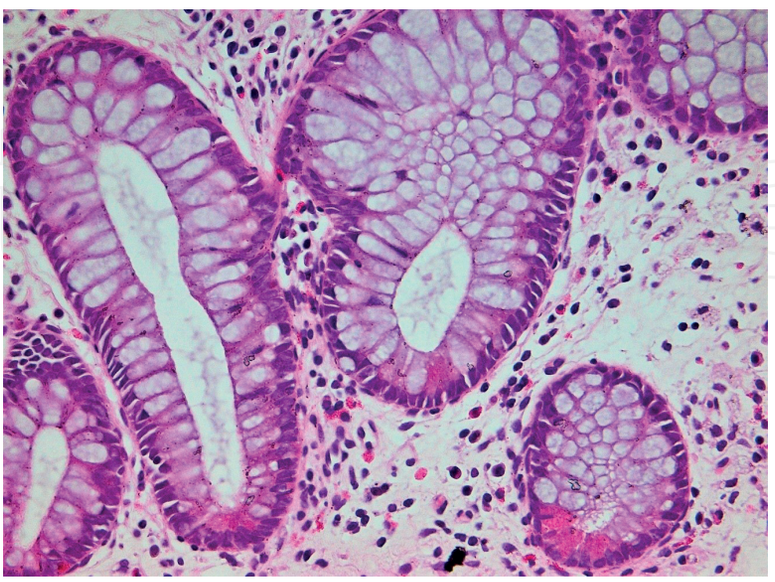

Figure 5. Paneth cells in the base of the crypts on a rectal biopsy, in a patient with a long-standing ulcerative colitis and minimal inflammation of rectal mucosa (hematoxylin & eosin 200×).

is considered a response to chronic injury and is identified in patients with long evolution of the disease, indicating their evolution toward malignant epithelial lesions [30, 31]. Practically, after ulceration, mucosa is repaired by various clones of epithelial cells; some of them with anomalies that make them differentiate as Paneth cells. In areas of Paneth cell metaplasia without dysplasia, there were identified mutations of β-catenin similar to those in dysplastic and malignant lesions of colon [31].

Paneth cells are involved in innate immunity of the gut, secreting antimicrobial proteins [8]. In inflammatory bowel disease, they probably are involved in offering antibacterial protection for the damaged mucosa [8]. It is still unknown if the defensins produced by Paneth cells are involved in the abnormal response of local immunity in UC [32].

3.7. Dysplasia

Dysplasia represents the morphologic changes of epithelial cells that are indicating accumulation of DNA damage and progression toward malignancy. Carcinogenesis in UC is inflammation-driven and has a different pathway than usual colorectal carcinogenesis. Epithelial cells are acquiring early mutations of *TP53* and *KRAS* genes and no mutations of *APC* genes, while in non-inflammatory carcinogenesis of colon, *APC* mutation is the earliest event [33].

Diagnosis of dysplasia is very difficult in UC, since usually, on biopsies taken in active disease, the pathologist identifies significant cellular changes (nuclear polymorphism, hyperchromasia and hypertrophy and sometimes high mitotic activity) related to inflammation and regeneration. But, regenerative changes are usually confined in the base of the crypts, exhibiting unequivocal maturation toward surface and are closely related with the activity of inflammation, while dysplasia lacks maturation and affects, in equal measure, superficial and cryptic epithelium. Also, usually dysplasia associates loss of nuclear polarity, changes in nuclear-cytoplasmic ratio and significant architectural changes. Diagnosis of dysplasia in UC requires architectural abnormalities and cellular alterations beyond regenerative changes [2].

After establishing the diagnosis of unequivocal dysplasia, the pathologist should characterize the nature of the lesion, using microscopic and macroscopic (endoscopic) data: flat dysplasia, adenoma-like dysplasia or dysplasia-associated lesion or mass (DALM) [2]. Furthermore, always it should be kept in mind the fact that patients with UC can have sporadic adenomas with dysplasia, which should be diagnosed like any sporadic adenoma. Usually, diagnosis of dysplasia in UC is formulated using the classical staging of low-grade dysplasia and high-grade dysplasia. Also, there is accepted a diagnosis of "indefinite" for dysplasia in cases with ambiguous cellular anomalies, usually in the vicinity of an ulceration [1, 2, 34]. Low grade dysplasia (LGD) indicates a superficial and cryptic epithelium with hyperchromatic and hypertrophic nuclei that maintain polarization, although with a discrete tendency toward pseudo-stratification. Architectural anomalies are usually mild [2]. High grade dysplasia (HGD) exhibits a more severe architectural distortion and significant cellular atypia with loss of nuclear polarization [2].

Some immunohistochemical markers, such as p53, p21, bcl-2, AMACR (alpha methyl-CoA racemase), can be used to sustain a morphologic diagnosis of dysplasia [1, 29]. Considering

that treatment for UC-associated dysplasia is usually colectomy and there is a poor inter- and intraobserver agreement, especially for the diagnosis of LGD, it is mandatory that the diagnosis is confirmed by an independent expert pathologist before any invasive therapy [34–36].

Dysplasia is an indicator of a poor prognosis for the UC patients, with a high risk of evolution toward invasive colorectal adenocarcinoma in the absence of treatment (about 40% for HGD) [37]. LGD has also a high risk of progression toward carcinoma, some recent studies showing that a patient with UC and LGD has a ninefold higher risk for carcinoma than a patient with UC but without dysplasia [1]. One third of patients with LGD, UC and primary sclerosing cholangitis will progress toward more severe neoplastic lesions [38]. About one half of the patients with UC and HGD have already an invasive colorectal carcinoma previously diagnosed [39].

For prognosis reasons, it is very important to know the location of dysplastic lesions, since carcinoma is more frequent in distal segments of the colon in patients with UC [1]. Patients with distal LGD have a higher risk and a shorter period to progression toward HGD than patients with proximal LGD. Also, flat LGD has a higher risk of progression than DALM [1, 40].

3.8. Histologic healing

Histologic mucosal healing can be considered the final goal of treatment in UC, but it is not a current target for treatment because definition is poorly standardized and it is not clear if the risks of additional drug toxicity are acceptable. It is also difficult to obtain, since about one third of the patients with clinical and endoscopical remission still have microscopic inflammation [41].

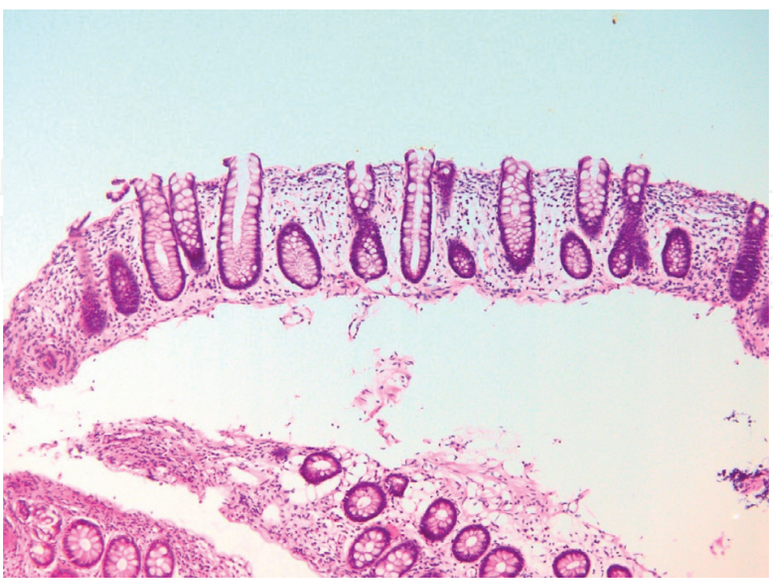

Figure 6. Histologic healing in a patient with repeated flare-ups included in a study for a biological agent. Note some crypts atrophy and irregularities, with normal inflammatory infiltrate and preservation of plasma cell gradient in lamina propria. No neutrophils or eosinophils can be identified (hematoxylin & eosin, 40×).

Histologic healing (**Figure 6**) is usually defined by the remission of inflammatory infiltrate and architectural changes. Some crypt atrophy or reduced crypt density, along with a slight increase of cellularity of lamina propria can persist. Only chronic inflammatory cells are allowed [1]. Complete remission of all lesions can be identified in about one quarter of patients [42]. There are some controversies about the degree of basal plasmacytosis that is acceptable in a patient with histologic healing, since plasma cells are not an indicator of disease activity [25]. Since basal plasmacytosis is, by itself, a poor prognosis marker, we consider that a true histologic healing has no basal plasmacytosis.

Also, it is very important that the diagnosis of histologic healing is formulated only when the pathologist has examined sufficient tissue fragments. Probably, best scenario includes at least two fragments from minimum five sites along the colon, including the rectum and the terminal ileum [1]. This method avoids errors of diagnosis, especially in patients with rectal sparing or skip-lesions, aspects frequently observed after treatment [43].

From all features with predictive value, histologic healing offers the best chance to maintain a sustained remission of the disease [25, 41]. It is, probably, the best indicator of treatment efficacy and the most logical moment for stopping maintenance therapy [44]. Ideally, remission includes clinical, endoscopical and histological resolution, which is called complete remission [45].

4. Conclusions

Histology is an important tool in management of UC patients. Colonic mucosa biopsies are not very difficult to obtain, and routine histologic slides can bring valuable information not only for diagnosis of the disease but also for predicting the patients' outcome.

The highest predictive value for relapse among histologic features is indicated by basal plasmacytosis and histologic healing, while presence of dysplasia indicates the risk for invasive malignancy.

There are still some issues to be clarified concerning histologic scores and their importance in UC management. Also, the term histologic healing needs a better definition until it becomes the ultimate goal of UC treatment.

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Conflict of Interest

The authors declare no conflict of interest.

Authors' contribution

Both authors contribute in equal measure to the conception of the work and have approved the final version of the chapter.

Author details

Cristiana Popp[1]* and Radu Bogdan Mateescu[2]

*Address all correspondence to: brigaela@yahoo.com

1 Colentina University Hospital, Department of Pathology, Bucharest, Romania

2 Colentina University Hospital, Department of Gastroenterology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

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