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Histomorphological Diagnosis of Ulcerative Colitis and Associated Conditions

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Abstract

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease that affects mainly young adults. The histologic examination of endoscopic biopsies or resection specimens plays an important part in the diagnosis and follow up of patients with inflammatory bowel disease, including UC. In this chapter, we discuss on main histological features that can be used when analyzing endoscopic biopsies, as well as features that can be evaluated in surgical samples of patients with UC. The differential diagnosis toward Crohn's disease and other mimickers is emphasized. In addition, the main complications associated with treatment and long-standing diseases, such as infection colitis and dysplasia are presented.

Keywords: ulcerative colitis, histology, biopsy, inflammatory bowel disease, inflammatory bowel disease-associated dysplasia, chronic active colitis, cryptitis, crypt abscess, CMV colitis, differential diagnosis, complications

1. Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease that affects mainly young adults with no sex predominance. Its incidence is rising worldwide and is higher in developed countries [1–3].

The disease is characterized by relapsing and remitting mucosal inflammation, starting in the rectum and extending to proximal segments of the colon. Clinically, UC usually presents with chronic bloody diarrhea. Extraintestinal manifestations, including peripheral arthritis, primary sclerosing cholangitis, and pyoderma gangrenosum occur in about a third of patients [4, 5].

The diagnosis of UC is based on a combination of clinical presentation, endoscopic findings, histology, and the exclusion of alternative diagnoses. The histopathological examination of biopsy specimens is fundamental, not only for making a specific diagnosis but also in determining the state of disease activity and evaluating the prospect of healing and risk of relapse [6]. Even further, histology is essential in assessing the response to treatment and diagnosing complications of treatment and longstanding UC, such as dysplasia and cytomegalovirus (CMV) infection.

2. Histological characteristics of UC

For a reliable diagnosis of IBD, at least two endoscopic biopsies each should be taken from at least five sites along the ileum, colon, and rectum [7–11]. The histological features of UC include non-active inflammation, active inflammation, structural changes, and epithelial abnormalities [5, 8]. The inflammation is concentrated in the mucosa, only occasionally the inflammation may spread into the superficial part of the submucosa.

Non-active inflammation includes the presence of lymphocytes and plasma cells in the lamina propria that could be associated with edema and hyperemia. Apart from areas of ulceration, the inflammatory infiltrate in untreated UC is limited to the mucosa, diffuse or continuous without any variations in intensity or skip lesions, and its severity increases characteristically toward the rectum [5, 12, 13]. When three or more plasma cells accumulate in the mucosal lamina propria around the crypt base or between the crypt base and the muscularis mucosae, a condition is termed basal plasmacytosis [11, 14]. This phenomenon is observed already in biopsies obtained at early onset, sometimes it is the first lesion to appear. Although limited and focal in the initial phase of UC, it later spreads to more colonic segments [15, 16]. The occurrence of eosinophils in the lamina propria, between the crypts, and within the muscularis mucosae, has been associated with aggressive disease and a high risk of relapse [17].

Active inflammation is defined by the presence of neutrophils in the lamina propria, crypts, or surface epithelium. The term cryptitis is used when neutrophils are found penetrating the crypt epithelium, and crypt abscess is a term describing neutrophils occupying the crypt lumens [11]. Neutrophils infiltrating the surface epithelium lead to mucosal erosions or ulcerations, on the other hand, cryptitis and crypt abscesses are associated with crypt destruction, all features of structural changes of the mucosa [8, 18].

Structural changes of the mucosa include crypt distortion and changes in surface topography (surface irregularity). Chronic inflammation leads to irregular size and shape of crypts (e.g., branching and shortening), irregular distribution of the crypts in the lamina propria, and crypts with loss of parallelism. Crypt atrophy is defined as shortened crypts, accompanied by an increased layer of lamina propria stroma between the crypt basis and the muscularis mucosae [5, 11, 19, 20]. Irregular mucosal surface or pseudovillous transformation means wide crypt mouths giving the mucosal surface a finger-like appearance [15].

Epithelial abnormalities include surface epithelial damage, metaplastic changes, and mucin depletion. Surface epithelial damage, such as flattening, focal cell loss, erosions, and ulcers reflect the activity of the disease. Ulcers in UC colitis are always associated with mucosal inflammation in contrast with Crohn's disease, in which the surrounding mucosa can appear uninfamed [5]. In addition, UC ulcerations tend to be more superficial, broad based and continuous [21]. In severe disease, these ulcers may undermine the adjacent mucosa, finally resulting in denudation of the mucosal surface or deep penetration through the muscularis mucosae [8]. Extensive ulceration with sparing of remaining mucosal islands may give rise to inflammatory pseudopolyps, which are common in the sigmoid and descending colon, but rare in the rectum [9, 20]. Hypertrophy of the muscularis mucosae and submucosal fibrosis is rarely identified in UC [22]. Paneth cell metaplasia, a term used when pyramidal crypt epithelial cells with supranuclear eosinophilic granular cytoplasm are present in the transverse and left

Figure 1.
Diffuse continuous inflammation with basal plasmacytosis, active inflammation with cryptitis, and structural changes including crypt distortion and atrophy. An erosion is present on the far right.

Figure 2.
Cryptitis and crypt abscess are shown on the left, while on the right Paneth cell metaplasia and cryptolytic granuloma are present.

colon [11], is an epithelial abnormality that can help in the diagnosis of long-standing UC [16, 19, 23]. Mucin depletion, defined as a reduction in number of goblet cells or depleted mucin within cells is additional epithelial abnormality frequently encountered in UC [11]. Characteristic histological features are shown in **Figures 1** and **2**.

3. Distribution of changes in UC

UC generally begins in the rectum, extending proximally in a continuous, circumferential pattern. The inflammatory infiltrate is diffuse or continuous without any variations in intensity and its severity increases characteristically toward the rectum. There are no skip-areas characteristics for Crohn's disease. The demarcation between inflamed and normal mucosa is sharp, although histological inflammation can be found in normal-appearing mucosa [22, 24]. Based on the spread of disease, three subtypes of UC are distinguished in Montréal classification—ulcerative proctitis where the proximal extent of inflammation is distal to the rectosigmoid colon, left-sided colitis, and extensive colitis when involvement extends proximal to the splenic flexure. The later also includes pancolitis [7, 25].

However, unusual inflammation patterns can occur, such as rectal sparing, cecal patch, and backwash ileitis. Rectal sparing should not be interpreted as evidence of Crohn's disease, as it can be the result of topical or systemic medications. The rectum may be spared in some adults with fulminant colitis [26, 27]. In up to 75% of patients with left-sided UC an isolated area of inflammation around the appendiceal orifice can be appreciated; this association is referred to as cecal patch [28]. In some patients with pancolitis, the ileum too is affected by acute or chronic inflammation. This condition has been termed “backwash ileitis” [29]. The ileal lesions in “backwash ileitis” are characterized by active inflammation in the villi and lamina propria, together with shortening and blunting of the villi. Focal erosions, mucous gland metaplasia, or patchy edema with mild active inflammation are features suggestive of Crohn's disease [29, 30].

4. Histological changes in different stages of the disease

UC is a chronic disease with the relapsing-remitting course and histological alterations are changing during the course of the disease. They are further influenced by medical treatment. In early-stage disease, the diagnosis of UC can be challenging due to the fact, that crypt architecture may still be preserved [17]. In longstanding disease, with widespread architectural crypt distortion and increased cellularity of the lamina propria the diagnosis of UC is more obvious. However, in this situation, rectal sparing, cecal patch, and backwash ileitis can be found that should not lead to misdiagnosis. Under treatment, the extent of involvement of the colon tends to decrease and the distribution pattern may change from diffuse (continuous) to patchy (discontinuous). Complete restoration of the rectal mucosa can be found in 34–44% of patients [5, 18]. In quiescent (clinically inactive) disease neutrophils are not observed, the mucosa may look nearly normal, however, some features, related to chronic mucosal injuries, such as architectural abnormalities, reduced crypt density, and basal plasmacytosis remain [13] (**Figure 3**). Histological mucosal healing is characterized by the resolution of crypt architectural distortion and inflammatory infiltrate. Nevertheless, the mucosa can still show some features of sustained damage, such as decreased crypt density with branching and shortening of crypts.

Figure 3.
Crypt architectural distortion and hypocellular stroma in quiescent disease.

5. Histologic disease activity

Assessment of disease activity is essential for developing and determining appropriate therapy in patients with UC. Disease activity and treatment response can be assessed using symptoms, biomarkers, endoscopy, and histology. Currently, clinical decision-making is predominantly based on clinical and endoscopic measures. Recently, histology has been recognized as an important prognostic factor and potential treatment target in patients with UC [31]. Both, epithelial damage in association with neutrophils and basal plasmacytosis have been proposed as markers of disease activity and the prediction of relapse. A recent meta-analysis revealed that histological remission was associated with lower rates of clinical relapse compared with those with histological activity and was a superior predictor of clinical relapse compared with endoscopic and clinical remission [32]. Furthermore, the presence of mucosal inflammation during follow-up in patients with UC was associated with a greater risk of subsequent colorectal neoplasia than in those with mucosal healing [33].

Histologically, the level of activity and the stage of the disease (e.g., flaring vs. quiescent UC) can be assessed by different scoring systems. Although more than 30 histological scoring systems in UC have been described, three have undergone extensive validation—the GS, Nancy Index, and Robarts Histopathologic Index [31, 34]. Recently a new consensus-based scoring index has been proposed, intended for both clinical practice and clinical trials that still needs to be validated [10]. Although these are not applied routinely, the pathology report should include some information on the level of activity in the biopsies to assess the effect of therapy and the risk of relapse. Pai [31] recommends that pathologists classify UC biopsies into 1 of 5 categories: normal colonic mucosa, quiescent chronic colitis without basal plasmacytosis, quiescent chronic colitis with basal plasmacytosis, chronic active colitis without basal

plasmacytosis, or chronic active colitis with basal plasmacytosis. If present, active inflammation should be graded. Assessing the degree of activity should be carried out on the worst affected biopsy sample [10].

5.1 Fulminant UC

Fulminant colitis is a term used for clinically acute severe colitis, usually involving the entire large bowel, often associated with systemic illness and sometimes accompanied by colonic dilatation (toxic megacolon). It is a well-recognized mode of presentation of UC that typically requires surgical resection [35]. In fulminant UC resections show mainly acute features (**Figure 4**), while chronic changes are rarely present. With the absence of the part of classical histological changes characteristic of UC both, identification and subclassification of inflammatory bowel disease can be very difficult.

In fulminant colitis, the macroscopic appearance of the mucosa is not sufficiently distinct to differentiate UC from Crohn’s disease and serositis may be observed [27, 36]. In parallel, fulminant colitis caused by UC may show Crohn’s-like histological features, such as deep ulcers, transmural inflammation, and rectal sparing. There may

Figure 4.
Surgical resection of the colon from a patient with fulminant UC. Sharp demarcation from macroscopically normal terminal ileum is apparent (arrow).

be deep ulcerations, typically eroding down to muscularis propria in a broad-based fashion. The transmural inflammation in this setting is typically more active and diffuse, lacking discrete lymphoid aggregates. This finding does not preclude a diagnosis of UC. In a study by Swan, the two most specific predictors of a final diagnosis of Crohn's disease were granulomas and transmural lymphoid aggregates, macroscopic features were unhelpful [27]. Apparent rectal sparing is also recognized in fulminant UC, where inflammation of the transverse colon is so severe as to make the rectum look comparatively spared [37].

6. Histological mimickers of UC

The main histological feature of UC is chronic active inflammation. In addition to Crohn's disease, many conditions can mimic UC on mucosal biopsies. Besides being familiar with histological features of a wide range of diseases and conditions that can be included in the differential diagnosis, a knowledge of the clinical, endoscopic, and in some cases even imaging features is required for the pathologist to come to the right conclusion. It is, therefore, recommended that the pathologist has access to the endoscopy report and possibly also radiological and microbiological investigations [21, 22]. Some more common mimickers are addressed in the following section.

6.1 Crohn's disease

Although Crohn's and UC are frequently discussed together under the term chronic inflammatory bowel disease, distinguishing UC from Crohn's is nevertheless important. One of the reasons is that only patients with UC are considered for ileal pouch formation, because of the high risk of complications after this procedure in patients with Crohn's disease. The most common macroscopic and microscopic features distinguishing UC from colonic Crohn's disease are listed in **Table 1**. Although non-caseating epithelioid granulomas are considered a classical feature of Crohn's disease, the presence of granulomas associated with cryptolysis are now well recognized in UC and their presence should not exclude the possibility of UC [21, 38] (**Figure 2**). Rectal sparing, cecal patch, and ileal disease, all features of UC that might suggest the diagnosis of Crohn's disease were discussed in one of the previous sections. Treatment of UC can also result in patchy disease, that is, a change from continuous to discontinuous inflammation and should not lead to reclassification to Crohn's disease [26]. Transmural inflammation, another classical feature of Crohn's disease may be encountered in fulminant UC [27]. Compared to surgical resection samples, the confident distinction of UC from Crohn's disease is even more challenging in endoscopic biopsy samples where only mucosal and limited submucosal tissue is sampled. When convincing features of chronic inflammatory bowel disease are evident, but further classification is not possible, the diagnostic term inflammatory bowel disease, unclassified (IBDU) is used [5, 22].

6.2 Infective colitis

Infective colitis is one of the most important differential diagnoses of chronic inflammatory bowel disease including UC since the steroid therapy used for treating inflammatory bowel disease can have adverse results in patients with infective colitis.

Typical features	Ulcerative colitis	Crohn's disease
Localization of inflammation	Limited to the mucosa, sometimes submucosa	Transmural
Non-active inflammation	Diffuse (continuous)	Focal (discontinuous), with skip lesions
Lymphoid aggregates	Frequent in mucosa, submucosa	Common, transmural
Granulomas	Absent, except cryptolytic	Common, transmural
Active inflammation (cryptitis, crypt abscesses)	Diffuse (continuous)	Focal (discontinuous)
Ulcers	Superficial	Deep, fissure-like, aphthous
Fistulae	Absent except in fulminant UC	Common
Inflammatory pseudopolyps	Common	Rare
Crypt architectural irregularity	Diffuse (continuous), marked	Focal (discontinuous)
Atrophy	Present, pronounced	Uncommon, mild
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present
Neuronal/muscular hypertrophy	Rare/absent	Common/present
Serositis	Absent except in fulminant UC	Present
Wall thickness	Normal	Increased
Strictures	Uncommon	Common
Fat wrapping	Absent	Common

Table 1.
Classical microscopic and macroscopic characteristics of ulcerative colitis and Crohn's disease.

One of the most common inflammatory patterns in enteric infections is the so-called nonspecific acute self-limited colitis that characteristically features intact crypt architecture with neutrophilic infiltrates of the surface epithelium. Basal plasmacytosis should not be seen as this is a marker of chronicity [39]. However, crypt abscesses and cryptitis may be present in the acute phase. As patients often do not come to endoscopy until several weeks after onset of symptoms, pathologists frequently do not see the classic histological features of acute infectious-type colitis. The protracted course of colitis, which may be seen for example in *Campylobacter* infections or shigellosis is more challenging to diagnose histologically as the development of “chronic” features such as crypt destruction and architectural disturbance may resemble inflammatory bowel disease including UC [40]. Extensive involvement of the surface mucosa by neutrophils is not often seen in inflammatory bowel disease and should alert the pathologist to the possibility of infection or toxin-induced injury [40]. In contrast, basal plasmacytosis, one of the earliest features of UC, crypt distortion, and irregular mucosal surface favor inflammatory bowel disease over infection [16, 19, 41]. However, in patients with early-onset UC (within 10 days of symptoms) structural changes may not yet be present [5, 42].

Lymphogranuloma venereum (LGV) and syphilis are sexually transmitted diseases caused by *Chlamydia trachomatis* and *Treponema pallidum*, respectively.

LGV and syphilitic proctitis are usually reported in men who have sex with men and can clinically mimic UC [43]. Histologically, both infections are characterized by an intense lymphohistiocytic infiltrate associated with prominent plasma cells within the mucosa and submucosa but minimal basal plasmacytosis. Characteristically, the associated acute inflammation with cryptitis and crypt abscesses is only mild to moderate. Crypt distortion and granulomas are minimal as well and Paneth cell metaplasia is rare [19, 43, 44]. Specific antibodies for *T. pallidum* are available that work well on paraffin-embedded tissue, however, real-time polymerase chain reaction on rectal swab specimens is the most reliable diagnostic test [43].

In addition to infections mimicking UC, in treated patients with clinical deterioration, superimposed infection, particularly CMV and *Clostridium difficile* should be considered [45, 46].

In some cases, diagnosis of infectious colitis is not possible on histological grounds alone. It is, therefore, vital to exclude infection by stool culture. In addition, a detailed clinical history addressing intestinal and extraintestinal symptoms, travel history, sexual history, and conditions influencing immune status should be collected [41].

6.3 Drug-induced colitis

Drug-induced colitis can show several histological patterns, one of them being a UC-like pattern with diffuse inflammation and ulceration. Histological features that favor drug-induced etiology include significant eosinophilic infiltrate, epithelial apoptosis, melanosis, cytoplasmic vacuolation, and increased intraepithelial lymphocytes [39].

Recently several monoclonal antibodies targeting immune checkpoint molecules became available for the treatment of advanced neoplasms. These immune checkpoint inhibitors (ICIs) induce immune activation and robust antitumor T-cell activity and can greatly improve survival. Following the administration of ICIs, immune-mediated adverse events including enterocolitis that can be severe are common [41, 47]. Microscopic features of ICI colitis include mixed inflammation of the lamina propria, cryptitis, crypt abscesses, crypt destruction, and granulomas [48] (**Figure 5**). In cases of distal distribution or pancolitis they may suggest UC. In ICI colitis crypt distortion, if present, is usually mild. Atrophic crypts often show marked attenuation of crypt epithelium and contain luminal apoptotic debris admixed with inflammatory cells [49]. If ICI colitis recurs, there may be chronic features such as basal lymphoplasmacytosis, crypt architectural irregularity, and Paneth cell metaplasia. Apoptosis and lymphocyte-mediated epithelial damage at the base of crypts favor ICI colitis, whereas severe inflammation, severe crypt distortion, and basal plasmacytosis favor UC [41, 50].

6.4 Segmental colitis associated with diverticulosis

Segmental colitis associated with diverticulosis (SCAD) is chronic colitis that is confined to the colonic segment containing diverticula [51]. By definition, the rectum and proximal colon are spared from inflammation [51]. SCAD is histologically characterized by a transmucosal chronic inflammation associated with crypt distortion, cryptitis, crypt abscesses, goblet cell depletion, basal plasmacytosis, or granulomas (UC-like or Crohn's disease-like pattern) [52]. However, these features are exclusively distributed in the sigmoid tract with sparing of the rectal and distal colonic mucosa [52–54]. Thus, for a correct diagnosis, it is fundamental to know the exact biopsy site

Figure 5.

Colitis associated with ICIs showing diffuse chronic inflammation with cryptitis and crypt abscesses without crypt distortion and basal plasmacytosis.

and to compare the morphology of the sigma and rectum in the differential diagnosis with IBD. In addition, patients with SCAD tend to be older compared to inflammatory bowel disease patients.

7. Associated conditions with ulcerative colitis

7.1 UC with primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease, characterized by the inflammation and fibrosis of both intrahepatic and extrahepatic bile ducts, leading to the formation of multifocal bile duct strictures [55]. It is frequently associated with other diseases and a classic extraintestinal manifestation of IBD. The diagnosis of PSC may precede diagnosing the patient with IBD but can present even after colectomy in IBD patients [56]. The course of UC differs significantly when PSC is present; the most notable differences are the presence of more extensive but colitis showing lower activity. It is also more often associated with rectal sparing and so-called backwash ileitis compared with patients with UC without primary sclerosing cholangitis [56]. Another important issue is the higher incidence of carcinomas in the PSC-UC patients [56, 57].

7.2 Histological evaluation after previous surgery

Absolute indications for surgery in UC patients include uncontrolled hemorrhage, perforation, and colorectal carcinoma or dysplastic lesions not amenable

to endoscopic removal. Surgery is also indicated in refractory acute severe UC or medically refractory disease [1]. The most commonly performed surgery for UC is restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) [58].

Adaptive changes of the pouch mucosa ("colonic metaplasia") are present several months after surgery in up to 87% of biopsies and consist of villous atrophy, crypt hyperplasia, and infiltration of the lamina propria by mononuclear cells, eosinophils, and histiocytes. In addition, mild ischemic changes can be observed in a few patients, while others may show features of mucosal prolapse. These changes should not be regarded as evidence of pouchitis. True pouchitis is associated with increased villous atrophy, acute and/or chronic inflammatory infiltrates, cryptitis, crypt abscesses, and ulceration [20, 59]. Based on the etiology pouchitis can be subdivided into idiopathic and secondary. Secondary pouchitis can occur in up to 30% of cases and can be classified as infectious (CMV, candida), ischemic, nonsteroidal antiinflammatory drugs-induced, collagenous, autoimmune-associated, or Crohn's disease [59]. Histology has a limited role in the evaluation of pouchitis; the main purpose for histology evaluation of the pouch is the exclusion of secondary pouchitis and dysplasia [60]. The diagnosis and differential diagnosis of pouchitis should be based on a combination of clinical, endoscopic, and histological findings [61].

When pouch biopsies show severe inflammation with neutrophils within the lamina propria and epithelium associated with erosions and ulcerations this should not lead to the reclassification into Crohn's disease. Even deep submucosal lymphoid aggregates and fistulous tracts were found in pouches excised from UC patients. A diagnosis of Crohn's disease after IPAA surgery should only be made when reexamination of the previous histological specimens shows typical pathologic features of Crohn's disease [62].

Pouchitis should be distinguished from cuffitis, which is inflammation in the columnar cuff mucosa distal to the pouch. After the IPAA procedure patients might often have residual rectal tissue, referred to as a rectal cuff, at the anastomosis between the ileum and anal canal. This area can become inflamed due to an exacerbation of UC leading to cuffitis [8, 60].

7.3 Cytomegalovirus infection and UC

In patients with UC, the risk for reactivation of latent cytomegalovirus (CMV) infection is a common complication, particularly in those with steroid-resistant disease [45]. On routine H&E stained slides, CMV typically presents as large cells, two- to four-fold larger than normal, with large amphophilic intranuclear inclusions, surrounded by a clear halo, and smaller cytoplasmic inclusions. However, CMV colitis in IBD patients tends to present with atypical, small viral inclusions, often lacking the characteristic owl-eye appearance, and it mostly affects endothelial cells in granulation tissue in ulcers [45, 63]. Therefore, CMV reactivation should be actively sought in all patients with severe colitis refractory to immunosuppressive therapy and on biopsies with prominent granulation tissue associated with large ulcers. Because the infected cells are usually scarce on limited biopsy material and morphologically less characteristic they may be missed on routine H&E stains. Immunohistochemistry, using monoclonal antibodies directed against CMV immediate early antigen, increases the diagnostic yield in comparison with H&E staining. Semiquantitative immunohistochemistry, reporting the number of infected cells and/or the number of CMV positive biopsy fragments, may have a predictive value [64].

7.4 Colitis cystica profunda

Colitis cystica profunda (CCP) is a rare benign condition characterized by cystic dilatation and misplacement of mature crypts through the muscularis mucosae into the submucosa and/or deeper layers of the bowel wall. It is a complication of various conditions including inflammatory bowel diseases, more commonly UC [65]. The condition usually affects the rectum and sigmoid colon, though it may diffusely involve the entire large bowel. It is believed to be the result of misplacement and entrapment of regenerating glands during healing. With gland formation extending deep into the bowel wall, it can be easily misdiagnosed as adenocarcinoma, particularly in endoscopic biopsies. Features favoring the diagnosis of CCP over cancer include multiple lesions, intact mucosa on the surface and no atypia on histology. Special care must be taken not to over-diagnose regenerative atypia as a well-differentiated adenocarcinoma [66].

7.5 Mucosal dysplasia and colon cancer

It has long been known that the risk of colorectal carcinoma in patients with colonic IBD is greater than in the general population [67, 68]. Recent population-based cohort studies indicate that current treatment approaches and surveillance measures have markedly reduced the risk making it more comparable to that of the general population [69]. Colorectal cancer risk, however, remains elevated in certain populations, such as those with young age at onset, long duration of disease, extensive and uncontrolled inflammation, and those with primary sclerosing cholangitis or family history of colorectal cancer [70].

Mucosal dysplasia is the best and most reliable marker of an increased risk of malignancy in patients with UC [70, 71]. Dysplasia should be distinguished into low and high degrees, using the architectural and cytological criteria of the World Health Organization [72]. In low-grade dysplasia, crypt architecture shows minimal distortion. Cytologically, the nuclei have slight hyperchromasia and the nuclear membrane has irregular edges. High-grade dysplasia is characterized by greater architectural complexity and marked nuclear pleomorphism, irregular nuclear membranes, and macronucleoli. There is more nuclear crowding and overlapping, and consequently greater nuclear stratification. Cytoarchitectural alterations not meeting the above-mentioned criteria that can also not be attributed to regeneration secondary to inflammation or medical procedure are considered “indefinite for dysplasia.”

Dysplasia related to UC develops in areas with chronic inflammation and is often multifocal. Dysplasia and neoplastic lesions in UC can often be non-polypoid, flat, or ill-defined. Flat dysplasia is not endoscopically visible and can be detected microscopically in random biopsies from unremarkable mucosa. For that reason, many biopsies are performed in patients at risk to increase detection of neoplasia. The interobserver variability for dysplasia is high among pathologists, particularly for low-grade and indefinite dysplasia, making this field one of the most challenging in gastrointestinal pathology [73]. Therefore, confirmation of dysplasia by a pathologist with expertise in gastrointestinal pathology has been recommended [22]. Although discussed in past recommendations [22], recent recommendations do not encourage the use of p53 immunohistochemistry for detecting and discriminating dysplasia (**Figure 6**) [6, 8, 11].

Figure 6.
Low-grade dysplasia in a patient with longstanding active UC (left) showing p53 positivity (right).

8. Conclusion

UC is a complex disease that requires a multidisciplinary approach. Histological evaluation of biopsies and resection specimens from the gastrointestinal tract plays a vital part in the management of UC patients. Despite the evolution of advanced endoscopic procedures that help in a detailed assessment of mucosa recent studies have confirmed the value of histology in predicting clinical outcomes.

Conflict of interest

The author declares no conflict of interest.

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