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The Role of the Pathologist in Ulcerative Colitis

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Abstract

Pathologists have an essential and wide role in the management of patients with ulcerative colitis (UC) which is a chronic inflammatory disorder of the bowel with remissions and relapses. The initial diagnosis of UC itself is challenging as the histological features vary widely with the clinical phase of the disease. Differentiating UC from other types of acute and chronic colitis, especially Crohn's disease is crucial in the management. Understanding the characteristic morphological features of UC as well as unusual morphological features of the disease are important in this task. The histological disease activity has now been identified as important in therapeutic decisions. There are several histological activity indices in UC and currently, the Nancy histological index has been recommended to be used in daily clinical practice. Identifying dysplasia associated with UC and its grading is a challenging task for the pathologist and it is a crucial step in the surveillance and management of this chronic disease.

Keywords: ulcerative colitis, histological features, diagnostic pitfalls, histological disease activity, dysplasia in ulcerative colitis

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon characterized by remissions and relapses. The disease almost always begins in the rectum and extends proximally to involve the colon. In some patients, the disease is confined to the rectum (ulcerative proctitis) and in others, the inflammation extends to a variable distance along the colon in a continuous manner. The entire colon is involved in some patients (pancolitis). The clinical presentation and the disease course vary widely amongst patients. Majority of the patients present with an acute episode that clinically mimics any of the acute colitis. The patients on surveillance could show minimal clinical symptoms and minimal histological changes during the periods of remission. Some patients have continuous low activity while some may have an initial episode of active disease followed by long periods of quiescence where the accuracy of the initial diagnosis becomes questionable [1]. Some patients present with the fulminant disease either as the first attack or in an acute exacerbation and this may lead to resection of the colon as an emergency measure.

The pathologist plays a major role in the diagnosis and the management of this chronic relapsing disease. The differing clinical presentations, the chronic relapsing

and remitting nature of the disease resulting in recurrent mucosal damage and healing, and the iatrogenic interventions both medical and surgical lead to a variable pathological picture (both macroscopic and microscopic) making the pathologists task a difficult one. Therefore, the diagnosis of UC should always be a combined effort of the clinician, endoscopist, and pathologist. The pathologist should be provided with information regarding clinical symptoms, their duration, the clinical course of the disease, the treatment received by the patient, and the endoscopic appearance of the bowel.

The pathologists are called upon to play various roles during the management of UC. These include the initial diagnosis of the disease and its differentiation from the other forms of colitis and in the classification of inflammatory bowel disease (IBD) in differentiating it from Crohn disease (CD). The morphological differential diagnosis of UC is wide and depends on whether the biopsies are performed during an acute relapse, in remission, or while on treatment.

Assessment of disease activity in UC is another responsibility of the pathologist. There are various clinical and endoscopic activity indices; however, histology is considered to be the gold standard in assessing the disease activity in UC [2]. There are various activity indices used by pathologists. The selection of the activity index that is used in practice is largely determined by the preference of the reporting pathologist and the responsible clinicians [3].

Pathologists are also required to identify dysplasia associated with UC. Dysplasia is an indicator of poor prognosis in UC patients, with a high risk of evolution towards invasive colorectal adenocarcinoma in the absence of treatment. Diagnosis and classification of dysplasia in UC is a challenge to the pathologist and it is a crucial step in the surveillance and management of the patients.

Basic knowledge of the histopathology of this disease is important for clinicians managing UC to interpret and act on the information provided in the pathology report. Here, the morphological features of UC are reviewed, with an emphasis on typical features as well as atypical features that could cause diagnostic pitfalls. The challenges the pathologist faces when examining the diagnostic material at different stages of the disease are highlighted. Further, the use of histological indices for the evaluation of disease activity, identification, and grading of dysplasia associated with UC are also discussed.

2. Macroscopic appearance of ulcerative colitis

UC is characterized by diffuse, continuous inflammation without skip lesions, restricted to the rectal and colonic mucosa. The bowel is characteristically filled with blood-stained dark fluid mixed with mucus. At the onset of the disease, the mucosa shows diffuse granularity, oedema, and erythema justifying the term 'red velvety' appearance. With the progression of the disease, the mucosa becomes friable with the appearance of punctate ulcers followed by irregular broad-based ulcers of various sizes. Ulceration may undermine the mucosa creating mucosal bridges. Ulcers distributed along the long axis of the colon extending down to muscularis propria are seen in UC but not the serpentine ulcers that are characteristic of CD. These mucosal changes involve the rectum and variable lengths of the proximal colon in continuity. The distal colon is more severely diseased than the proximal colon. The margin between the inflamed and normal mucosa is distinct and abrupt.

Figure 1.
Macroscopic appearance of the colon in UC showing involvement of the entire colon with ulceration and pseudopolyp formation.

Against a backdrop of mucosal ulceration, there are islands of non-ulcerated residual and regenerating mucosa, bulging into the lumen creating inflammatory pseudopolyps which are usually small, multiple, and bizarre in shape. Sometimes these pseudopolyps could be large and may mimic malignancy (**Figure 1**) [4].

The mucosa is atrophic and smooth with the absence of mucosal folds in long-standing UC. In the quiescent stage of UC, the mucosa may appear normal or exhibit diffuse granularity and inflammatory pseudopolyps.

The extent of UC is classified according to the Montreal classification as follows [5];

a. Ulcerative proctitis	Only the rectum is affected
b. Left-sided or distal UC	Colonic involvement distal to the splenic flexure
c. Extensive UC or pancolitis	Involvement of the colon extending proximal to the splenic flexure

3. Microscopy appearance of ulcerative colitis

For the optimum assessment of the microscopy, the pathologist should be supplied with adequate and good-quality colonoscopic biopsies. The endoscopist should obtain samples from the ileum, at least four colonic sites, and the rectum, with a minimum of two biopsies from each site [6].

Biopsies from each colonic segment should be submitted in separate containers for each colonic segment, which should be accurately labeled. This is of paramount importance as the pathologist has no means of identifying the separate colonic segments/sites based on histology. This in turn will hinder the pathologists' attempts at mapping the pattern and distribution of disease activity throughout the colon.

Samples should be fixed immediately by immersion in buffered formalin solution before transport and should be accompanied by clinical information, including endoscopic findings, duration of disease, and current treatment. It is important to sample both endoscopically normal as well as abnormal mucosa

as there could be histological activity identified in even endoscopically normal mucosa [7, 8]. Proper orientation of the biopsy during tissue embedding is important as tangentially sectioned biopsies hinder the assessment of the crypt architecture. Serial sectioning is also vital as certain focal features like granulomas may appear at different levels. However, the ideal number of sections is not defined and varies with the laboratory. At least two tissue levels, and preferably three, are advisable [2]. Some laboratories produce step-sections on two slides, but this may incur extra costs. Routine staining with hematoxylin and eosin is appropriate. Special stains and immunohistochemistry are not routinely necessary for the diagnosis or classification of IBD [2].

3.1 Main histological characteristics of ulcerative colitis

The knowledge of the normal histology of the gastrointestinal mucosa is essential for the optimal interpretation of biopsy specimens in IBD. Four main histological characteristics are assessed in the diagnostic process of IBD.

3.1.1 Crypt architectural abnormalities

Normal colonic crypts are straight, parallel, and extend from the surface, up to the muscularis mucosae. The crypt architecture is assessed based on the crypt size, crypt branching, crypt shortening, and variability in inter-crypt spacing. The crypt architectural distortion observed in UC is characterized by irregularly arranged, dilated, branched, fused, and shortened crypts. The crypt size and spacing could vary. This is a manifestation of ongoing inflammation and regeneration [9]. However, the crypts in the anorectal junction and ileocaecal junction can show minor abnormalities resembling architectural distortion due to regional variations. Another point to remember is that the crypt architecture should not be assessed close to lymphoid aggregates as these could result in distortion.

3.1.2 Cellularity in the lamina propria

Lymphocytes and plasma cells are always found in the colorectal lamina propria (LP). Normally, these chronic inflammatory cells are most dense in the upper third of the mucosa and their density decreases towards the base, resulting in the 'plasma cell gradient'. The absence of the plasma cell gradient is accepted as normal in the caecum and ascending colon. The cellularity in the LP varies depending on the anatomical site of the colon. In general, the caecum and the right colon are most cellular with a progressive decrease in the cellularity from the right to the left side. Dense lymphoid tissue may be found in the normal large bowel, particularly in the rectum. The abundance of eosinophil granulocytes varies a lot between normal individuals and is found to have a seasonal and geographic variation and is more in the right colon and the ileum than the left colon [2, 10].

Abnormal cellularity of the LP refers both to increased and altered distribution of cell types that are normally present. Basal plasmacytosis or plasma cells extending below crypt endings in more than two foci in a biopsy is considered to denote an increase in chronic inflammation (**Figure 2**).

Figure 2.
 Main histological features of UC. (A) Basal plasmacytosis and mucin depletion. (B) Villiform surface, variation in size and shape and branching of crypts. (C) Surface ulceration, diffuse heavy inflammatory cell infiltrate in the lamina propria and crypt abscess formation ((A–C): H&E $\times 200$).

3.1.3 Neutrophil granulocytes in the lamina propria

Normal colonic mucosa does not contain neutrophils except a few scattered neutrophils, that may occur as a result of bowel preparation [11]. Neutrophils are the hallmark of activity in IBD/UC. These are found in the LP or they can infiltrate the crypt surface epithelium (termed cryptitis) or enter the lumen of crypts forming crypt abscesses (**Figure 2**).

3.1.4 Epithelial abnormalities

These include mucin depletion, surface epithelial damage, and metaplastic changes. Mucin depletion can be defined as a decreased number of goblet cells or decreased amount of intracellular mucin. Focal epithelial cell loss, flattening, erosions, and ulcers denote epithelial damage and reflect the activity of the disease. Metaplastic changes are seen in the form of Paneth cell or pyloric gland metaplasia. None of these findings is disease-specific and might be observed in UC, CD, and other types of colitis.

Working definitions of some of the microscopic features of IBD/UC are given in **Table 1** [11].

3.2 Typical histological features of ulcerative colitis

The histologic findings in UC vary depending on the clinical phase of the disease and the grade of inflammatory activity. The histological features that define chronicity are crypt architectural distortion, crypt atrophy, diffuse mixed lamina propria inflammation, basal plasmacytosis, basally located lymphoid aggregates, and Paneth cell metaplasia [9]. Inflammatory activity is defined by the presence of neutrophils. Neutrophilic cryptitis, crypt abscesses, hemorrhage, erosions, ulceration, and necrosis are features of active inflammation.

It is convenient to divide the histologic appearances into those seen in active disease, resolving disease, and disease in remission.

3.2.1 Active ulcerative colitis

The characteristic features of acute UC include architectural distortion which is more in the distal colon than the proximal bowel, diffuse chronic inflammatory cell infiltrates

Microscopic abnormality	Definition	Additional remarks
Crypt distortion	Branching, loss of parallelism, irregularity, tortuosity, dilatation, and variation in shape and size of the crypts	Should not be assessed adjacent to crypt abscesses/lymphoid aggregates/follicles Anal transition zone/columnar cuff unsuitable for assessment
Crypt branching	Two or more branched crypts in a well-oriented biopsy	Branching between mucosal hillocks is normal
Crypt atrophy	Crypt shortening, with an increased gap between crypt base and muscularis mucosae Additional evidence is the wider spacing of crypts; >1 crypt diameter between crypts (normal: 6 crypts/mm in a biopsy with muscularis mucosa)	Caution adjacent to lymphoid aggregates/follicles Anal transition zone/columnar cuff is unsuitable for assessment Mucosal oedema may mimic atrophy
Villiform/irregular mucosal surface	Undulating or broadly villiform surface Wide crypt mouths	
Basal plasmacytosis	Plasma cells at the base of mucosa. May separate crypts from muscularis mucosae but not always sub cryptal Loss of plasma cell gradient	Basal plasma cells are normal in the caecum and the ascending colon
Basal lymphoid aggregates	Nodular collections of lymphocytes with or without germinal centres. It may be seen between muscularis mucosae and crypts	One or two transmucosal lymphoid nodules can be seen in normal mucosa; can extend across muscularis mucosae. Pathological aggregate may be difficult to distinguish from normal
Cryptitis	Neutrophils in the crypt epithelium	
Crypt abscess	Neutrophils in crypt lumen	Often located near the crypt base
Granuloma	A discrete collection of at least five epithelioid macrophages	Consider crypt rupture as a cause. Serial sections may help
Mucin depletion	Unequivocal reduction of goblet cell mucin in the crypt epithelium	Mucin in normal mucosa may be reduced near lymphoid follicles. Depletion can reflect bowel preparation
Ulceration/erosion	Loss of epithelium replaced by 'immature' granulation tissue or the presence of a fibrinopurulent exudate An ulcer extends more deeply than the muscularis mucosae while an erosion does not	It May be difficult to differentiate ulcer and erosion The epithelium can denude artifactually during biopsy procedures or processing
Paneth cell metaplasia	Pyramidal crypt epithelial cells with supranuclear eosinophilic granular cytoplasm	Normal in the caecum and right colon, probably as far as the splenic flexure
Diffuse chronic inflammation	An overall increase in chronic inflammatory cell density throughout the biopsy/biopsies	The caecum and ascending colon may have a higher density of chronic inflammatory cells
Patchy chronic inflammation	Areas of increased chronic inflammatory cell density in a background of variable cellularity	

Microscopic abnormality	Definition	Additional remarks
Focal chronic inflammation	Well circumscribed foci of increased chronic inflammatory cell density in a normocellular background	Differentiate from lymphoid aggregates
Focal active inflammation	Focal crypt infiltration by neutrophils in the absence of significant inflammation in the adjacent LP	Uncommon in UC but could be seen in early or treated UC

Table 1.
Working definitions of histological features seen in UC/IBD.

extending up to the muscularis mucosae, and neutrophil infiltration. The neutrophils seem to migrate directly from capillaries into the crypt epithelium (cryptitis) and often form crypt abscesses. Ulcers covered with granulation tissue and regenerative epithelium could be seen. The surface epithelium may take an undulating or low villiform appearance. The inflammation may extend into the superficial submucosa but the muscularis propria and serosa remain free of inflammation, except in fulminant colitis.

Neutrophils are predominant within the lumina of the crypts in UC and comparatively small numbers are seen migrating between the epithelial cells. Crypt abscesses are the precursors of mucosal ulceration and inflammatory polyp formation. In severe active UC, crypt abscesses burst into the loose submucosal tissues and there is a tendency to spread beneath the mucosal membrane, which sloughs off leaving an ulcer. The remaining mucosa is relatively raised from the ulcerated area and forms ‘inflammatory pseudopolyps’.

The inflammatory damage to the crypts produces a variety of degenerative and regenerative changes in the crypt epithelium. There is loss of mucin from goblet cells, often with enlargement and hyperchromatism of nuclei of the absorptive cells. Such changes must not be mistaken for dysplasia. In the presence of attenuated or reconstituting superficial epithelium, the changes in the crypts are almost certainly reactive [1].

There is a heavy diffuse infiltrate of inflammatory cells in the LP. These include neutrophils, lymphocytes, plasma cells, eosinophils, and mast cells. The presence of deep plasma cells is characteristic of longstanding UC. Many eosinophils may be seen in the LP in some of the biopsies but the role of eosinophils in UC is uncertain and has been subject to many studies [10]. Lymphoid aggregates, that may show germinal centres, are common in UC. These are situated basally between crypt bases and the muscularis mucosae (**Figure 3**). Epithelioid granulomas, which are a hallmark of CD, are not identified in UC, where only foreign body granulomas evolved as a response to mucin from ruptured crypts (termed cryptolytic granulomas) are observed.

3.2.2 Resolving ulcerative colitis

With the resolution of disease, the numbers of inflammatory cells of all types show a variable density, therefore, the LP could be either hyper or hypocellular. Further, the distribution of inflammatory cells becomes uneven. The goblet cell population returns to normal. The crypt architecture will show variable evidence of distortion, depending on the severity of the attack. The crypts may appear short and branched, the changes invariably being more marked distally. The resolution may occur at different rates in different parts of the colon, and this may give rise to the false impression of segmental disease (**Figure 4**).

Figure 3. Histological appearances of active UC. (A) Depletion of mucin in the epithelium, cryptitis, heavy infiltrate of lymphocytes, plasma cells, and eosinophils in the LP (H&E $\times 400$). (B) Marked crypt distortion and crypt abscess formation. (C) Surface ulceration. (D) A lymphoid aggregate with the germinal centre formation in the LP ((B–D): H&E $\times 200$).

Figure 4. Resolving UC; a mild crypt architectural distortion, normal mucin content in the glands, hypocellular LP, no activity (H&E $\times 100$).

3.2.3 Quiescent ulcerative colitis

Varying degrees of crypt atrophy and distortion are the hallmarks of the quiescent disease. Active inflammation is absent. The muscularis mucosa is thickened and a characteristic finding in UC, especially in rectal biopsies, is the double muscularis mucosae [1]. Paneth cell metaplasia in the left colon and pyloric-type metaplasia in any location of the colon are also features of chronic disease [1].

Although most UC patients have some residual changes of previous damage, such as crypt distortion, atrophy, and Paneth cell metaplasia, it has become increasingly recognized that a group of UC patients may show complete resolution with no evidence of previous disease [12, 13]. This must always raise the question of whether the original diagnosis is UC or infective colitis. In such situations, a careful review of the previous clinical records including the initial biopsies and ancillary investigations may be of help [1].

4. Unusual morphological patterns of ulcerative colitis

There are some exceptions to the classic morphological patterns described above, that may lead to diagnostic confusion. A summary of the unusual morphologic patterns of disease in UC is noted in **Table 2**. Pathologists need to recognize these patterns to avoid falling into a diagnostic trap.

4.1 Morphological features of treated ulcerative colitis

Endoscopically or histologically discontinuous disease may be observed in the setting of medically treated UC. This occurs as a result of uneven healing [6]. The same process may also lead to absolute or relative rectal sparing in 30–40% of patients [9]. As patchiness of the disease and rectal sparing mimicking CD is commonly seen in treated UC, evaluation of disease distribution to subtype IBD should not be attempted in this setting. This emphasizes the importance of pre-treatment histology and the value of communication between the clinician and the pathologist.

4.2 Appendiceal ‘skip’ lesions and the ‘caecal patch’ in ulcerative colitis

Appendiceal involvement is demonstrated in about 75% of the total colectomies performed for UC. This may be continuous with extensive colitis or may represent a ‘skip lesion’ of UC with involvement of the more distal colon only [9]. Such a skip lesion may raise the suspicion of CD and be erroneously considered as a contraindication for pouch surgery. The mucosal inflammation in the appendix may extend to the appendiceal orifice and contiguous large bowel as a periappendiceal patch.

Similar to the appendiceal skip lesion, there could be isolated involvement of the caecum and/or ascending colon, which is discontinuous with the left-sided colitis. It is shown that patchy right-sided inflammation in patients with left-sided colitis has

1. Treatment effect
2. Appendiceal ‘skip’ lesion and ‘caecal patch’
3. Ileal involvement
4. Rectal sparing
5. Paediatric UC-initial presentation
6. Fulminant colitis

Table 2.
Unusual patterns of disease in UC.

little clinical significance but should be recognized by pathologists to prevent a false diagnosis of CD in this setting [14].

It is also interesting that in appendices removed for possible acute appendicitis, inflammation confined to the mucosa with associated crypt distortion should raise the possibility of an appendiceal involvement in UC.

4.3 Involvement of the ileum

Ileitis is found in about 10% of patients with UC, the extent of involvement varying from 50–250 mm [1]. The mucosal changes are similar to those seen in the colon and are always in continuity with the disease in the large bowel. The involvement of the ileum is associated with an open dilated and incompetent ileocaecal valve. Although the term ‘backwash ileitis’ is in common use for this condition, it is not necessarily accurate as evidence for such a mechanism is not yet proven [1]. This condition should not be confused with CD of the terminal ileum which typically shows longer lengths of involvement and is normally associated with chronic active inflammation, and other features of CD. Unfortunately, strict histopathologic criteria for backwash ileitis have not been defined [15].

4.4 Rectal sparing

According to traditional belief, UC is a diffuse continuous disease that begins in the rectum and extends proximally, without skip areas. The term ‘absolute rectal sparing’ refers to the rectum with a normal endoscopic appearance and normal histology. Another term sometimes used is ‘relative rectal sparing’, in which the rectum has inflammation that is less severe than the more proximal colon [16]. Rectal sparing and patchiness of inflammation are seen in medically treated UC, especially with therapeutic steroid enemas. This too emphasizes the importance of the provision of clinical details to the pathologist. The pathologists should also be vigilant not to interpret these findings as definite evidence of CD.

4.5 Ulcerative colitis in pediatric populations

Pediatric-onset of IBD can show fewer characteristic symptoms and histological findings than adult-onset IBD. In general, diagnostic biopsies from children with UC often show less severe inflammation, fewer architectural abnormalities, and less epithelial injury despite extensive disease [2, 6, 17, 18].

The available evidence strongly suggests that UC in children is typically a pancolitis with variable degrees of inflammation on histology [16]. In a subset of pediatric patients, relative rectal sparing and patchy inflammation both endoscopically and histologically may occur at the pre-treatment stage of UC. These features are also observed in treated pediatric patients presumably similar to adults. In a minority, absolute rectal sparing occurs [16]. It is prudent not to preclude the diagnosis of UC in children when these atypical features are present. The precise reason why pre-treatment stage pediatric patients have a higher prevalence of rectal sparing compared to adults is unclear. Younger age (<10 years) at presentation and shorter duration between the symptoms and endoscopy are proposed explanations [19].

4.6 Fulminant ulcerative colitis

Fulminant colitis is defined as severe, acute inflammation of the colon with associated systemic toxicity. Most cases (89%) of fulminant colitis represent IBD, with the remainder relating to ischemia or infection, amongst other aetiologies [20].

In fulminant UC, the inflammatory cell infiltrate extends beyond the mucosa with thinning of the wall. There is separation and oedema of the muscle layer known as myocytolysis. There is diffuse haemorrhagic necrosis of the mucosa, deep fissuring ulcers, and transmural polymorphous inflammation. Unlike in classical UC where the serosa is shiny and intact, there is a purulent or seropurulent exudate seen on the peritoneal surface in many cases of fulminant colitis. The bowel wall is also markedly thinned out and dilated and this usually occurs in the region of the transverse colon. Macroscopic features, such as dilation, skip lesions, rectal sparing, linear ulcers, terminal ileal disease, pseudopolyps, and creeping fat, are poor discriminators of UC and CD, in the setting of fulminant colitis.

5. Histological differential diagnosis of ulcerative colitis and diagnostic pitfalls

5.1 Infective colitis

Infective colitis may clinically mimic acute UC. However, most cases of infectious colitis demonstrate a histological pattern of acute colitis, which may be diffuse, patchy, or focal, without evidence of architectural distortion. Less commonly, chronic infectious colitis may produce a histological pattern of chronic active colitis resembling IBD. Most of these cases have no specific diagnostic features on histological examination and in such cases, knowledge of the clinical history and correlation with serologic studies or stool cultures are required for diagnosis.

Some features help in differentiating acute self-limiting colitis from UC in the acute stage. In acute self-limiting colitis, the neutrophils are plentiful in the LP and are more superficially arranged. In UC, the neutrophils are predominant within the lumina of the crypts and comparatively small numbers are seen migrating between the epithelial cells [1]. Chronic changes, such as crypt distortion in UC, take about 4–6 weeks to develop and this could, therefore, cause a diagnostic difficulty in the early stages of the disease.

In amoebic colitis, presenting as chronic active colitis, there could be trophozoites of *Entamoeba histolytica* in biopsy material and identifying the trophozoites becomes crucial because, if immunosuppressive therapy is started for presumed IBD in these patients, it can result in perforation due to fulminant amoebic colitis. Superimposed infection with many organisms can occur with established UC and cytomegalovirus (CMV), campylobacter and *Clostridium difficile* are some of the important secondary infections to be considered when UC presents with an acute exacerbation [21].

5.2 Chronic ischaemic colitis

Chronic ischemia may produce a pattern of chronic active colitis and can present a difficult differential diagnosis. Chronic or recurrent ischemia may cause

significant crypt distortion, Paneth cell metaplasia, and chronic active inflammation, all features which mimic UC. However, atrophic and regenerative changes in the epithelium, hyalinization of the LP, and the presence of microthrombi in the adjacent mucosa should suggest ischemia [21]. Overall, in ischemia, the chronic active inflammation is mild relative to the degree of epithelial injury [21]. Further confounding this differential diagnosis, UC has been reported to cause a hypercoagulable state, particularly in genetically predisposed patients. In this setting, a superimposed arterial and venous thrombosis may occur, leading to severe steroid-refractory colitis [21].

5.3 Diverticular disease-associated colitis (DAC)

Chronic active colitis resembling UC may be seen in the setting of diverticulosis. In addition, diverticulosis is a relatively common disease of the elderly and, thus, both diverticulosis and IBD (either CD or UC) may coexist in the same patient. Unlike chronic active colitis of UC, DAC is confined to segments involved by diverticular disease, most commonly the sigmoid colon, and, by definition, spares the rectum. However, UC and diverticular colitis may in some cases represent overlapping entities, as a small subset of diverticular colitis patients has progressed to typical rectosigmoid UC and DAC may respond to medical therapy utilized for IBD [21].

5.4 Drug-induced colitis

Some forms of medication-induced colitis may demonstrate chronic active colitis, which may enter the differential diagnosis of UC. Nonsteroidal anti-inflammatory drugs (NSAIDs) may result in the reactivation of UC. However, in some patients, this group of drugs has also been implicated in initiating UC [1].

The most useful histological feature in distinguishing NSAID-related colitis from UC is an increase in apoptotic bodies in the crypt epithelium and lymphocytes and mononuclear cells of the superficial LP. The morphological changes that occur with NSAIDs include a generalized increase in chronic inflammatory cells in the LP, a prominent eosinophil infiltrate, increased intra-epithelial T lymphocytes and thickening of the subepithelial collagen plate may resemble eosinophilic colitis, lymphocytic colitis, and collagenous colitis, respectively [1].

5.5 Diversion colitis

Diversion colitis develops in segments of the bowel that have been excluded from the fecal stream, such as in a Hartmann's pouch. This chronic inflammatory condition usually develops within a few months to several years following surgical diversion, and typically regresses completely within 3–6 months of re-establishment of the fecal stream [22]. The disease may mimic IBD on biopsy samples and may show crypt atrophy, distortion, and lymphoid hyperplasia, involving the mucosa and/or submucosa. Symptomatic patients can show superimposed cryptitis, crypt abscesses, and superficial aphthous-type erosions or frank ulceration.

This warrants the importance of obtaining a biopsy of the segment at the time of the surgery to get a baseline analysis and review of the clinical, radiological, and endoscopic information prior to diagnosis.

5.6 Crohn disease (CD)

In most instances, UC and CD may be readily distinguished from each other pathologically, particularly when each exhibits classic histological features assisted by clinical data and other ancillary investigations. There are several circumstances in which the ‘classic’ morphological features that help to distinguish UC from CD are altered or absent. When these atypical morphological features are present, they may mimic CD (**Tables 3** and **4**). Most of these atypical features have already been discussed in Section 3.

5.6.1 Granulomas in UC

Approximately 30–40% of CD cases contain either mucosal or mural, non-necrotic granulomas [22]. When present, it is a helpful feature to confidently diagnose CD, especially in mucosal biopsies. Granulomas in CD are composed of loose collections of CD 68 immunostain positive epithelioid histiocytes. When there is rupture of a crypt or extravasated mucin in UC, there could be the formation of a granuloma which is termed a ‘cryptolytic granuloma’ that could be difficult to

Pathological feature	Ulcerative colitis	Crohn’s disease
Disease distribution	Diffuse and continuous	Segmental
Rectal involvement	Almost always (adults)	Occasionally
Disease severity	Increased distally	Patchy and variable
Ileal involvement	Occasional (‘backwash’)	Often
Inflammation of the colonic wall	Superficial (mucosal)	Transmural
Transmural lymphoid aggregates	Rare, underneath ulcers	Any location
Fissures	Rare superficial in fulminant colitis	Deep, any location
Sinuses and fistulas	Absent	Present
Granulomas	Related to ruptured crypts ‘cryptolytic granuloma’	Not crypt-related and are epithelioid cell granulomas

Table 3.
Classic morphological features helpful in differentiating UC from CD [13].

1.	Discontinuous or patchy disease (‘caecal patch’)
2.	Absolute or relative rectal sparing
3.	Inflammatory changes in the ileum (‘backwash’ ileitis)
4.	Treatment-related change
5.	Granuloma formation
6.	Transmural inflammation

Table 4.
Unusual morphological patterns of UC that may mimic CD.

Figure 5.

(A) Cryptolytic granuloma following a rupture of a crypt in UC. Extravasated mucin, multinucleated giant cells, and inflammatory cells are seen. (B) Epithelioid cell granuloma formed by histiocytic cells in CD ((A and B) H&E $\times 400$).

distinguish from granulomas of CD (**Figure 5**). Examination of multiple tissue levels that will demonstrate the relationship between granulomas and the crypt epithelium is a helpful measure in this situation. Cryptolytic granulomas often contain an admixture of neutrophils and lymphocytes, in addition to foamy macrophages and multinucleated foreign body-type giant cells and these are not usually seen in CD-related granulomas [22].

5.6.2 Transmural inflammation in UC

In CD, transmural lymphoid aggregates are seen randomly in the wall of the bowel. In fulminant UC when superficial fissuring ulcers that extend into the deep submucosa or superficial muscularis propria are present and in toxic megacolon when myocyte necrosis and serosal inflammation are prominent, there could be mural mononuclear inflammation. However, in contrast to CD, these do not form typical discrete lymphoid aggregates and are usually seen underlying the areas of severe ulceration [22]. Thus, lymphoid aggregates in areas under intact mucosa are not a feature of UC and, in fact, favor a diagnosis of CD.

5.6.3 CD with UC-like features

Typical features of CD such as granulomas, fissuring ulcers, and transmural lymphoid aggregates are seen less commonly in the colon compared to the small intestine [15]. Therefore, some cases of colonic CD may mimic UC by demonstrating only superficial mucosal involvement without inflammatory changes in the submucosa or muscularis propria, diffuse and continuous disease, and even pancolitis. Nearly 20% of CD patients develop colitis without the involvement of the upper GI tract [22]. In these cases, careful evaluation of colonic and ileal biopsies for granulomas, identifying focal or patchy inflammation and activity within the LP, identifying transmural lymphoid aggregates in resections, correlation with a detailed clinical history and imaging will be of help in differentiating UC from CD.

6. Indeterminate colitis (IC) and inflammatory bowel disease unclassified (IBDU)

In up to 5% of IBD cases, an exact classification of IBD into UC or CD proves difficult due to either the overlapping histological features of the two diseases or to the fact that UC and CD represent two ends of the spectrum of a single disease [1, 6].

Several different terms have been used to refer to this condition, including ‘indeterminate colitis’ (IC), ‘inflammatory bowel disease unclassified’ (IBDU), ‘chronic inflammatory bowel disease unclassified’, and ‘chronic idiopathic inflammatory bowel disease not otherwise specified’. The European Crohn’s and Colitis Organization (ECCO) and the European Society of Pathology (ESP) jointly addressed the ambiguous usage of this terminology, in their consensus report in 2013 [6]. Accordingly, the term IBDU could be used for patients with chronic colitis who have IBD based on the clinical history, but endoscopy and histology of the biopsies show no definitive features of either UC or CD [6]. This term is reserved for biopsy examination as the post-operative examination of resections of such IBDU cases usually provides definitive evidence of UC or CD.

The entity of IBDU is more common in the pediatric population. The possible reasons for this being more colitis than ileitis occurs in CD in early cases and the presence of rectal sparing in UC in the pediatric population [6]. Upper GI biopsies are particularly helpful in these cases.

The pathological diagnosis of IC is made only on resected specimens with the presence of overlapping features or the absence of a clear diagnostic pattern to distinguish CD from UC.

Usually, macroscopically IC shows diffuse disease with involvement of transverse and right colon and less severe inflammation in the distal colon. There is extensive ulceration. Microscopy confirms extensive ulceration with a sharp transition to normal adjacent mucosa and multiple V-shaped ulcers lacking surrounding inflammation. The overlapping histological features of IC are given in **Table 5**.

It makes no difference whether the large bowel resection is called ‘UC’ or ‘IC’, but CD needs to be excluded conclusively since an ileal pouch-anal anastomosis (IPAA)/‘pouch’ procedure is generally contradicted in CD.

• Severe mucosal and wall involvement
• Non-aggregated transmural inflammation
• Fissures reaching the muscularis propria
• Discontinuous pattern
• Diffuse mucosal disease with normal ileum
• Deep mural lymphoid aggregation
• Non-necrotizing granulomas in lymph nodes
• Anal fistula

Table 5.
Overlapping histological features in indeterminate colitis (IC).

7. Measuring the disease activity in ulcerative colitis

The complete assessment of disease activity in UC involves symptomatic evaluation, physical examination, measurement of laboratory indices, endoscopic visualization, and the histological assessment of the mucosal inflammation [3]. However, measuring disease activity using all these different parameters is cumbersome and time-consuming in practice and will delay therapy. In routine clinical practice, the disease activity and subsequent medical treatment are usually assessed largely by the clinical symptomatology. Histological assessment of the degree of inflammation is the gold standard for evaluating the true disease activity but its conventional use is limited owing to its inconvenience, invasiveness, and cost [3].

Traditionally, clinical and endoscopic remission were the two main therapeutic targets for UC. However, up to 40% of patients in clinical and endoscopic remission show persistent histological activity [2]. Furthermore, histological activity predicts the worst outcome and histological inflammation represents a significant risk factor for the subsequent development of UC-related colorectal neoplasia. Therefore, histological remission is now increasingly regarded as an important therapeutic target for UC [2].

There are about 30 histological activity indices in IBD, that have been introduced over the last few decades [23]. These systems use different stepwise grading scales for the assessment of inflammation which is used as the basis of grading the disease activity. These scales have four to seven steps and quantitatively assess the following features—architectural changes in the mucosa, chronic inflammatory cell infiltrate, amount and location of neutrophils within the mucosa, crypt abscess formation, erosion, and ulcers.

Of these scores, the ‘Geboes score’ developed in 2000 has been the most widely used and can serve as an independent risk factor for disease progression in UC [24, 25]. The more recent ‘Nancy histological index’ (NHI) and ‘Robarts histopathological index’ (RHI) both from 2016 have proven feasible, easy to use, and are the most extensively validated [26, 27]. There is currently no general agreement on which index should be used. The 2020 ECCO position paper concluded that the NHI can be recommended for daily clinical practice and for clinical trials both the NHI and RHI are feasible [2].

RHI requires assessment of four features which include ulceration/erosion, neutrophils in the epithelium, neutrophils in the LP, and the chronic inflammatory cell infiltrate. Each of the features is subdivided on a scale of 0–3 to calculate the ultimate disease activity score. This may reduce its clinical usefulness and probably is more useful for clinical trials and in research. In NHI, three main histological characteristics which include ulceration, the acute inflammatory cell infiltrate and the chronic inflammatory cell infiltrate are assessed. The NHI is defined by a 5-level classification ranging from grade-0 (absence of significant histological disease activity) to grade-4 (severely active disease) (**Table 6**) [27].

In the NHI, chronic inflammation includes lymphocytes, plasma cells, and eosinophils and it is assessed without quantification. Furthermore, if neutrophilic inflammation is present, regardless of extent, the degree of chronic inflammation is not assessed.

It has been shown that both NHI and RHI have a similar degree of inter and intra-observer agreement and share equivalent feasibility in terms of time taken for scoring the biopsies [28].

Histological criteria and defining features	Disease activity	Score
Ulceration Loss of colonic crypts replaced with immature granulation tissue or presence of a fibrinopurulent exudate	Severe	4
Acute inflammatory cells infiltrate Presence of neutrophils in LP and/or epithelial cells	Moderate to severe Presence of multiple clusters of neutrophils in LP and/or in the epithelium that is easily apparent.	3
	Mild Few or rare neutrophils in LP or in the epithelium that are difficult to see	2
	Absence Assess the chronic inflammatory cell infiltrate	
Chronic inflammatory infiltrate Presence of lymphocytes and/or plasma cells and/or eosinophils in LP	Moderate to severe Presence of an increase in chronic inflammatory cell number that is easily apparent	1
	Mild No or mild increase in chronic inflammatory cell number	0

Table 6.
Nancy histological index (NHI).

Despite the development and validation of novel histologic scoring systems, there are no agreed definitions for histologic healing and remission. Histologic healing is the ultimate goal of the treatment and could be defined as complete normalization of the mucosa [7]. What constitutes complete normalization needs to be precisely defined. Rare architecturally distorted crypts should not be overinterpreted as evidence of persistent architectural abnormalities. A rare, branched crypt can be seen even in a normal colon. Furthermore, the crypts in a normal rectum often do not extend to the muscularis mucosae [7].

The best definition of histologic remission in UC is also unclear. Traditionally, this has been regarded as persistent architectural abnormalities without neutrophilic (active) inflammation, with varying degrees of lymphoplasmacytic inflammation. The presence of mucosal eosinophils is allowed [7]. Ideally, remission includes clinical, endoscopic, and histological resolution, which is called complete remission.

8. Dysplasia andv malignancy in ulcerative colitis

The risk of colorectal carcinoma (CRC) is increased in patients with long-term UC compared to the general population. Carcinogenesis in UC is inflammation-driven and has a different pathway than usual colorectal carcinogenesis. Epithelial cells acquire early mutations of TP53 and KRAS genes and no mutations of APC genes, while in non-inflammatory carcinogenesis of the colon, APC mutation is the earliest event [7].

Epithelial dysplasia is the precursor lesion of UC-associated CRC. The features associated with increased risk of dysplasia/CRC in UC include the duration of the disease, the anatomical extent of the disease, early age of onset, concomitant sclerosing

cholangitis, family history of CRC, and endoscopic/histological activity of the disease [29]. The prognosis of CRC in IBD may be worse than CRC in the general population and shows higher mortality [9].

8.1 Colorectal dysplasia in ulcerative colitis

The presence of dysplasia in endoscopic biopsies is the most reliable marker of cancer risk. There are no specific clinical features related to dysplasia in UC. Most cases of dysplasia occur in the left/distal colon, and this mirrors the higher incidence of UC-associated colorectal carcinoma (CRC) in the rectosigmoid region. The endoscopic appearance of dysplasia is categorized according to the SCENIC classification and includes visible and invisible lesions. The visible lesions are subdivided into polypoidal (either pedunculated or sessile) and non-polypoidal (superficial, flat, depressed [29].

Dysplasia of the colorectum is defined as an unequivocal epithelial alteration that remains confined within the basement membrane within which it originated. The microscopic features of dysplasia in UC are based on a combination of cytoarchitectural features of the crypt epithelium that remains confined to the mucosa and are identical to those used in the general assessment of dysplasia elsewhere [9]. Dysplasia is classified according to either the Riddell or the Vienna system [30, 31]. In the Riddell system, there are four categories for dysplasia, which are negative, indefinite, low grade, and high grade. The Vienna system has five categories with the addition of invasive carcinoma.

The most common histological subtypes of dysplasia include intestinal (adenomatous) and serrated types [29]. Regardless of these subtypes, dysplasia is divided into low grade and high grade according to the cytoarchitectural features. In low-grade dysplasia (LGD) the crypts may be tubular and/or villous or serrated and they show either no or only mild crypt budding or crowding. The dysplastic cells show enlarged, hyperchromatic nuclei with a high nuclear/cytoplasmic ratio, nuclear stratification limited to the basal half of the cytoplasm, and clumped chromatin or multiple small nucleoli. In serrated dysplasia, the dysplastic cells may show hypereosinophilic, mucin depleted cytoplasm, or a microvesicular epithelium that is similar to the sporadic sessile serrated adenomas. These atypical nuclear features usually involve both the crypt and surface epithelium.

High-grade dysplasia (HGD) exhibits enlarged nuclei with marked nuclear hyperchromasia, pleomorphism, stratification involving the full thickness of the cytoplasm, increased mitoses, and loss of nuclear polarity. It shows complex glandular architecture with crowding, cribriforming, complex branching, and budding [29].

The category indefinite for dysplasia refers to ambiguous epithelial alterations that cannot with certainty be classified either as negative or positive for dysplasia. Some of the settings in which indefinite for dysplasia is considered are shown in **Table 7**.

8.2 Some issues in histopathological reporting in UC-associated dysplasia

- A.** Examination of multiple biopsies is necessary to rule out the possibility of dysplasia confidently, as dysplasia is also identified in endoscopically normal mucosa.
- B.** The active and resolving phase of UC may cause diagnostic difficulties as the damaged or the regenerative epithelium may harbor mucin depleted cells and

1.	Atypical cytological features in an inflammatory background where differentiating regenerative change from LGD/HGD could be difficult
2.	Marked cytological atypia in the crypt bases where surface maturation cannot be assessed due to ulceration or poor orientation
3.	Various artifactual cytological changes occur as a result of poor histological techniques—processing, cutting, staining
4.	Only a very small focus (only a few crypts) shows dysplasia.

Table 7.
Some settings where indefinite for dysplasia are considered.

atypical nuclear changes, such as enlargement, hyperchromasia, stratification, and brisk mitoses. Careful observation for surface maturation, which is a feature in reactive conditions helps to solve this problem. Another good practice is to perform colonoscopic surveillance during a period of remission of UC.

C. Inter-observer agreement amongst pathologists for dysplasia associated with UC is suboptimal. Poor reproducibility is seen mainly in indefinite dysplasia and LGD groups. (6). Reporting the biopsies for dysplasia ideally by two histopathologists will help to overcome this problem. A review of the biopsies with the diagnosis of dysplasia by a more experienced gastrointestinal pathologist, before any surgical intervention is undertaken, will optimize the management of these patients.

D. Adenomas can arise in both affected and non-affected mucosa in UC patients. They are treated like any other adenomas by complete local excision. The stalk or the tissue around the base of the lesion needs to be examined carefully to confirm that these are adenomas or part of a more widespread area of dysplasia associated with UC.

E. Colonic biopsies of patients treated with immunosuppressive agents, such as cyclosporin for severe UC, are known to show ‘pseudo dysplastic’ changes in the

Figure 6.
Dysplasia in UC. (A) Flat low-grade dysplasia with villous configuration. There is no significant pleomorphism or loss of polarity (H&E $\times 100$). (B) High-grade dysplasia with crowding glandular proliferation (H&E $\times 100$). Reprinted by ([21], pp. 178-192). Published by Oxford University press and digestive science publishing Co Limited.

epithelium [32]. Perhaps the most helpful feature is that the ‘pseudo-dysplasia’ induced by cyclosporin is strikingly diffuse, with many, and sometimes all, crypts showing similar changes, a pattern not usually seen in UC associated dysplasia. Therefore, the clinician needs to alert the pathologist to the fact that the patient has been on cyclosporin and that the pathologist in turn should be cautious when diagnosis dysplasia in this situation (**Figure 6**).

8.3 The demise of the term ‘DALM’ in ulcerative colitis

A diagnosis of dysplasia is made on biopsy material taken from a polyp or a mass evident on endoscopy was historically termed ‘dysplasia associated lesion or mass’ (DALM) and was considered as an indication for colectomy to rule out the possibility of invasive malignancy. In 2015 SCENIC international consensus statement on the surveillance and management of dysplasia in IBD, abandoned the term DALM and replaced it with endoscopically visible and non-visible lesions [33]. With advancements in endoscopic polypectomy and endoscopic mucosal resections (EMR), the concept of DALM is now outdated because most lesions that are noninvasive can be removed using these techniques [1].

8.4 Carcinoma in ulcerative colitis

Carcinomas arising in UC are mostly similar to their counterpart in non-colitis patients except for the background colitis. However, there are some features that are more frequent in UC-associated carcinomas. The tumors could be multiple and often are flat lesions with ill-defined edges, therefore, these tumors are easily felt than seen. Histologically there is a higher incidence of high-grade tumors and mucinous subtypes [1].

9. Conclusions

The pathologist plays a vital role in the diagnosis and follows up of patients with UC. The histological features in the biopsies vary widely depending on the stage of this chronic relapsing and remitting disease, making the differential diagnosis lengthy and challenging. The final diagnosis should be ideally concluded at a clinico-pathological meeting. Understanding the typical and atypical histological features of UC is vital in the task of differentiating UC from other types of colitis, mainly CD. Histological disease activity and identifying histological remission are increasingly considered important therapeutic targets. Identifying dysplasia associated with UC and its grading is a crucial step in the surveillance and management of this chronic disease.

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