

INFLAMMATORY BOWEL DISEASE

Distinguishing features, diagnostic pitfalls and dysplasia

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Introduction

Chronic idiopathic inflammatory bowel disease encompasses ulcerative colitis, Crohn's disease and indeterminate colitis. The pathologist has an important role in the initial diagnosis and also follow-up of these conditions and usually has to provide this information from relatively small biopsy fragments. Even when the entire colon is available for analysis, the accurate diagnosis often depends on careful clinicopathological correlation, and it is critical to maintain an open dialogue between clinician and pathologist.

Ulcerative colitis is an ulceroinflammatory condition that can be diagnosed when **all** of the following are present: it begins in the rectum and extends proximally and continuously for a variable distance

- affects the mucosa and upper submucosa, and
- does not have granulomas (other than to foreign bodies or ruptured crypts)

Crohn's disease, on the other hand, can affect any part of the gastrointestinal tract from mouth to anus and is characterised by **any or all** of the following:

- skip lesions
- fissuring ulceration
- transmural inflammation, and
- granulomas

In a small proportion of cases, particularly colectomy specimens with severe disease, the definitive diagnosis of either Crohn's disease or ulcerative colitis cannot be made, and the interim diagnosis of indeterminate colitis may be used for these cases. This lecture considers the above features in more detail and concentrates on problems that face both pathologists and clinicians.

Table 1. Standard criteria used in IBD diagnosis.

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Usual criteria for UC

ALL of: continuous from rectum
mucosal
no granulomas

Usual criteria for CD

ANY of: skip lesions
fissuring ulceration
transmural inflammation
granulomas

Aetiology & Pathogenesis

The aetiology and pathogenesis of chronic inflammatory bowel disease remain obscure. It is likely to be multifactorial and related to **genetic susceptibility, environmental factors** and **dysregulation of normal inflammatory responses**. Twin and family studies have demonstrated a clear genetic predisposition to IBD, although second affected family members can develop either form of IBD indicating a relationship between the two diseases.¹ Chromosomal loci linked to susceptibility to both forms of IBD have been found on various chromosomes, particularly 12 and 16 (as well as 1,3,4,6,7,10 and 22), but the linkage varies between populations and up to 10-20 genes are likely to be involved.^{2, 3} Recently, the first gene clearly linked to CD was identified as *NOD2* on chromosome 16, but this probably identifies only a subpopulation of CD patients and appears to drive ileal disease only.^{4, 5}

MHC associations have been found, particularly with class II MHC genes. However, this may relate to polymorphisms of other immune-related genes embedded within the MHC locus on chromosome 6 such as *TNF*. Polymorphisms of *TNF* gene promoter regions can affect the levels of this cytokine produced during immune responses, and it has been estimated that the *TNF* haplotype or genes in that area of chromosome 6 contribute between 10-33% of the genetic risk in CD.⁶ A variety of environmental agents have been suggested over the years, but more recently it has been postulated that inflammatory bowel disease represents an exaggerated and inappropriate response to colonic flora due to inappropriately activated cytotoxic lymphocytes that fail to undergo apoptosis. Cytokine imbalance and skewing of responses toward Th1 cytokines such as interferon- γ could compound this.⁷⁻¹²

Macroscopic features

The macroscopic assessment of colectomy specimens remains important despite the widespread use of colonoscopy and endoscopic biopsy in IBD diagnosis. A careful and thorough description, ideally with gross photographs, can be critical in assigning the correct diagnosis. Factors that are particularly important to note are:

the **distribution** of colitis,
appearance of **ulcers** and intervening mucosa, and
the appearance of the **colonic wall**.

Ulcerative colitis begins in the rectum and extends proximally. Disease confined to the rectum and associated with prominent lymphoid follicles has been regarded as a separate disorder by some (follicular proctitis¹³) based on reduced responsiveness to therapy. Apparent rectal sparing can occur due to prior topical steroid therapy and skip lesions in the appendix and caecum are allowable (see below). Crohn's disease can affect any part of the

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colon and may produce a pancolitis, but the ascending colon and rectum are the most common colonic sites.

In colectomies performed for severe UC the ulcers can have several forms. Typically, broad and flat areas of ulceration due to mucosal undermining and loss are seen between obviously inflamed, hyperaemic and granular mucosa, often with pseudopolyp formation. Intermittent ulceration can occur giving the impression of skip areas¹⁴ and in these cases histology is necessary to confirm milder colitis (rather than normal mucosa) between the ulcerated areas. The second type of ulceration seen in severe UC is linear, occurring where the plicae semilunares converge along the lines of attachment of the three taeniae coli. This should not be confused with the fissuring ulceration of CD. Finally, fine fissuring into submucosa occurs in toxic dilatation, although this is better appreciated microscopically. The ulcers of CD, on the other hand, vary from small aphthous ulcers aligned longitudinally and surrounded by normal mucosa to deep and narrow, fissuring ulcers separating mounds of normal appearing mucosa. This latter appearance is termed cobble-stoning. In the ileum, fissuring is most prominent on the mesenteric side of the bowel wall compared with the antimesenteric location in ischaemic enteritis.

The colonic wall is not significantly thickened in UC. There may be some shortening and simplification of the haustral pattern due to fibrosis in the mucosa and upper submucosa as a result of repeated flares. Although generally a mucosal disease, UC can show limited transmural inflammation in areas of severe ulceration, resulting in serosal hyperaemia. This occurs in the absence of wall thickening or fat creeping.

In CD the colonic wall is typically thickened due to oedema, fibrosis and smooth muscle proliferation. Strictures and fissures are common and the appearance, particularly in the small intestine, may resemble hose-pipe. This thickening and stricturing is sometimes so severe as to suggest malignancy macroscopically. The serosal fat is increased and wraps around the intestinal wall. Some authors have advocated the separation of Crohn's disease into perforating and non-perforating (cicatrizing) types on the basis of perceived differences in clinical aggressiveness and complications but this subdivision remains clinically controversial.¹⁵

More confusing for the pathologist, some cases of CD are very similar to UC and produce a superficial (mucosal +/- submucosal) colitis that is continuous from the rectum.¹⁶ In many of such cases there is typical CD elsewhere in the gut. In others, the diagnosis relies on finding atypical histological features in the area of colitis that argue against a diagnosis of UC; the most reliable of these are¹⁶:

- i) well-developed **lymphoid aggregates** in the submucosa or deeper colonic wall
- ii) **granulomas** not associated with ruptured crypts,
- iii) **neural proliferation** in the submucosa, or
- iv) irregular hypertrophy of the **muscularis mucosae** (Table 2).

Microscopic features

Normal mucosa

Before discussing the salient microscopic features of inflammatory bowel disease, it is necessary to outline the normal appearances of mucosa and submucosa. The crypts within the mucosa are of uniform length, diameter and spacing giving an appearance that has been likened to test tubes in a rack. The crypts should reach the muscularis mucosae in all areas of the colon except the rectum, where it is normal to have uniform mild shortening. In the

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region just above the anorectal junction, significant crypt distortion is common and this area is generally avoided at biopsy. The crypt density is 7-8 per mm except in areas of lymphoid follicle formation where the density reduces significantly. Branched crypts can be seen in normal biopsies but should not exceed 10% of all crypts; from a practical point of view more than two branched crypts in a biopsy is excessive.¹⁷ The lamina propria contains a mixed inflammatory infiltrate in which lymphocytes and plasma cells predominate, neutrophils are particularly rare and eosinophils may be present in variable numbers. Inflammatory cells are generally more numerous in the superficial lamina propria. Lymphoid aggregates can be present in the mucosa and upper submucosa, particularly in the rectum, and they may cause the mucosa to bulge slightly. Macrophages containing mucin (muciphages) are commonly seen in normal rectal biopsies, and are increased nonspecifically following mucosal injury. The normal submucosa is composed of loose fibrovascular connective tissue. The thickness is not uniform, and areas of relative thinning occur where the mucosa almost touches the muscularis propria. If this area becomes inflamed it may be misinterpreted as fissuring ulceration.

Inflammatory bowel disease

In routine practice, the usual approach to diagnosing chronic IBD occurs in several stages. The sections are assessed to determine firstly whether there are features that are diagnostic of IBD, and then to assess whether the changes favour UC, CD or are not specific. Colectomy specimens can be examined for the presence of transmural inflammation and fissuring ulceration but usually the diagnosis must be made on small mucosal biopsies.

Is it chronic inflammatory bowel disease?

Idiopathic IBD is generally diagnosed in the presence of **abnormal mucosal architecture** with or without **superimposed inflammation in the lamina propria**. The guidelines outlined by the British Society of Gastroenterology are currently the favoured ones for histological diagnosis.¹⁷ As discussed below and in a related lecture, it is important to remember that the changes of idiopathic IBD can be exactly mimicked by number of other conditions and the clinical details should always be considered.

The typical mucosal architectural changes develop several weeks after the onset of the first attack of colitis so that biopsies taken very early in the course, or in children¹⁸, may not be diagnostic. Architectural changes take about 15 days to develop¹⁹ but the basal lymphoplasmacytosis occurs earlier¹⁹. There is a variable degree of crypt shortening, reduced crypt density, variable crypt diameter and crypt branching that can be subtle, particularly in quiescent colitis. These architectural changes are generally more extensive and better-developed in cases of UC, and the normally flat surface contour of the mucosa may have a villous appearance. This latter change is more typical of UC.¹⁷

The pattern of mucosal inflammation is often distinctive in active IBD (Table 2). In many cases the inflammatory infiltrate is predominantly composed of lymphocytes and plasma cells distributed throughout the lamina propria, often with a prominent basal lymphoplasmacytosis. Neutrophils are also prominent and are associated with cryptitis and crypt abscess formation.

Rupture of large crypt abscesses with undermining of the adjacent mucosa may be seen, or large abscesses can rupture into the upper submucosa. Non-caseating epithelioid granulomas can be seen in some but not all cases of CD, but it must be remembered that a granulomatous reaction is relatively common around ruptured crypts in UC and this pattern is not diagnostic of CD.

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Because of the size and nature of mucosal biopsies, fissuring ulceration and transmural inflammation cannot be diagnosed reliably from usual-sized biopsies, but fissuring may be suspected if granulation tissue is seen running down one side of a biopsy which has relatively unremarkable mucosa at the other end.

Do the biopsy changes favour ulcerative colitis or Crohn's disease?

In most cases of active IBD some or all of the above changes will allow the diagnosis to be made. A more difficult decision is to determine which type of IBD is favoured. Although this was once a relatively academic distinction, UC and CD are often treated differently. Colectomy with sphincter-sparing pouch formation is performed in severe cases of UC but is contraindicated in CD due to the high rate of complications, so that accurate preoperative clinicopathological diagnosis is important. That said, chronic pouchitis develops in about 10% of pouches done for UC, 20% for IC, and 40% of those for CD.²⁰

The presence of non-caseating granulomas (except those associated with ruptured crypts) strongly favours a diagnosis of CD, but these are present in only a minority of biopsies. Step sectioning of multiple biopsies can increase the diagnostic yield. Granulomas are more common in early disease, and they may be seen between the crypts in otherwise non-inflamed mucosa. Typically the granulomas are described as noncaseating, although very rarely a small amount of central necrosis may be seen. However, the presence of necrosis should lead to careful analysis of multiple levels and special stains for organisms. Granulomas are not specific for CD and are also seen in infection (tuberculosis, yersiniosis, atypical Mycobacteria, fungi, schistosomiasis and rarely Campylobacter), diversion colitis, diverticulum-associated colitis, obstructive colitis and pouchitis.

Biopsies of macroscopically normal bowel in some cases of CD, particularly early in the disease course, can show only **isolated granulomas** without any architectural distortion or increased mononuclear cells in the lamina propria. Granulomas occur in UC when crypts rupture, releasing mucin into the surrounding lamina propria. In colonic biopsies it may not be appreciated from a single level that a granuloma is associated with crypt rupture, and generally the levels before and after should be examined to ensure that granulomas are independent of crypt abscesses.

Guidelines from the British Society of Gastroenterology have discussed the various criteria for distinguishing between cases of chronic colitis and have highlighted the histological features that favour either UC or CD using an evidence-based approach.¹⁷ Features favouring a diagnosis of ulcerative colitis include severe crypt architectural distortion, a widespread reduction of crypt density, frankly villous surface, a heavy and diffuse mucosal inflammatory infiltrate and severe mucin depletion. Histological features that favour Crohn's disease include epithelioid granulomas, discontinuous crypt distortion, discontinuous inflammation and focal cryptitis. These distinguishing features are listed in Table 2. Patchy inflammation can be seen in resolving UC and infective colitis, but if changes of active IBD are seen in a single biopsy fragment that also has entirely normal mucosa then CD can be diagnosed.²¹ Although CD has been found by some to have increased numbers of histiocytes compared with UC²², this feature may not have a high degree of reproducibility. Obviously, a definitive diagnosis may not be reached in some cases, particularly for CD.

Table 2. Diagnostic histological features of idiopathic IBD, UC and CD

<u>IBD</u>	<u>UC</u>	<u>CD</u>
Crypt architectural distortion	Severe crypt distortion	Discontinuous crypt distortion

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Basal lymphoplasmacytosis	Heavy diffuse inflammation	Discontinuous inflammation
Irregular surface contour	Frankly villiform surface	
Epithelioid granulomas	No granulomas	Granulomas

Indeterminate colitis

Approximately 10-15% of cases of IBD cannot be classified as either UC or CD and Price termed them 'colitis indeterminate'.¹⁴ Most of the cases that he studied were colectomy specimens from patients with fulminant disease, with the severity of the illness resulting in histological overlap. The problems associated with indeterminate colitis are cogently discussed in an excellent recent review, and this is recommended.²⁰ Other problematic cases are CD without typical transmural inflammation and fissuring ulceration. It should be stressed that colectomy specimens must be carefully assessed macroscopically, for this will often give important information to help in distinguishing the type of IBD. Indeterminate colitis should be regarded as an interim diagnosis and should prompt review of all previous histological material and clinical details, and if one form of IBD is favoured this can be stated in the report, eg. "indeterminate colitis, probably/possibly ulcerative colitis". Over 85% of these favoured diagnoses ultimately prove to be correct.¹⁴ Reasons for diagnostic difficulty are discussed further in the next section, and are summarized in Table 3.

Terminal ileal involvement in UC

Cases of active ulcerative pancolitis can show ileal inflammation, termed backwash ileitis. These cases show congestion and active inflammation of the ileal mucosa, but ulceration and crypt architectural distortion are not typical features. If these are present a diagnosis of CD should be considered. However, the full spectrum of backwash ileitis remains incompletely described in the literature.²⁰

Table 3. Useful features in atypical cases of IBD – indeterminate colitis

<u>UC</u>	<u>CD</u>
Multiple shallow fissures – sawtooth pattern denuded	Mucosa adjacent to fissures not
Underlying myocytolysis	Thickened (not atrophic) mucosa
Transmural inflammation localised to beneath ulcers	Prominent lymphoid infiltrate
Lymphoid aggregates superficial	Perivascular lymphoid aggregates
Intervening mucosa inflamed with crypt abscesses ++	Hyperaemia inconspicuous
Prominent hyperaemia	Thickened submucosa including muscle & nerve proliferation
Absent submucosal muscle & nerve hyperplasia	Areas of normal mucosa between ulcers
Muscularis mucosae may be thickened	

Problems in diagnosis – when can you 'break the rules'?

Although the histological diagnosis of biopsy or colectomy specimens is usually relatively straightforward in cases of IBD, there are a number of potential pitfalls. These are also summarised in Table 4. Problems occur for several reasons. Fulminant colitis is the most common, when dilatation leads to atypical ulceration. Overlapping histology may also be a pointer to disease heterogeneity – more than 2 groups (UC and CD) are likely to exist. The following discussion outlines the major problem areas that can arise, and considers the features that help to give a correct diagnosis. The six areas that offer the greatest challenges to diagnosis are skip lesions in UC, abnormal ulceration in UC, transmural inflammation in UC, return of mucosa to normal appearances, superficial CD and uncommon patterns of CD.

i. Skip lesions in UC

By definition, UC begins in the rectum and extends proximally in a continuous fashion for a variable distance. However, skip lesions can be seen in five instances. The **appendix** is quite often involved as a skip lesion in cases of UC when the ascending colon and caecum are not inflamed.²³ The reason for this remains unclear. Similarly, the **caecum** sometimes shows a 'patch' of inflammation opposite the ileocaecal valve in cases where there is only more distal colitis, although in my experience the inflammatory changes are not as IBD-like as the appendiceal skip. It occurs in up to 75% of patients.²⁴

Topical steroid therapy can result in **apparent rectal sparing**, but in these cases histological examination of the rectum will show typical architectural distortion and may also show some activity.

The other potentially confounding microscopic change is **irregular healing** during treatment, mimicking CD, and highlighting the importance of full clinical information. Irregular healing is not well-described in the literature, and its cause(s) underappreciated. **Cytomegalovirus** (CMV) infection in particular may be a culprit. There is an increasing literature on CMV as a cause of fulminant colitis in patients with refractory UC.²⁵⁻²⁷ It is estimated that 20-40% of refractory cases are CMV-related, and antiviral treatment with reduced steroids can reduce the need for colectomy. Viral inclusions are not always evident, so immunoperoxidase studies should be performed, increasing the detection rate five-fold. In several cases that I have seen, an apparent skip lesion occurred in the resected colon. However, this failed to correlate with the history of extensive UC, and the 'skip' areas had been inflamed earlier. Immunoperoxidase stains revealed CMV in the proximal ulcer and I believe this can be a cause of focal failed healing.

Finally, the **proximal GIT** can be inflamed in cases with UC, and recent papers point to a higher than expected frequency of duodenitis (27%) and gastritis (69%).^{28, 29}

ii. Atypical ulceration

Although most cases of UC have broad, flat ulcers, several variants occur. UC with severe ulceration can be superficially fissuring. The ulcers occur because of toxic dilatation. UC can be favoured if the fissuring ulcers are shallow, multiple and V-shaped in a saw-tooth pattern, usually with subjacent mild transmural inflammation, vascular engorgement and early myocytolysis. The fissures are often paucicellular or lined by acute exudate rather than granulation tissue with fibrosis, and the intervening mucosa often contains numerous crypt abscesses with undermining ulcers due to crypt abscess rupture.

Another problem occurs when there is undermining crypt abscess rupture into the upper submucosa²⁰, particularly at the base of the plicae where the submucosa is thin and crypt abscess rupture can reach the muscularis propria, thus mimicking a fissuring ulcer.

The third problematic ulcer is a form of linear ulceration that occurs predominantly over the plicae (so there are usually three), giving the appearance of "rake" ulceration seen in CD. Histological examination of these ulcers shows that they are superficial, and the diagnostic changes of CD are not present.

iii. Transmural inflammation in UC

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Transmural inflammation can be seen in colectomy specimens of severe UC.²⁰ It typically occurs only in association with severe ulceration (see above) and is generally mild. To allow this change, it is critical to rule out changes seen in CD, so that the inflammation is not associated with fibrosis, and perivascular lymphoid aggregates are rare or absent. Lymphoid follicles do occur in ulcerative colitis, but they are generally **superficial** and any deeper aggregates tend to be small.

Even when the changes are not as dramatic, severe mucosal activity with multiple ruptured crypt abscesses will generally lead to a mild degree of transmural inflammation that is strictly limited to the severely inflamed segment. Serosal inflammation may be observed macroscopically in these areas.

iv. Return to normal mucosa

Normal biopsies are relatively common in quiescent Crohn's disease because of the segmental nature of the inflammation, but it is now recognised that interval biopsies from patients with chronic UC can show normal mucosa, even in the rectum.³⁰ Improvements in therapy seem to be resulting in more of these cases.

v. Superficial Crohn's disease

Crohn's disease can also present a diagnostic challenge if it is superficial, when fissuring ulceration, transmural inflammation and granulomas are inconspicuous or absent.¹⁶ Areas of mucosal ulceration separated by completely normal mucosa favour a diagnosis of CD, particularly if infection is excluded. Other changes that are seen more commonly in CD include a prominent lymphocytic reaction to the ulcers, a thickened (rather than atrophic) mucosa, re-duplication of the muscularis mucosae and neural proliferation in the submucosa¹⁶, few crypt abscesses and little or no hyperaemia in submucosal vessels. In most cases (80%) of superficial CD, small intestinal involvement is present¹⁶, which obviously aids the diagnosis.

vi. Atypical patterns of Crohn's disease

In biopsy specimens in particular, CD may have a variety of non-diagnostic inflammatory patterns. Biopsies from mildly inflamed areas can have relatively preserved architecture, patchy cryptitis and increased inflammatory cells in the lamina propria, a pattern called **focal active colitis**.³¹ Although some have suggested that CD does not give this appearance, others have found that a minority of cases do turn out to be CD. Importantly, though, more than 95% of cases with this appearance are not due to inflammatory bowel disease, and infection, bowel preparation, ischaemia, NSAIDs, and antibiotic-associated colitis are more likely.

Biopsies of macroscopically normal bowel can show only **isolated granulomas** without any architectural distortion or increased mononuclear cells in the lamina propria. In these cases, parasitic and other infections should be excluded by special stains, faecal examination and culture.

It has been reported that a small number of patients with CD may present with **lymphocytic colitis** or collagenous colitis.³² These cases did not have distinguishing features of CD in the colonic biopsies and it has been suggested that the patients may have had two diseases occurring concurrently.³³

Rarely, **squamous metaplasia** occurs in areas of CD. In one case seen, the squamous epithelium extended into fissures and was associated with enteritis cystica profunda, giving a pattern that mimicked malignancy.

Table 4. Potential pitfalls in IBD diagnosis – key facts

A. Unusual features in UC

- UC can be associated with 3 linear ulcers along the taeniae coli
- Histologically these can mimic fissuring ulceration
- Skip lesions are allowable in UC in the following circumstances:
 - Appendix
 - Caecal patch
 - Duodenitis
 - Patchiness following therapy (including rectum)
 - CMV colitis complicating treatment
- Fulminant colitis modifies UC appearances and can cause sawtooth fissures extending into the submucosa, as well as transmural inflammation (**without** prominent lymphoid aggregates)
- Mucosa can return to normal in chronic UC

B. Unusual features in CD

- Superficial CD and fulminant CD can mimic UC. Helpful features include:
 - Other areas of typical CD eg. in ileum
 - Lymphoid aggregates in submucosa and adventitia
 - Granulomas
 - Neural and muscle proliferation in the submucosa
- Rare (and non-diagnostic) biopsy changes described in CD include
 - i) isolated granulomas in otherwise normal mucosa
 - ii) lymphocytic & collagenous colitis
 - iii) focal active colitis
 - iv) squamous metaplasia
- Care is needed in diagnosing CD localised to sigmoid or appendix, where diverticulum-associated (crescentic) colitis and idiopathic granulomatous appendicitis can be close mimics

Close pathological mimics of CD

Any inflammatory condition that causes localised segment of colitis can be confused for CD, but there are several entities that are particularly prone to be misdiagnosed. It is interesting to note that CD has been described in the older literature as having a less aggressive course when localised to the appendix or sigmoid, possibly because the following two conditions have not been recognised in the past.

Idiopathic granulomatous appendicitis is a condition localised to the appendix. It is characterised by transmural inflammation and fibrosis, fissuring ulceration and granuloma formation and is therefore at high risk of being diagnosed as Crohn's disease. One study found that cases of idiopathic granulomatous appendicitis had many more granulomas

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(mean of 20 per section compared with 3 per section in CD) and did not develop disease in other sites.³⁴ We suggest a diagnosis of idiopathic granulomatous appendicitis in cases where the ileum is normal at operation, no other sites of intestinal disease exist and large numbers of granulomas are seen.

Diverticular colitis (diverticulum-associated colitis) is probably under-diagnosed. It causes a segment of mucosal inflammation in areas of diverticular disease, usually the sigmoid. Aphthous ulcers, mucosal hyperaemia and occasionally fissuring can occur, and granulomas may be seen in biopsy specimens.³⁵⁻³⁷ Because of the close resemblance to Crohn's disease macroscopically and histologically, caution is warranted when considering a diagnosis of Crohn's disease based on a sigmoid biopsy. In these cases it is prudent to seek further clinical information about other sites of inflammation and to raise the possibility of diverticulum-associated colitis if only the sigmoid is involved. I have a policy of never diagnosing CD in a sigmoid biopsy if it is the only site of involvement and the patient is middle-aged or older.

Other mimics of IBD

These entities are considered in detail in a separate lecture. Many conditions can mimic IBD either macroscopically or histologically, including the following: acute self-limited colitis and other forms of infective colitis, ischaemia, radiation and chemoirradiation, mucosal prolapse syndromes, diversion colitis, obstructive colitis, pouchitis, vasculitis (Behcet's, enterocolic lymphocytic phlebitis, etc), drugs, graft versus host disease and others. IBD has a second peak of onset in the elderly, but the above conditions must be considered in this group. One study found that 75% of cases of UC diagnosed in patients over 50 years of age were ischaemic colitis on review.³⁸

Dysplasia and carcinoma in IBD

Patients with chronic IBD have an increased risk of colorectal carcinoma which is probably preceded by dysplasia.³⁹ For this reason long-term colonoscopic screening is performed in patients with chronic IBD, although the value of this surveillance in detecting dysplasia and reducing the incidence of adenocarcinoma is limited.⁴⁰ The risk of adenocarcinoma increases after about 7-8 years and is related to the duration and extent of disease, with the combined incidence of cancer or dysplasia in patients with pancolitis being estimated at:

7% after 20 years of disease
10-20% after 30 years of disease
up to 30% after more than 35 years

This may be an overestimate because of selection bias in tertiary referral centres.⁴¹ Patients with extensive disease are at higher risk than are those with left-sided colitis. Pancolitis is associated with an overall risk of 15% but left-sided colitis has a lower cumulative risk of 5%.

The significance of dysplasia

Dysplasia is defined as **unequivocal neoplastic change without invasion**, but the practical application of this definition is somewhat limited. The standardised classification that was proposed in 1983 and is still in use divides it into low-grade, high-grade and indefinite for dysplasia.⁴² This last indefinite group can be further subdivided into probably negative, probably positive and unknown, but this subdivision has poor reproducibility.

Dysplastic epithelium shows nuclear enlargement, hyperchromasia, crowding and stratification. The dysplastic cells generally affect both the crypts and extend onto the

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surface of the mucosa, although nuclear abnormalities may be more prominent either in the crypts or at the surface. When the surface nuclei show relatively less atypia, the cells still show reduced amounts of cytoplasmic mucin giving the cytoplasm an eosinophilic appearance. Dysplastic mucosa with this pattern is invariably villous^{42, 43}, and may have a cytoarchitectural pattern that resembles a serrated adenoma including serrated crypts and runs of epithelium that appear relatively non-dysplastic, but are sandwiched between unequivocally dysplastic epithelium.

The grade of dysplasia is based on the most severely affected epithelium, although at least three crypts should be involved before high-grade dysplasia is diagnosed. In **low-grade dysplasia** the nuclei are confined largely to the basal half of the cells, and there may be abnormalities of the goblet cells. **High-grade dysplasia** shows nuclear stratification that extends into the superficial (luminal) aspect of the epithelial cells and the cells generally show more prominent pleomorphism and loss of nuclear polarity. Carcinoma in situ is not considered a separate entity. The third group, **indefinite for dysplasia**, can be used when nuclear abnormalities are present but active inflammation may be contributing or is partly obscuring the histological interpretation. Regenerative mucosa can show nuclear stratification and increased mitotic activity, but these changes are often localised to the basal third of the crypts where replication occurs, may be associated with reduced crypt density (rather than increased crypt density in dysplasia), and have associated active inflammation.

Dysplasia and IBD

- Classified as low grade, high grade and indefinite
- Second opinion and/or second biopsy recommended
- Highest frequency in pancolitis with ongoing activity
- If HGD, up to 42% harbour adenocarcinoma – consider colectomy
- If LGD, up to 19% (?less) harbour adenocarcinoma – watch or consider colectomy

The histological diagnosis of flat dysplasia, confirmed by two pathologists, is an important diagnosis. If colectomy is performed in a patient with a diagnosis of high-grade dysplasia, 42% have been shown to harbour adenocarcinoma.⁴⁴ A further 1/3 will subsequently develop adenocarcinoma. Definite low-grade dysplasia also carries a significant risk. Up to 19% of patients with a diagnosis of low-grade dysplasia have carcinoma if immediate colectomy is performed⁴⁴, and a further third or more of patients in whom the colon is left intact go on to develop high-grade dysplasia or carcinoma. These figures may be inflated because of referral bias, but certainly there is consensus that at least some cases of LGD will have adenocarcinoma if colectomy is performed. Thus, a diagnosis of high-grade dysplasia is considered an indication for colectomy and some but not all would advocate colectomy even for low-grade dysplasia. Importantly, though, a significant proportion of patients with low-grade dysplasia remain stable long-term and some regress.

Sporadic adenomas and dysplasia-associated lesion or mass (DALMs)

In patients with chronic IBD, the DALM refers to an endoscopically observed mass that histologically shows the presence of dysplastic epithelium. These are not a heterogeneous group, however, because the endoscopic appearance varies from sinister plaque-like areas or irregular stricturing to less worrying discrete sessile or even pedunculated masses. Early studies found a high association with concurrent carcinoma⁴⁵ (43-58%) and the DALM was

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regarded as an ominous finding that warranted colectomy. However, sporadic adenomas are also dysplastic masses and occur in over 30% of the general population, so there has been recent interest in attempting to separate out those DALMs that are “bad” and require more aggressive management such as colectomy. Several groups have studied this problem and there is general consensus that (at least) 3 types of dysplastic masses can be found in patients with chronic IBD.⁴⁶⁻⁴⁸

True **sporadic adenomas** do occur and to diagnose these the adenomatous polyp must come from an area proximal to or away from the affected part of the colon. Polypectomy is sufficient treatment.

Polyps occurring in the zone affected by colitis require more careful assessment and a co-operative clinicopathological approach. **Adenoma-like lesions (ALL)** are **discrete**, isolated polyps that resemble typical adenomas macroscopically and histologically. The majority are sessile and <10% are pedunculated.⁴⁶ Follow-up studies of these lesions after conservative therapy by complete polypectomy have shown that they generally follow a benign course if there is not associated adenocarcinoma and if careful biopsy assessment of the surrounding colonic mucosa fails to detect the presence of flat dysplasia. Patients with these ALLs had a **high rate of polyp recurrence** (40-58%) but on follow-up **none developed carcinoma**, and subsequent low-grade dysplasia was rare⁴⁸ (4%). If, however, flat dysplasia is detected in biopsies from the adjacent mucosa, if adenocarcinoma is present, or if complete polypectomy with clear margins cannot be achieved the lesion is regarded as an ominous DALM and colectomy is indicated. In the future, immunohistochemical and molecular studies for p53, k-ras, β -catenin, APC and some other tumour suppressor genes may have a role. Carcinogenesis and the dysplasia-carcinoma sequence differ for IBD-associated and sporadic adenocarcinomas. Early loss of *P53*, *vHL*, 9p tumour suppressor gene and *c-KRAS*, and late loss of *APC* are seen in IBD cancers, the reverse of the usual sequence in sporadic colorectal carcinoma.⁴⁸ These differences may also apply to precursor lesions.⁴⁹

To summarise, sporadic adenomas can be diagnosed in chronic IBD if the polyp occurs in non-colitic mucosa. In affected colon careful assessment of the polyp and multiple biopsies from the surrounding mucosa must be taken. A discrete adenoma-like lesion (ALL) without carcinoma or adjacent flat dysplasia can be treated conservatively by complete polypectomy and follow-up, although there is a high rate of further polyps. One study also suggested that an admixture of normal and dysplastic glands at the polyp surface may indicate a more worrying lesion at increased risk of progression. If carcinoma or flat dysplasia are present, or if the polyp cannot be completely excised, the lesion should be regarded as a DALM with a high risk of progression, warranting colectomy.

Adenoma or DALM? – management considerations

1. Typical adenomatous appearance, **proximal** to colitic zone
 - Polypectomy, treat as sporadic adenoma
2. Typical adenomatous appearance, **IN** colitic zone
 - Polypectomy AND biopsy adjacent mucosa
 - If typical histology, consider polypectomy as sufficient
 - Lesion should satisfy these criteria:
 - ✓ discrete lesion
 - ✓ complete excision with clear margins
 - ✓ no surrounding flat dysplasia
 - ✓ patient and colon easy to survey
 - ✓ patient in adenoma age group (>40yo)
3. Atypical appearance OR adjacent flat dysplasia OR adenocarcinoma
 - Regard as DALM, consider colectomy

Adenocarcinoma in IBD

Adenocarcinoma in patients who have chronic colitis occurs on average 10 years earlier than sporadic cases and the tumours are more often multiple. There is a greater frequency of mucinous and well-differentiated tumours that nevertheless often present as flat or infiltrative lesions. In several of the adenocarcinomas associated with DALMs in the original series of Blackstone et al, tumour was predominantly in the submucosa with only dysplastic mucosa over the surface.⁴⁵ All of these differences explain why biopsy diagnosis of adenocarcinoma can be particularly difficult in chronic IBD.

Recommendations for screening

An adequate screening programme aims to detect significant precursor lesions without exposing patients to excessive risk or cost. Because the risk of dysplasia and malignancy increases with time, the screening interval should reduce with time. The current standard practice is for patients with pancolitis to begin screening after 7 years of disease. From 7 to 12 years screening can be performed every 3 years, between 13 and 18 years every 2 years, with yearly colonoscopies after 19 years.⁴⁰ Two to four biopsies are obtained every 10 cm and any abnormal or velvety areas are carefully sampled. A second pathologist who is experienced in gastrointestinal pathology should confirm any diagnosis of dysplasia.

Summary

A clear understanding of the range of macroscopic and microscopic changes that occur in UC and CD will assist in assigning difficult or severe cases with the correct diagnosis, but some patients remain difficult to classify. It is important to consider the possibility of alternative diseases that can closely or even exactly mimic IBD and to maintain a close relationship with clinicians. The ongoing refinement of our diagnostic criteria for precursor lesions will hopefully have any impact on the early diagnosis and appropriate management of patients with IBD and its attendant complications.

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