Introduction

Once diagnosed, chronic inflammatory bowel disease (CIBD) generally remains a lifelong disease with a natural course of relapses and remissions. An early and accurate pathological diagnosis of CIBD and its subtypes is of utmost importance in managing these diseases. During the course of the disease, pathologists encounter a multitude of endoscopic biopsies and surgical resection specimens, some of which may cause diagnostic difficulties. The most challenging of these is the subtyping of IBD into ulcerative colitis (UC) and Crohn’s disease (CD), which occasionally show non-specific pathological features that may overlap and result in an interim diagnosis of ‘indeterminate colitis’ (IC).

Correct classification of IBD in patients who require surgery is important since most with UC and IC are candidates for a total colectomy and an ileal pouch anal-anastomosis (IPAA) procedure, whilst CD is generally considered a contraindication for this operation due to the high risk of severe pouch-associated complications (1). Following a brief summary of classification, this review addresses some of the most common challenges pathologists face in interpreting morphological changes of CIBD, namely: use of the term ‘indeterminate colitis’ and its relevant diagnostic features, unusual morphological variants of UC, and the effects of various treatment regimes on the pathological diagnosis of CIBD.

Classification of CIBD

Although both UC and CD show characteristic histological features in their classical form, none of the morphological changes seen in either condition are entirely specific. Pathologists generally rely on a combination of morphological features to make the appropriate diagnosis (Table 1). This is especially so in Crohn's disease in which there is great variation of pathological features from case to case. The two most characteristic features, fissuring ulceration and granulomas, can be seen in many other conditions. Transmural inflammation is a little more specific but this feature is also seen in several other conditions. In about 10% of cases, particularly in acute fulminant colitis, it may be impossible to differentiate the conditions and the term "indeterminate colitis" is used (2,3).
Table 1. Classic features of ulcerative colitis and Crohn’s disease

| Feature                                      | Ulcerative colitis                  | Crohn’s disease        |
|----------------------------------------------|-------------------------------------|------------------------|
| Disease distribution                         | Diffuse and continuous              | Segmental              |
| Rectal involvement                           | Always (adults)                     | Occasionally           |
| Disease severity                             | Increased distally                  | Patchy and variable    |
| Ileal involvement                            | Occasional (‘backwash’)             | Often                  |
| Disease location in 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          | Not crypt related       |

Indeterminate colitis

In 1978, Ashley Price used the term ‘indeterminate colitis’ to describe the pathological changes of colectomy or proctocolectomy specimens removed from patients with CIBD where a diagnosis of classical CD or UC was not possible (2). The recently published World Congress of Gastroenterology Montreal recommendations state that the diagnosis of IC should be made only after colectomy and the term, “inflammatory bowel disease - unclassified” (IBDU) should be used in all other cases where definitive features of CD and UC are absent (4,5). They emphasize that, if the term indeterminate colitis is restricted to colectomy specimens, it then defines a patient group with a much more specific and defined pathology, in whom management and prognostic implications are relatively clear.

A common mistake made by pathologists is to use this term to describe the pathological changes equivocal for CIBD in biopsy material (IBDU), whilst some clinicians use the term in any clinical context where definitive features of UC and CD are absent. It is important that the terms IC and IBDU are not confused as such confusion can have potentially major consequences in subsequent management, especially in pouch surgery (6).

Another important observation is that pathologists are often reluctant to make a diagnosis of IC, perhaps because they perceive that such a diagnosis may be interpreted as an indicator of their own diagnostic uncertainty. It must be emphasized that IC may be an entirely appropriate diagnosis and should not be perceived as a reflection of the quality of the pathological assessment. Pathologists must accept that diagnostic equivocation may well be appropriate in fulminant CIBD and that there
is now sufficient evidence from the literature to guide pathologist, clinician and patient to the relevant management of these cases (7,12,13).

Since IC is an interim diagnosis which is used until a diagnosis of either UC or CD is established, as many as two-thirds to 80% of cases labeled as IC, will eventually be reclassified as either UC (the vast majority) or CD (8,9). Clues to the correct diagnosis may be found in previous or subsequent biopsy specimens. Careful follow-up of the diverted rectum is often helpful, with CD often recovering from diversion, but UC being often exacerbated (10). Where pouch surgery is offered, patients labeled as IC carry an overall risk of subsequent complications intermediate (20%) between that of patients with either UC (10%) or CD (30–40%) (11,12,13).

**Pathological features**

The diagnosis of IC is considered when categorization of disease into UC or CD is impossible based on morphological features of the colectomy specimens, usually as a result of severe inflammation, more commonly in the setting of fulminant colitis (8,10). The diagnostic difficulties are caused mainly by the destructive nature of inflammation masking classical macroscopic and microscopic features of CD or UC. Whilst extensive colitis with involvement of more than 50% of the mucosal surface of the colon is a cardinal feature of IC, the entity shows two main macroscopic patterns. The first pattern is that of severe continuous disease throughout the colon, often with relative rectal sparing (2,14,15). The second is that of extensive intermittent ulceration that can give the false impression of skip lesions, sometimes with normal mucosa in between (2,16). The right and transverse colon are affected more severely than the left, with occasional cases exhibiting toxic megacolon and fissures (16,17) (Fig.1).
Microscopically, the predominant feature is severe and extensive ulceration. Because of the fulminant disease, IC also shows myocytolysis, telangiectasia and some fissuring (2,18). However, the quality of the fissuring ulcers is different from that seen in CD. The fissures may extend into the submucosa and superficial muscularis propria and take one of two morphological forms. The first is a superficial squat V-shaped cleft lacking significant surrounding inflammation. The second is a sharp ‘knife-like’, ‘slit-like’ or even ‘rake-like’ defect, vertically oriented and lined by granulation tissue. Because of the extensive ulceration, there may be some ‘non-specific transmural inflammation’. However, like fat-wrapping, the presence of transmural inflammation in the form of lymphoid aggregates is a feature which is effectively pathognomonic of CD (10,14-18) (Fig.2). These may be seen scattered throughout the wall or along the outer border of the muscularis propria giving the so-called ‘Crohn’s rosary’ appearance. The transmural chronic inflammatory infiltrate in IC may be multifocal and may thus be misinterpreted as ‘skip lesions’ (10). The intervening mucosa tends to be minimally congested and there may be a sharp transition to normal adjacent mucosa displaying no evidence of inflammation, crypt distortion or atrophy (16, 17).

Mucosal granulomas in the resected specimen are not, per se, inconsistent with a diagnosis of IC (19-21). It is now widely

![Fig.2. A ‘cryptolytic’ granuloma. Collections of epitheloid histiocytes associated with crypt damage, can occur in most colitides and should not be considered as a feature of Crohn’s disease](image)
recognized that the presence of well-defined transmural epithelioid granulomas distant from crypts is considered to be a reliable feature of CD. However, mucosal granulomas, especially the so-called ‘cryptolytic lesions’ which are located adjacent to inflamed and disrupted crypts, are certainly not specific for CD, and are not uncommonly seen in IC and classical UC (19,21). This is further discussed below in the context of UC.

**Unusual morphological features of UC**

There are several circumstances in which the ‘classic’ morphological features of UC (Table 1) may be altered or entirely absent, but still a definitive diagnosis can be made based on the overall features. For example, some UC cases may show discontinuous or patchy disease, absolute or relative rectal sparing, inflammatory changes in the ileum (‘backwash’ ileitis), granulomatous inflammation or transmural inflammation. Naturally, the presence of these CD-like features may cause diagnostic confusion, or raise the possibility of IC if noted in a resection specimen. However, if the pathologist is aware of these morphological variants, making a confident diagnosis of UC is eminently possible.

**Discontinuous disease**

Whilst UC is classically considered to involve the rectum and distal colon in a diffuse and continuous fashion, there are certain situations where UC may appear patchy or segmental (22). These include: (i) the tissue healing effect of topical or oral medical therapy, including the quiescent phase of mild chronic UC; (ii) the initial pretreatment presentation of UC in paediatric patients; and (iii) the rare instances in which left-sided UC is associated with either right-sided colonic involvement (with sparing of the transverse colon) or appendiceal involvement.

Treatment by enemas can accentuate apparent sparing of the rectum and lower left colon. Both oral steroids and sulphasalazaine may also cause patchiness of disease. Topical and/or systemic treatment can lead to complete histological reversal of the morphological features of UC activity and even chronicity on biopsy (16). Therefore, floridly active UC treated with anti-inflammatory enemas can lead to significant amelioration of the disease in the rectum and sigmoid colon and relative sparing of the distal colorectum. This may encourage the pathologist to label such a case erroneously as CD. Pathologists should be aware of any recent treatment when assessing IBD resection specimens. In contrast to adults, children who present with UC prior to treatment, may demonstrate patchy involvement and/or absolute or relative rectal sparing in their colonic biopsies (23).

In rare cases, UC patients may present with limited left-sided colitis and either caecal or ascending colonic involvement, but with sparing of the transverse colon (24). This finding is often referred to as an ‘isolated caecal patch’ even though the right colon may also be involved. There is some debate as to whether or not this pattern of involvement eventually progresses to pancolitis. Appendiceal involvement as a ‘skip lesion’ in UC is relatively common, occurring in up to 86% of cases (25). Originally described as a ‘skip lesion’ of UC, such acute mucosal appendicitis in UC may occur with the proximal colon being entirely normal and is not, in isolation, a rationale for a diagnosis of CD.
**Backwash ileitis**

In contrast to CD, UC does not typically involve non-colonic areas of the gastrointestinal (GI) tract. However, it is commonly believed that, in some circumstances, severe colonic disease may lead to incompetence of the ileocaecal valve, resulting in the retrograde flow of colonic contents into the distal ileum and inflammation. In the context of UC, this is referred to as ‘backwash’ ileitis. It occurs in up to 15% of UC colectomy specimens (24) and should not be mistaken for terminal ileal involvement by CD. In most cases of UC with backwash ileitis, inflammatory changes consist of a mild degree of neutrophilic inflammation in the lamina propria, which is often patchy in distribution and occasionally associated with focal cryptitis, crypt abscesses and a mild degree of villous atrophy and regenerative epithelial changes. Rarely, inflammation of the ileum is associated with superficial mucosal ulceration and pseudopyloric metaplasia. However, other features normally associated with CD, such as submucosal inflammation, granulomas and deep fissinguring ulcers, are not typically seen (24). Thus, inflammation in the ileum may be considered part of the spectrum of UC if the inflammatory changes are (i) mild, superficial and confined to the distal 2–3 cm of ileum, and (ii) occur in a patient in whom all of the clinical, radiological and pathological features support a diagnosis of UC.

**Granulomas in UC**

Approximately 30–40% of CD cases contain either mucosal or mural, non-necrotic granulomas (20, 26). Epithelioid granulomas represent one of the few features that, when present in mucosal biopsies, may aid in the distinction between UC and CD (14, 20). Unfortunately, granulomas associated with ruptured crypts, or extravasated mucin, can occur in UC as well as in other non-IBD forms of colitis and may cause diagnostic confusion (19-21). In these instances, multiple tissue levels can often help demonstrate the relationship between granulomatous inflammation and crypt damage. Furthermore, granulomas associated with ruptured crypts frequently contain an admixture of neutrophils and lymphocytes, in addition to foamy macrophages and multinucleated foreign body-type giant cells, which are not usually seen in CD-related granulomas (Fig.3).

**Fig.3.** Diverted rectum in ulcerative colitis showing inflammation of the rectal wall with a few scattered lymphoid follicles. Mural thickening and connective tissue changes of Crohn’s disease are absent.
Transmural inflammation

Transmural lymphoid aggregates are present in most cases of CD involving the ileum (Fig. 4) but are less frequently encountered in the colon. In CD, transmural lymphoid aggregates may occur randomly in the wall of the bowel. Occasionally, mural mononuclear cell inflammation may be present in UC as well, particularly when downward rupture of crypts associate with superficial ulcers that extend into the deep submucosa or superficial muscularis propria. This may also be seen in the setting of toxic megacolon when myocytolysis and serosal inflammation are prominent features. However, in contrast to CD, mural inflammation in UC is typically not in the form of discrete lymphoid aggregates and usually underlies areas of severe ulceration (2, 14). Thus, lymphoid aggregates in areas under intact mucosa are not a feature of UC and instead favour a diagnosis of CD.

Effects of treatment

Various therapeutic maneuvers, both surgical and medical, may directly cause inflammatory pathology in the intestines. Certain surgical procedures can result in morphological changes, which simulate CIBD: these changes are largely independent of the original indication for surgery and represent a tissue response to an altered environment. Drugs can cause

Fig. 4. Transmural inflammation and mural thickening in Ileal Crohn’s disease. Lymphoid aggregates are scattered throughout the wall with a prominent subserosal distribution
inflammation of the mucosa of the intestines. In the small bowel, enteric coated preparations and non-steroidal anti-inflammatory drugs (NSAIDs) are common causes of inflammation whilst in the large intestine, mucosal inflammatory changes are seen particularly with anti-neoplastic agents and after enemas and suppositories.

**Effects of drugs**

Small bowel ulceration may be caused by any number of conditions although drugs appear to be a common cause. Now accepted as one of the most common causes of significant ileal ulceration are NSAIDs. These cause mucosal inflammation and ulceration in the colorectal mucosa. The picture is complicated by the fact that NSAIDS may cause exacerbations of CIBD (27).

Mucosal healing can occur rapidly after treatment of CIBD, but usually takes several months to years. In UC, near normalisation has been observed within two weeks following the start of topical treatment (28, 29). Mucosal architectural abnormalities are commonly observed following treatment with cyclosporine (30). The regenerating mucosa often shows a villiform architecture, which may sometimes mimic dysplasia. Not surprisingly, the duration of treatment has a significant impact on evolution of these lesions.

Both UC patients treated with sulphasalazine and CD patients treated with antibodies directed against tumour necrosis factor α (TNFα) show an important reduction of inflammatory features without a significant change in architectural abnormalities (31,32). A reduction of epithelioid granulomas has been observed following long term treatment with prednisolone, sulphasalazine, and 6-mercaptopurine, whereas chronic inflammation may persist (31). Drugs can also induce patchiness or discontinuity of mucosal inflammation in UC, making a differential diagnosis between UC and CD more difficult and confirming the low discriminatory value of this feature after treatment (33).

**Pouch surgery**

IPAA is an operation which involves the removal of all (or nearly all) the diseased colorectum, preserves normal defaecation and provides acceptable continence, obviating the need for a permanent ileostomy. Up to 50% of UC patients who undergo an IPAA procedure develop at least one episode of symptomatic inflammation of their pouch mucosa, termed ‘pouchitis’, within the first year after surgery (1,13).

The histological diagnosis of pouchitis relies on the identification of active inflammation in the lamina propria and crypt epithelium, either with or without ulceration. Unfortunately, some patients with treatment-unresponsive pouchitis may show IBD-like manifestations, such as pouch fistulas, stenosis, anal fissures or fistulas, and prepyloric metaplasia (ulcer associated cell lineage) that raise the possibility of CD as the primary cause of the patient's illness (34,35). In these settings, pathologists may be tempted to question the validity of their original diagnosis.
(presumably UC) and entertain the possibility of CD instead. Current literature however favours that ‘Crohn’s-like’ complications in pouch mucosa result from chronic pouchitis and do not necessarily represent a mistaken diagnosis of UC (34,36). As discussed earlier, the presence of non-necrotic, epithelioid granulomas unassociated with ruptured crypts may be seen in ileal pouch biopsies from patients with established UC and does not necessarily imply CD. Thus, in difficult diagnostic situations, a careful review of all of the patient’s clinical, endoscopic and previous biopsy or resection pathology material may help resolve the issue.

**Diversion colitis**

When part of the colon or rectum is excluded from the faecal stream for any reason, the colorectal mucosa may become inflamed. The pathogenesis of this diversion colitis probably relates to the lack of essential short-chain fatty acids, normally produced by anaerobic bacteria, which maintain the healthy colonic mucosa (37). The pathological features of diversion colitis closely resemble those of UC and CD and include mucosal erythema, friability, nodularity and ulceration (38). The diverted bowel shows a mild to moderate degree of lymphoid hyperplasia, characterized by prominent lymphoid aggregates with germinal centres involving the mucosa and/ or submucosa. In these areas, the crypts may appear atrophic or distorted.

Symptomatic patients typically show superimposed cryptitis, crypt abscesses and superficial aphthous-type erosions or frank ulceration, on a background of intense lymphoid hyperplasia. More pronounced degrees of crypt architectural distortion as well as other features of chronicity, such as Paneth cell metaplasia, and increased lymphoplasmacytic infiltration of the lamina propria may be present (39). In fact, diversion of the faecal stream may accelerate or exacerbate the underlying IBD. Warren et al. found transmural inflammation (60%), fissuring ulcers (53%) and epithelioid granulomas (27%) in diverted rectal stump resection specimens from 15 patients with a prior history of UC (40). Therefore, it should be emphasised that the pathological examination of a defunctioned segment of bowel may be very misleading: the diagnosis of CIBD should be restricted to the examination of colon excised before faecal stream diversion (40).

**Conclusion:**

When all of the macroscopic and microscopic features of Crohn's disease and ulcerative colitis are present, the correct diagnosis is usually attained without difficulty. When some of the changes are absent, the accuracy of diagnosis is reduced. The morphological features of CIBD are vastly affected by various treatment regimes. This review has discussed some of the challenges in the interpretation of pathology specimens that demonstrate ‘chronic colitis’ simulating CIBD and provided information helpful in distinguishing these different entities.
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