Pathological mimics of chronic inflammatory bowel disease

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Introduction
Ulcerative colitis, Crohn's disease, and their intermediate forms collectively referred to as idiopathic chronic inflammatory bowel disease, show a spectrum of pathological changes. Essentially their pathological diagnosis is one of exclusion of the many causes of inflammation in the intestines. The ultimate diagnosis may require corroboration with clinical, microbiological, and radiological data. With the advent of fibreoptic endoscopy, pathologists are more often confronted with mucosal biopsy specimens of the gastrointestinal tract, and the success of newer surgical techniques has meant that pathologists are increasingly pressured to make unequivocal diagnoses of ulcerative colitis and Crohn's disease. For instance, many would now consider restorative proctocolectomy with ileal reservoir to be the operation of choice in ulcerative colitis when medication has failed to control the disease, and yet Crohn's disease is an absolute contraindication for this operation. It is essential, therefore, that the correct diagnosis is made before surgery is contemplated.

The importance of macroscopic examination of surgical specimens to differentiate ulcerative colitis and Crohn's disease has been emphasised, but the pathologist more often has to make important diagnostic decisions, which will directly affect patient management, on biopsy specimens. Although both ulcerative colitis and Crohn's disease show characteristic histological features in their classic form, none of the morphological changes seen in either condition is entirely specific. Pathologists generally rely on a combination of morphological features to make the appropriate diagnosis. This is especially so in Crohn's disease in which pathological features vary greatly from case to case. The two most characteristic features, fissuring ulceration and granulomas, are 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. For the purposes of this review it is not intended to concentrate on the pathological differentiation of ulcerative colitis and Crohn's disease as this has been the subject of standard texts and reviews. This review is primarily concerned with recently described conditions and newly recognised situations where the microscopic features may inappropriately suggest a diagnosis of chronic inflammatory bowel disease.

Iatrogenic inflammatory bowel disease
Various therapeutic manoeuvres, both surgical and medical, may directly cause inflammatory pathology in the intestines. Certain surgical procedures can result in morphological changes which simulate chronic inflammatory bowel disease: these changes are largely independent of the original indication for surgery and represent a tissue response to an altered environment. Drugs can cause inflammation of the intestinal mucosa. In the small bowel enteric coated preparations and non-steroidal anti-inflammatory drugs are common causes of inflammation, while in the large intestine mucosal inflammatory changes are seen particularly with anti-neoplastic agents and after enemas and suppositories.

DIVERSION COLITIS AND THE DEFUNCTED RECTUM
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, particularly butyrate, normally produced by anaerobic bacteria, which maintain the healthy colonic mucosa. Such diversion colitis or proctitis occurs in the defunctioned large intestine in patients with functional disorders, diverticular disease, and colorectal cancer. Macroscopically, the condition is said to resemble ulcerative colitis. Histologically, diversion colitis shows diffuse chronic inflammation of the lamina propria and crypt abscesses may be present: in general the lack of gross crypt architectural distortion and goblet cell depletion militates against a diagnosis of ulcerative colitis (fig 1). In severe cases, however, diversion colitis may closely simulate ulcerative colitis microscopically. Furthermore, the presence of mucosal granulomas, together with the inflammatory pathology, may create a histological appearance reminiscent of Crohn's disease. The picture is further complicated by the fact that ulcerative colitis and Crohn's disease are both common indications for faecal stream diversion. In ulcerative colitis the rectum is often defunctioned as a mucus fistula after total colectomy, and severe colonic Crohn's disease may result. It should be emphasised that the pathological examination of a defunctioned segment of bowel may be very misleading: the diagnosis of chronic inflammatory bowel disease.
bowl disease should be restricted to the examination of colon excised before faecal stream diversion.18

THE ILEAL REServoIR
Restorative proctocolectomy with ileal reservoir is now one of the more favoured surgical alternatives among both surgeons and patients, for patients with ulcerative colitis requiring total colectomy, and for those with familial adenomatous polyposis.19-20 The creation of an ileal reservoir, both pelvic as in restorative proctocolectomy, or abdominal as in Kock’s continent ileostomy, is complicated by inflammatory changes with varying degrees of villous atrophy in the ileal mucosa.21-22 The villous atrophy and crypt hyperplasia produce a morphological appearance of colonic metaplasia. In those cases with extensive acute and chronic inflammation, particularly those patients with the chronic relapsing inflammatory condition known as pouchitis, the mucosa shows a close resemblance to the colorectal mucosa in ulcerative colitis (fig 2A). Both clinically and pathologically there are close links between pouchitis and ulcerative colitis; it may be that pouchitis and ulcerative colitis share immunopathogenetic mechanisms23 or that pouchitis represents a form of ulcerative colitis in metaplastic ileal mucosa.24

It has been suggested that Crohn’s disease may develop in the reservoir after proctocolectomy for indispensible ulcerative colitis25 and even that pouchitis may be a manifestation of Crohn’s disease. The pathological hallmarks of Crohn’s disease, however, namely granulomas, transmural inflammation and fissures, may all be seen as a consequence of surgical manipulation and reservoir construction.26 As in many other sites in the gut, granulomas are a major source of diagnostic confusion. They are occasionally seen, particularly in lymphoid follicles, in the reservoir mucosa of patients with an indispensible diagnosis of ulcerative colitis (fig 2B).26 Such granulomas probably represent a reaction of the ileal mucosa, particularly the lymphoid tissue, to an altered intraluminal environment or to extraneous material. Crohn’s disease remains an absolute contraindication for pelvic reservoir surgery27: pathological changes within the reservoir may closely resemble those seen in Crohn’s disease but such a diagnosis should not be made solely on the pathological changes seen in the reservoir.

DRUGS
Small bowel ulceration may be caused by any number of conditions, although drugs seem to be a common cause.27 Enteric coated potassium supplements cause small bowel ulceration, probably by an ischaemic effect due to vascular constriction induced by high concentrations of potassium ions: the histological changes affect only the mucosa and submucosa and are unlikely to be confused with active Crohn’s disease.28 Now accepted as one of the commonest causes of chronic ileal ulceration are non-steroidal anti-inflammatory drugs (NSAIDs).29 These also cause mucosal

Figure 1 Divertion proctitis. This rectal biopsy specimen was taken after defunctioning of the rectum following a rectocolic fistula complicating diverticular disease. There is diffuse chronic inflammation of the lamina propria in the absence of gross crypt distortion. Active inflammation with crypt abscesses was also present (haematoxylin and eosin).

Figure 2 Mucosal biopsy specimens from pelvic ileal reservoirs. (A) There is subtotal villous atrophy, diffuse chronic inflammation, and gross crypt distortion. (B) A well circumscribed epitheloid granuloma in the characteristic position within a lymphoid follicle in a rather distorted mucosal biopsy specimen. In the absence of other stigmata of Crohn’s disease such granulomas probably represent a tissue reaction to absorbed intraluminal material (haematoxylin and eosin).

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inflammation and ulceration in the colorectal mucosa.36 The picture is complicated by the fact that NSAIDs may exacerbate chronic inflammatory bowel disease.37 Attention has recently focused on the late stage pathology of small intestinal disease induced by NSAIDs.29 So-called diarrhagm disease has highly characteristic macroscopic and microscopic appearances, which, once recognised, are readily differentiated from Crohn's disease.79 NSAIDs, methyldopa, gold, antineoplastic agents and penicillins are the most widely recognised drugs known to cause active inflammation in the large intestinal mucosa. Methyldopa causes an acute colitis in a small proportion of cases35 and gold causes a characteristic eosinophilic infiltrate.84 6Fluoro-uracil has been the most widely studied of the chemotherapeutic agents to cause acute colitis. In the acute phase epithelial necrosis is the predominant feature while in the resolving phase crypt regeneration and distortion reminiscent of healed ulcerative colitis are observed.85

ENEMAS AND SUPPOSITORIES
Most enemas and suppositories cause little mucosal pathology but hypertonic saline enemas and bisacodyl, in particular, produce crypt epithelial proliferation and degeneration with inflammatory change.38 39 In general the pathological changes due to enemas more closely resemble ischaemia or infective colitis and lack the chronic inflammatory component of chronic inflammatory bowel disease. Suppositories, particularly those containing NSAIDs, may also cause mucosal damage and result in rectal bleeding.86 The resulting histological changes are generally those of mild, non-specific chronic inflammation, but occasionally active inflammation is seen.86

Diverticular disease
Although diverticular disease is essentially a functional disorder of the colon, a wide variety of inflammatory pathology may be associated with the condition. For instance, mucosal redundancy is a characteristic feature of the condition, and inflammation, with histological features of mucosal prolapse, is sometimes seen in the sigmoid colon.36-41 This syndrome was originally described as segmental colitis, although it has become clear that inflammatory pathology restricted to the segment affected by diverticular disease shows a wide spectrum of microscopic disease, from non-specific inflammatory changes to florid active inflammatory change associated with crypt architectural distortion simulating ulcerative colitis (fig 3).41 42 In a small proportion of cases it has been suggested that such segmental or crescentic colitis, the latter named for the characteristic involvement of the mucosal folds in the sigmoid, may precede the development of distal ulcerative colitis.43 This form of colitis, being predominantly an inflammation of the luminal mucosa, is quite distinct from diverticulitis, a condition in which stasis, infection, and inflammation occur primarily in the diverticula themselves.44

The clinical and histological diagnosis of chronic inflammatory bowel disease restricted to the sigmoid colon can be very difficult when diverticular disease is present. While segmental or crescentic colitis, associated with diverticular disease, can produce histological changes that closely mimic ulcerative colitis, the three pathological hallmarks of Crohn's disease—granulomas, transmural inflammation, and fissuring ulceration—may all be seen as a result of diverticular disease of the sigmoid colon.41 An association between Crohn's disease and diverticular disease has been postulated, but is probably no more common than would be expected by the natural prevalence of the conditions.44 If all the pathological features of ulcerative colitis and Crohn's disease can be seen as a result of the inflammatory complications of diverticular disease, can one make a firm diagnosis of chronic inflammatory bowel disease in the sigmoid colon with diverticulosis? Caution is needed, and other areas of the intestines should be investigated and biopsied, particularly the rectum if ulcerative colitis is suspected. Radiological studies of the sigmoid colon may be helpful in establishing a double diagnosis.45 Isolated involvement of the sigmoid colon in Crohn's disease is relatively unusual and doubt should be cast on any such diagnosis in the presence of diverticular disease and the absence of any other stigmata of Crohn's disease.

Infective enterocolitis
Infectious (acute, self-limiting) colitis in general has rather characteristic histological features which are unlikely to be confused with ulcerative colitis. The predominance of acute over chronic inflammatory cells, the lack of crypt architectural abnormalities, and the presence of oedema and neutrophils within the crypt epithelium rather than in the crypt lumen are all helpful features in favour of infective colitis.47 48 Occasionally, ulcerative colitis-like changes may be seen in more chronic forms of infectious colitis, particularly chronic
Pathological mimics of chronic inflammatory bowel disease

Microgranulomas (arrowheads) in resolving phase of culture confirmed salmonella enterocolitis (haematoxylin and eosin).

Figure 4

Microgranulomas (arrowheads) in resolving phase of culture confirmed salmonella enterocolitis (haematoxylin and eosin).

shigellosis and amoebiasis.\textsuperscript{49} Acute chlamydial proctitis may resemble active ulcerative colitis.\textsuperscript{50} These ulcerative colitis-like changes occur more often with the bacteria that cause inflammation by direct invasion of the mucous membrane as opposed to those which elaborate a toxin such as Salmonella and Yersinia.\textsuperscript{51} It may be difficult to differentiate infectious colitis, particularly in a resolving phase, from Crohn’s disease in colonic biopsy specimens.\textsuperscript{5} Poorly circumscribed microgranulomas are a feature of some infective colitides, particularly salmonella\textsuperscript{47} (fig 4) and Campylobacter.\textsuperscript{5} Microbiology is not always helpful—in only about 40% of cases is an infectious agent identified.\textsuperscript{48}

Most helpful histological variables are evidence of inflammatory and architectural chronicity and the presence of well formed epithelioid granulomas, these changes favouring a diagnosis of Crohn’s disease. Pseudomembranous enterocolitis, due to Clostridium difficile toxin, is most likely to be mistaken for acute ischaemia rather than chronic inflammatory bowel disease, although early lesions show non-specific patchy inflammation with surface epithelial degeneration.\textsuperscript{54}

Well formed granulomas are a feature of some infective colitides, chlamydial infection,\textsuperscript{55} yersiniosis,\textsuperscript{56,57} and tuberculosis being the most characteristic. Yersiniosis is perhaps the most likely infectious enterocolitis to produce pathological confusion with Crohn’s disease. The most helpful differentiating features are central necrosis within granulomas and the relative lack of transmural inflammation in yersiniosis.\textsuperscript{57} Examination of local lymph nodes, if available, is also helpful.\textsuperscript{58} If there is any doubt yersinia serology should be performed. In cases of Crohn’s disease associated with a florid sarcoid-like granulomatous response it may be impossible to rule out tuberculosis on histological grounds alone. Tuberculosis is favoured if there is florid coalescent granulomatous inflammation, extensive caseous necrosis (some central necrosis is seen in Crohn’s granulomas, particularly in the anal region), and nodal granulomas in the absence of intramural granulomas.\textsuperscript{59} Acid fast bacilli are only demonstrable in about 50% of intestinal tuberculosis cases but clinical data, including chest radiology and Mantoux testing, may be of value.\textsuperscript{60} Other infective granulomatous conditions, such as schistosomiasis, deep mycoses, and larval infestations are not often confused with Crohn’s disease as the infecting organisms are usually readily identifiable.

Viral infection, in particular by cytomegalovirus (CMV) and herpes simplex virus (HSV), may result in acute enteroocolitis, especially in the immunosuppressed. Both produce characteristic histological appearances reminiscent of chronic inflammatory bowel disease (fig 5): the clinical history and the presence of inclusion bodies and multineucleate giant cells help to substantiate the diagnosis of viral enteroocolitis. CMV colitis is a recognised complication of ulcerative colitis and may induce acute fulminant colitis with toxic dilatation.\textsuperscript{62} CMV, HSV, and cryptosporidiosis may produce a florid active enterocolitis, masquerading as active ulcerative colitis, in patients with AIDS. The correct diagnosis relies on the demonstration of the organisms or their cytopathic effects. The enterocolitis of atypical myobacteriosis in AIDS is not usually confused with Crohn’s disease as the histiocytic infiltrate diffusely involves the lamina propria and Ziehl-Neelsen stains show overwhelming numbers of bacteria.

Non-specific (microscopic) colitis and lymphocytic colitis

Microscopic colitis denotes a patient group with chronic watery diarrhoea and normal

Figure 5 CMV colitis. The inflammatory changes with crypt architectural abnormalities resemble ulcerative colitis. Inset: CMV inclusions are present (haematoxylin and eosin).

Inset: CMV inclusions are present (haematoxylin and eosin).
radiological and sigmoidoscopic findings but microscopically abnormal colorectal biopsy specimens.56 64 The term is ambiguous as other conditions, including both ulcerative colitis and Crohn's disease, may show histopathological abnormalities in the face of normal macroscopic appearances.56 64 A characteristic pathological feature of the disease is surface epithelial degeneration with a noticeably increased intraepithelial lymphocyte infiltrate,67 and it has been proposed that the condition be renamed lymphocytic colitis.67 68 Histologically, lymphocytic colitis shares some of the features of collagenous colitis, but these colitides can be differentiated on examination of the biopsy specimen.67 The chronic inflammatory changes that occur in lymphocytic (microscopic) colitis may suggest a diagnosis of chronic inflammatory bowel disease: the lack of crypt architectural distortion and active cryptitis, together with the characteristic changes of lymphocytic colitis, enables the pathologist to distinguish the condition from chronic inflammatory bowel disease.67

**Ischaemic enterocolitis and Behçet's syndrome**

Acute forms of ischaemic enterocolitis present little differential diagnostic dilemma. Chronic strictures in ischaemic enterocolitis may suggest a diagnosis of Crohn's disease. Histologically, the reparative and chronic phases of ischaemia disclose microscopic fissures, crypt epithelial regeneration and distortion, and chronic inflammation, features suggestive of chronic inflammatory bowel disease. Helpful microscopic features for establishing a diagnosis of ischaemia are the presence of hae-mosiderin laden macrophages in the lamina propria, fibrosis of the lamina propria, a relative paucity of chronic inflammatory cells and selective damage to the more superficial epithelium of the crypt.69 70

The multisystem disorder Behçet's syndrome may affect the intestines: colonic disease is sometimes a prominent feature of the syndrome.71 Ulceration is the most characteristic feature, either localised to the ileo-caecal region or more diffusely affecting the colon.72 Colitis in Behçet's syndrome shows typical aphthoid ulcers and mucosal cobblestoning; granulomas may be present.72 73 Vasculitis is often seen in Behçet's colitis, affecting small veins and venules.74 Controversy still abounds about the enterocolitis of Behçet's syndrome: it has been intimated that it is not a specific entity but rather a variant of chronic inflammatory bowel disease.6 71 72 Although many of the pathological features are similar to those in Crohn's colitis, Behçet's syndrome is said to lack the aggregated lymphocytic transmural inflammation of Crohn's disease.75 Current opinion is that Behçet's enterocolitis should be regarded as a distinct entity until more information on the pathogenesis of the disease is forthcoming.75 The diagnosis of Behçet's enterocolitis clearly relies on corroboration of pathological findings with clinical data.

**Malignant lymphoma**

There are two situations in which primary malignant lymphoma of the gut may mimic inflammatory bowel disease. Deep, destructive fissuring ulceration is a highly characteristic feature of high grade small and large intestinal lymphomas of both B and T cell phenotype76 (fig 6A) and this may mimic Crohn's disease, particularly in those tumours with relatively few neoplastic cells and innumerable eosinophils.77 In the large bowel diffuse lymphoma is relatively unusual but may be seen in both primary and secondary disease.78 Occasionally the disease is predominantly mucosal and shows similar microscopic and histological changes to those of acute ulcerative colitis (fig 6B).79 81 In this situation immuno-histochemistry may help to differentiate the conditions.81 Very occasionally ulcerative colitis and
malignant lymphoma may coexist: primary malignant lymphoma of the large bowel is a rare but well recognized complication of chronic ulcerative colitis.85

Miscellaneous

IMMUNE DEFICIENCY SYNDROMES

It is the acquired immunodeficiency syndromes that are most often confused histologically with chronic inflammatory bowel disease. Graft-versus-host disease (GVHD) in the acute phase shows crypt distortion and degeneration with crypt abscesses86 as the disease progresses there is gross crypt atrophy.86 The absence of a predominant inflammatory component and the presence of the "exploding crypt lesion", in which individual cell necrosis can be shown histologically and ultrastructurally in the crypt epithelium, are helpful in distinguishing GVHD from chronic ulcerative colitis.86 Although clinically important intestinal pathology is caused by specific infection in patients with AIDS, AIDS is also complicated by a non-specific enterocolitis.86 This is the result of immunologically mediated damage to the intestinal epithelium similar to that seen in GVHD, with similar histological appearances.86 In the absence of other histological clues the diagnosis may be reached by confirming the presence of HIV in rectal crypt epithelium by in situ hybridisation.86

The autosomal recessive disorder chronic granulomatous disease of childhood (CGD) is complicated by a colitis with similarities to Crohn’s disease.85 The conditions may be differentiated by the presence of a histiocytic infiltrate containing lipid vacuoles and pigment histochemically similar to lipofuscin in CGD89 and by the normal leucocyte bactericidal activity in Crohn’s disease.81 Inherited immune deficiency syndromes cause malabsorption, probably as a result of chronic enteric infection, particularly giardiasis, with histological features like those of coeliac disease,92 and occasionally they cause nodular lymphoid hyperplasia particularly in the ileum.93 Inflammatory pathology similar to chronic inflammatory bowel disease is generally not encountered.

NEUROMUSCULAR AND VASCULAR CHANGES IN THE INTESTINES

The lesions of Crohn’s disease may undergo spontaneous healing.94 In these cases a confusing histological picture is produced with hyalinised granulomas and little or no inflammation. The most striking findings are often seen in the connective tissues. Neuronal hyperplasia, both of ganglion cells87 and nerve trunks,86 may mimic diffuse neurofibroma or intestinal ganglioneuromatosis,97 while the vascular degenerative changes may suggest a primary vasculitis. Another striking feature of late stage Crohn’s disease is the muscularisation of the fibrotic submucosa, a feature also seen in ischaemic and radiation enterocolitis.97 The late stage of any localised intestinal ulcer could be misinterpreted as Crohn’s disease. In these cases the presence of fissuring ulceration, granulomas, or active inflammation elsewhere are features which can be used to diagnose Crohn’s disease.

EOSINOPHILIC INFILTRATES OF THE GUT

Several heterogeneous conditions may cause a tissue eosinophilia in the intestines:95 eosinophils may be a prominent component of the inflammatory infiltrate in both ulcerative colitis and Crohn’s disease.96100 Eosinophilic gastroenteritis101102 is characterised by a florid tissue and peripheral blood eosinophilia, with some histopathological similarities to chronic inflammatory bowel disease. Nevertheless, eosinophilic gastroenteritis has characteristic clinical associations: the condition lacks the characteristic histopathological changes of Crohn’s disease and the crypt architectural abnormalities of ulcerative colitis are not present.99

ISOLATED MUCOSAL GRANULOMAS

Small isolated granulomas are not an unusual feature in rectal mucosal biopsy specimens. In the absence of collateral evidence to support a diagnosis of Crohn’s disease a cause may not be found. Refractile crystals are always demonstrable in barium granulomas103 and it is most unusual to see evidence of sarcoidosis in rectal mucosa.104 It is likely that most of these incidental granulomas represent a tissue response to mucin, possibly as a result of crypt obstruction, inflammation, and disruption.

PNEUMATOSIS CYSTOIDES INTESTINALIS

Pneumatosis is a rare condition characterised by gas filled cysts which particularly affect the colonic submucosa.105 Clinically, the condition is more likely to simulate polyposis syndromes,106 but histologically the overlying mucosa shows features which may suggest chronic inflammatory bowel disease if biopsies are superficial.107 These include chronic inflam-
mation, crypt distortion as a result of the underlying submucosal gas cysts, and intra- mucosal granulomas (Fig. 7). Only when biopsy specimens that include the submucosa are examined does the true nature of the disease become apparent.

Summary
When all of the macroscopic and microscopic features of Crohn's disease and ulcerative colitis are present, the correct diagnosis is usually made without difficulty. When some of the changes are absent, the accuracy of diagnosis is reduced. This review has outlined those diseases which feature some of these pathological changes and may masquerade as idiopathic chronic inflammatory bowel disease. Some of the pathological mimics are iatrogenic while other common diseases, such as bacterial infection, ischaemia, and diverticulosis may produce confusing histological appearances. The picture is complicated by the fact that many of these pathological mimickers may themselves cause or predispose to chronic inflammatory bowel disease, or may complicate chronic inflammatory bowel disease. For example, drugs and infectious agents are recognised causes of relapse in ulcerative colitis; Crohn's disease may cause diverticulitis in patients with diverticulosis; and lymphoma may complicate ulcerative colitis. It behoves all practising histopathologists to recognise these mimics of ulcerative colitis and Crohn's disease to ensure appropriate management for patients with inflammatory pathology of the intestines.

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52 Price AB, Jewkes J, Sanderson PJ. Acute diarrhoea:...
Pathological mimics of chronic inflammatory bowel disease

733


