

The Effects of Treatment on Histology in Inflammatory Bowel Disease

a report by

Baljit Singh and **Bryan F Warren**

*Clinical Lecturer, Nuffield Department of Surgery, and Consultant Gastrointestinal Pathologist,
Department of Cellular Pathology, John Radcliffe Hospital*

Baljit Singh is a Clinical Lecturer in Surgery in the Nuffield Department of Surgery at John Radcliffe Hospital, where he is currently on the Surgeon Scientist Programme. He qualified at Oxford University, where he also completed his DPhil. His speciality is colorectal surgery and, in particular, inflammatory bowel disease.

While the characteristic features of Crohn's disease (CD) and ulcerative colitis (UC) are well known, these are not always discovered when the pathologist encounters a scenario where treatment has been instigated and the initial diagnosis is then called into question. It is also becoming clear that the histological features of IBD are not static.

Changes in IBD Histology with Time and Treatment

The traditional description of UC is that of a disease affecting the rectum and extending to a variable degree into the colon. Therefore, common practice in patients with colitis is often to perform only a limited examination, i.e. a flexible sigmoidoscopy and rectal biopsy. However, Kleer et al. noted that over time, both histological and endoscopic areas of UC could revert to normal mucosa. Similarly, Levine et al. found normal rectal histology or minor changes in 46% of asymptomatic UC patients despite previous definitive histology for UC. In children, an initial presentation of UC with rectal sparing has been found in up to 3% to 4% of UC patients. However, in adults, a *de novo* presentation of UC with rectal sparing has been reported, but is much rarer. Therefore, relative rectal sparing can be a presentation of UC and must not solely be taken as evidence for CD. In a situation where the pathologist is now confronted with rectal sparing, a mistaken diagnosis of CD can arise. Other features of UC that can lead to confusion with CD are its similar, patchy nature and a propensity for disease to be more severe in the proximal colon compared with the distal colon.

Kleer et al. also noted a 65% correlation between histology and endoscopic findings in UC. In other words, disease could be present in an area with normal endoscopic findings; hence, a biopsy of so-called 'normal endoscopic mucosa' should be performed to determine the extent of disease. Interestingly, in 73% of UC patients (30 of 41 patients), the maximal extent of disease was a pancolitis, but more than 80% of these patients had a lesser extent of disease over the seven-year study period. This latter finding implies that repeated colonoscopic biopsies are


required to assess the extent of disease as it may not be obvious from the first presentation and may change with time. Langholz et al. found that, all in all, about half of patients with UC will have a change in disease extent over time. Two other findings in UC that can be mistaken for CD are skip lesions in the form of caecal patch or appendiceal involvement that occurs in left-sided UC. In summary, the pathologist must be aware that UC can occur in the absence of rectal disease, it may be patchy and the true extent of disease may not be obvious from the initial biopsies.

Medical Therapy and Effects on Histology in UC

In UC, administration of therapies such as rectal 5-aminosalicylic acid (5-ASA) can lead to complete resolution of acute and chronic mucosal rectal inflammation such that an inexperienced pathologist may take this to represent rectal sparing. This may ultimately lead to the diagnosis being changed from UC to CD. Alternatively, medical therapy may only lead to relative rectal sparing. In this setting, the histology may show reduced or absent acute and/or mucosal inflammation, architectural changes only or a persistent increase in Paneth cells. This patchiness of disease, both histologically and endoscopically, is a feature of treatment in UC. The effect of treatment may also account for skip lesions in the appendix and caecum.

An interesting observation has also been made with intravenous cyclosporin, which has been used in the medical management of severe UC. In a study by Hyde et al., UC patients treated with both cyclosporin and steroids had a much higher incidence of villous transformation and epithelial regeneration compared with patients treated with steroids alone. These appearances can be mistaken for dysplasia, but it is only in the latter that nuclear enlargement continues to the crypt surface. It is important to discriminate the effects of cyclosporin from those of dysplasia in long-standing UC as it may affect the decision to construct an ileal pouch.

Evans et al. found that non-steroidal anti-inflammatory drugs (NSAIDs) may precipitate an



When judging the performance
of an oral mesalazine

Look for efficacy
at every site

For the treatment of mild to moderate acute ulcerative colitis and the maintenance of remission of UC and Crohn's ileo colitis

Asacol MR® Abbreviated Prescribing Information:

Presentation: Asacol MR Tablets, each modified release containing 400 mg mesalazine (5-aminosalicylic acid)
Indications: Ulcerative colitis: Treatment of mild to moderate acute exacerbations. Maintenance of remission
Crohn's ileo-colitis: Maintenance of remission **Dosage and administration: Adults:** Oral: Acute disease: 6 tablets a day, in divided doses, with concomitant corticosteroid therapy where clinically indicated. **Maintenance therapy:** 3 to 6 tablets a day, in divided doses. **Children:** No dosage recommendation. **Elderly:** normal adult dosage unless renal function impaired. **Contra-indications:** A history of sensitivity to salicylates or renal sensitivity to sulphasalazine. Confirmed severe renal impairment (GFR <20 ml/min). Children under 2 years of age. **Precautions:** Asacol should be used with extreme caution in patients with confirmed mild to moderate renal impairment. Renal function should be monitored (with serum creatinine levels measured) prior to start of treatment, and periodically during treatment, taking into account individual history & risk factors. Mesalazine should be discontinued if renal function deteriorates. If dehydration develops, normal fluid & electrolyte balance should be restored as soon as possible. Serious blood dyscrasias have been very rarely reported with mesalazine. Perform haematological investigations if patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat. Stop treatment if suspicion or evidence of blood dyscrasia. Lactulose or similar preparations which lower stool pH should not be concomitantly administered. Concurrent use of other known nephrotoxic agents, e.g. NSAIDs & azathioprine, may increase risk of renal reactions. Asacol should only be used during pregnancy if benefits

outweigh the risk. Avoid during lactation. **Undesirable Effects:** Nausea, diarrhoea, abdominal pain, headache. Rare reports of leucopenia, neutropenia, agranulocytosis, aplastic anaemia and thrombocytopenia, alopecia, peripheral neuropathy, pancreatitis, abnormalities of hepatic function and hepatitis, myocarditis & pericarditis, allergic & fibrotic lung reactions, lupus erythematosus-like reactions and rash (inc. urticaria), interstitial nephritis and nephrotic syndrome with oral mesalazine treatment, usually reversible on withdrawal. Renal failure has been reported. Suspect nephrotoxicity in patients developing renal dysfunction. Very rarely, mesalazine may be associated with exacerbation of the symptoms of colitis, Stevens Johnson syndrome & erythema multiforme. **Pack Quantity & Cost:** Blister packs of 120 (12 x 10), £38.71. Blister packs of 90 (6 x 15), £29.03 **Legal category:** POM. **Marketing Authorisation Number & Holder:** PL 00364/0073. Procter & Gamble Pharmaceuticals UK Ltd, Egham, Surrey, TW20 9NW. Asacol is a trade mark. © 2002 Procter & Gamble Pharmaceuticals. Refer to Summary of Product Characteristics before prescribing. Date of preparation January 2005 AS7052.

Asacol®
(MESALAZINE)
Confidence in colitis

acute episode of IBD. Similar findings have also been reported by Gleeson et al. and should be differentiated from *de novo* colitis caused by NSAIDs.

Medical Therapy and Effects on Histology in CD

While the initial treatment for CD may be steroids, they have been reported to have a differential effect on healing. They can lead to endoscopic resolution of lesions in the oesophagus and colon, but seem to have minimal effect on lesions in the stomach and ileum despite clinical improvement. It is the introduction of anti-tumour necrosis factor alpha (anti-TNF α) strategies that has significantly improved the medical management of CD. In a study by D'Haens et al., a chimeric anti-TNF α antibody led not only to endoscopic healing of lesions, but to histological improvement. In this setting, the architectural changes of CD persist, but the inflammatory infiltrate is reduced. In some cases, treatment can also lead to the formation of fibrotic strictures that – if the pathologist is unaware of the clinical history – can be mistaken as a feature of CD and not therapy.

Surgery and Effects on IBD Histology

Surgery also leads to marked histological changes in IBD. With the use of endoscopy, it is possible to observe both histological and endoscopic changes following bowel resection. Studies have shown that following ileal resection, up to 73% of CD patients have endoscopic lesions, mainly aphthous ulcers, in the neoterminal ileum. However, only 20% of these patients are symptomatic, so evidence of local inflammation following bowel resection must be taken in context with the whole clinical picture of the patient. An interesting feature of CD following bowel resection is that it almost always occurs at the proximal side of the anastomosis. This is best appreciated looking at the macroscopic appearance of the specimen. The recurrence can involve the anastomotic site and should be differentiated from the entity referred to as obstructive colitis in which inflammatory changes occur in the bowel proximal to an obstructing lesion, commonly a carcinoma. In the latter, there is always an area of normal mucosa between the inflammatory changes and the tumour.

Another surgical technique employed in CD is strictureplasty. Using this technique, the affected bowel is not resected, but may be divided in a longitudinal manner and resutured transversely. The result is an enlarged bowel lumen. Following this procedure, which is important as a method of preserving bowel length, inflammation in the involved CD bowel is improved. Recurrence of CD

rarely occurs at the site of a strictureplasty, but tends to be at an alternative site.

Diversion and UC

UC patients with toxic megacolon require urgent surgery. In this group of patients, a sub-total colectomy is performed and a diverted rectal stump is commonly left *in situ* with an end ileostomy. This allows the patient to recover from the acute episode and, at the same time, allows the pathologist to assess the colon to confirm the diagnosis. This may also be a prelude to pouch formation, which may be constructed in two or three stages. In this group of patients, the diverted rectum is predisposed to inflammatory changes and patients may present with lower abdominal pain and rectal bleeding. Endoscopic findings may show proctitis with nodularity and, in some instances, these nodules may have associated ulceration. Histologically, in addition to the changes of UC, there may be transmural inflammation in the form of lymphoid follicular hyperplasia, ulceration, fissures, crypt abscesses, mucosal granulomas and granulomatous vasculitis. The most common lesion is lymphoid hyperplasia and pseudomembranes have also been described. The lymphoid hyperplasia is a characteristic lesion of diverted bowel. In addition, diverted normal colon can also have mucosal changes ranging from chronic inflammatory and architectural changes to acute inflammation, which in its most severe form may be mistaken for UC. These histological changes occur after approximately three months, but are prevented following reversal of the stoma. Furthermore, diversion leads to involution of the rectal stump. From this description it is evident that in isolation, a diverted normal colon may have features suggestive of UC and, similarly, a diverted rectum in UC may have features suggestive of CD. It is important, however, that the diagnosis is made from the macro- and microscopic appearances of the colectomy specimen and not based solely on histology from the rectal stump.

Diversion and CD

In some patients with CD, a proximal stoma is employed to divert the colon in cases of refractory disease or instances of severe perianal disease. In the former, it can ameliorate disease in two-thirds of patients. Interestingly, infusion of the efferent limb with intestinal contents reconstitutes the mucosal inflammation. Histologically, diverting the bowel in CD leads to improvement in both acute and chronic inflammatory changes in the bowel. ■

This article is continued, with references, graphics and tables in the Reference Section on the website supporting this business briefing (www.touchbriefings.com).