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Editorial

Colitis: Problems in definition and diagnosis

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Introduction

Diarrhoea is a common complaint and is increasingly being investigated by all the available modalities. Thus it is now widely recognised that not only it is necessary to try to establish a microbiological cause, but that all cases of prolonged diarrhoea need evaluation by histological examination of tissue biopsies. Moreover, it is becoming plain that a single rectal biopsy is of limited value and a case for multiple stepwise total colonic biopsies can easily be made. Further, in the patient with chronic persistent diarrhoea, the bowel should be evaluated histologically even if the endoscopic appearance is within normal limits. Thus it is that the spectrum of different forms of colitis is ever widening as newer entities are delineated. Because of the limitation on the patterns of tissue response to a varied range of insults, the evaluation of colitis in its many forms increasingly requires the close working relationship between clinician and pathologist. In the last few years it has become increasingly plain that the range of disease which can mimic ulcerative colitis and Crohn's disease, i.e. so-called idiopathic inflammatory bowel disease, both clinically and pathologically, is growing rapidly. It is these forms of colitis which need consideration.

Infective colitis

Although baciliary dysentry is usually ascribed to *Shigella* infection, it has been increasingly realised that in some infections with *Salmonella* traditionally regarded as primarily a small bowel pathogen, the colon is also involved and may bear the brunt of the disease (Boyd 1985). *Campylobacter jejuni* is also increasingly being recognised as a cause of colitis, as are certain strains of *Escherichia coli*. Apart from the enteroinvasive forms there is a recent literature concerning the verotoxin-producing enterohaemorrhagic *E. coli* serotype 0157, which is now well recognised as a cause of colitis characterised by bleeding (Smith et al. 1987; Levine 1987). This is often a severe systemic illness with a concomitant haemolytic uraemic syndrome. In fact, the association of an acute colitis and the haemolytic uraemia syndrome had been noted long before verotoxin-induced colitis was described. It is perhaps not recognised widely enough that bloody diarrhoea, which is most frequently associated with inflammatory bowel disease, can be due not only to *E. coli* strains, but also *Shigella* and *Campylobacter*. Despite assertions that infective colitis and first attack ulcerative colitis have different histopathological appearances, individual cases pose diagnostic problems for the pathologist, for an "infective colitis" label is, in practice, frequently only attached in retrospect. Furthermore, the colitis caused by *Campylobacter*, for example, may be segmental (Loss et al. 1980); mucosal giant cells are seen on occasion (Green et al. 1984) and toxic megacolon can occur (Kalkay et al. 1983). Other forms of infective colitis such as might be due to amoebae, cytomegalovirus or fungi are commonly less of a problem for the tissue pathologist because the infective organism or some other characteristic histological feature is recognised microscopically. It is, however, well to be constantly aware of the possibility that a colitis biopsied and considered by the clinician to be idiopathic inflammatory bowel disease can be of infective origin. Of particular difficular difficulty in countries where intestinal tuberculosis is common is its differentiation in diffuse colitic form from Crohn's disease (M. Mathan, personal communication).

Antibiotic-associated colitis

The classical pseudomembranous lesions of antibiotic-associated colitis and even those which immediately precede it (Price and Davis 1977) cause few problems for the experienced pathologist, even if a history of antibiotic therapy is withheld. Not infrequently, however, in the clinical situation of mild diarrhoea, usually without blood, biopsies from patients with a history of antibiotic

exposure will show a somewhat less characteristic microscopic appearance. The inflammation tends to be patchy, however, even within a single biopsy fragment. It tends to be superficial, involving the upper quarter or half of the mucosa, and is associated with vascular dilatation and an acute inflammatory infiltrate of the lamina propria. The superficial epithelium is degenerate and flattened and desquamated cells may be trapped in adherent mucus. The polymorphs invade the upper crypt and superficial epithelium and the latter often forms syncytial knot-like projections between the crypt mouths. Classical crypt abscesses are absent. The evidence for the association of these changes with the finding of *Clostridium difficile* toxin in the stool was reviewed by Rocca et al. (1984). From a practical viewpoint a patchy, mainly superficial non-specific colitis should alert the pathologist to the possibility of a *C. difficile*-associated colitis.

Drug- and chemical-induced colitis

It is claimed that some 10% of cases of recent onset colitis are due to the use of non-steroidal anti-inflammatory drugs (NSAIDs) (Kauffman and Taubin 1987; Tanner and Raghunath 1988). Colonoscopically ulceration is unusual, but biopsies will show a mild non-specific colitis with a neutrophil component in the inflammatory infiltrate. Occasional crypt abscesses may be seen but are infrequent. It is also recognised that these drugs can also exacerbate quiescent idiopathic inflammatory bowel disease. A Crohn's-like colitis is described in patients taking oral contraceptives (Rhodes et al. 1984) and proctitis similar to ulcerative colitis has been attributed to salicylates (Pearson et al. 1983). Colitis has also occurred in association with the use of cylosporin (Innes et al. 1988) and toxic megacolon with segmental colitis to methotrexate (Atherton et al. 1984). Patients with rheumatoid arthritis being treated with gold may also exibit a colitis which is usually mild, non-ulcerative and characterised by a pronounced eosinophil leucocyte infiltrate (Martins et al. 1981).

The use of enemas, e.g. soap (Orchard and Lawson 1986), phosphate (Sweeney et al. 1986) and sorbitol (Lillemoe et al. 1987), have all been associated with a colitis on occasion and may vary from a mild disease to one associated with gangrenous changes. Colitis has also followed the inadvertent installation of alcohol (Herrerias et al. 1983) and has been ascribed to disinfection solutions used in cleaning endoscopes (Jonas et al. 1988). Sulphasalazine, the very drug used in the treatment of ulcerative colitis, has also been incriminated as a cause of precipitating the disease (Ruppin and Domshke 1984). Fishel et al. (1985) have reported colitis following cocaine use, but it has pseudomembranous features and could probably be ascribed to ischaemia.

Collagenous colitis

Since Lindstrom (1976) described the first case there can be few pathologists seeing colonic biopsy tissues with any regularity who have not encountered one or more cases of their own. A diagnosis can be made with confidence when the collagen layer exceeds 15 μm. In some cases it can be as thick as 60–70 μm. The usual accompaniment is a mixed inflammatory cell component of the lamina propria with prominent eosinophils, minor degenerative changes and flattening of the superficial epithelium and occasionally Paneth cell metaplasia. Flejou et al. (1984) claims that an increase in mast cells occurs. The deposition of collagen is not even throughout the colon (Wang et al. 1987) and the rectum is often less affected than the proximal bowel. This probably accounts for some claims that the lesion is reversible because of the variation in the biopsy site at repeat examinations. Collagen also sometimes occupies the deeper parts of the lamina propria and is not solely in the subepithelial zone.

Of late, it has become apparent that not only is this condition much more common in elderly females but it has a predeliction to occur in association with thyroid and rheumatoid joint disease and autoimmune disease of other types (Steadman et al. 1987; Jessurun et al. 1986).

Microscopic colitis

Kingham et al. (1982) coined the term "microscopic colitis" for a condition characterised by large volume watery diarrhoea and a normal endoscopic and radiological appearance that was associated with mild histological inflammatory changes of the whole colonic mucosa. Bo-Lim (1985) and Jessurun et al. (1987) put the existence of microscopic colitis on a firmer basis and examined the evidence that it was the forerunner of collagenous colitis. It affects the whole colon and is characterised by a diffuse increase in lymphocytes and plasma cells in the lamina propria. Eosinophils are usually prominent and neutrophils variable in number, but not infrequently they invade the superficial and lumenal tubular epithelium. As in collagenous colitis an increase in mast cells has been described (Baum et al. 1989). The surface epithelial cells show degenerative changes and apototic bodies are usually conspicuous. In some cases intraepithelial lymphocytes are a prominent feature but there is no architectural deformity or significant inflammatory epithelial destruction.

Teglbjaerg et al. (1984) and subsequently Kingham et al. (1986) have independently described a clinical and histological colitis similar to microscopic colitis in which the colonic mucosa developed a collagen band in follow-up biopsies. Thus a view has evolved that microscopic colitis is the early phase of collagenous colitis and there is much in their clinical presentation to support this. Lazenby et al. (1989), however, feel that despite their similarities they are distinctive. They stress in particular the intraepithelial lymphocyte component of the histological picture in microscopic colitis and have proposed that it be referred to as "lymphocytic colitis". The advantages of such designation when the relationship between microscopic and collagenous colitis is far from clear and when the nature of neither is fully understood

are extremely doubtful. Intraepithelial lymphocytes, as in other instances in gastrointestinal disease when they appear increased in number, such as in coeliac disease, are no more than a manifestation of an underlying pathogenetic mechanism.

Diversion colitis

It has been proposed that short-chain fatty acids produced by the anaerobic faecal flora are an essential trophic factor for the colonic mucosa (Korelitz et al. 1984; Editorial 1989). When the faecal stream is diverted, mild chronic inflammatory mucosal lesions occur in the deprived colon. Attention was first drawn to this by Glotzer et al. (1981). When continuity is restored the changes disappear. On occasion so-called diversion colitis can be severe enough to cause rectal bleeding (Boshardt and Abel 1984; Ona and Boger 1985). When this occurs the mucosa is severely inflamed and ulcerated. The ulceration may be aphthoid and mimic Crohn's disease (Lusk et al. 1984). This has serious implications because diversion of the faecal stream is sometimes performed for this disease (Korelitz et al. 1984) and when diversion colitis occurs it can easily be mistaken for Crohn's disease in the divergent segment. Murray et al. (1987) incleed have described not only ulceration, but mucin granulomas and lymphoid hyperplasia. Cognisance of the condition, however, will usually allow its diagnosis, for it is normally an essentially mucosal rather than a mural disease.

Colitis in diverticular disease

Although mucosal biopsy is usually unrewarding in diverticular disease, there are occasions when it can reveal histological changes which are misleading. Cawthorn et al. (1983) described a segmental colitis with inflammatory changes similar to those seen in the solitary rectal ulcer syndrome. This is probably due to repeated prolapse of the mucosa lying between diverticulae as a result of the abnormal colonic muscular dynamics. Certainly endoscopists recognise irregularities and polypoidal bulging of the mucosa in diverticular disease, especially in the later stages when there is pericolic fibrosis and cicatrisation. The more confusing and ill-understood lesion is the segmental colitis which occurs in diverticular disease and is characterised by a patchy inflammation, crypt abscess formation and goblet cell depletion (Sladen and Filipe 1984). This colitis is frequently associated with rectal bleeding and can cause significant diagnostic difficulty. However, although it is segmental, it has features more like ulcerative colitis, except that it lacks its diffuse character.

Colitis in infants and children

Although inflammatory bowel disease is uncommon in infants and children, it does occur and there are several reports of onset in the 1st year of life. Of late, it has become apparent that a much more frequent cause of bloddy diarrhoea due to colitis is food intolerance. Under the age of 2–3 years cows milk and soy protein not infrequently cause a sigmoidoscopic and histological colitis which will resolve if the offending protein is removed from the diet (Gryboski 1967). Lake et al. (1982) described acute and chronic inflammation with a prominent eosinophil infiltration in rectal biopsies of babies with rectal bleeding in the 1st month of life. Immediate remission resulted when the diet was changed from breast milk to a substitute milk formula. Thus it has become clear over the years that in infancy at least, food allergy can present as a significant colitis with bloody diarrhoea and a histological mucosal inflammation with surface erosion and that it is the commonest cause of colitis in infants (Berezin et al. 1989). Other allergic phenomena, including raised serum IgE and blood eosinophilia, may also occur and it has been shown that numerous IgE containing plasma cells appear in the colonic lamina propria.

Miscellaneous forms of colitis

The colitis of Behcet's disease can mimic Crohn's colitis macroscopically but the ulcers are normally more regular in outline and the surrounding mucosa appears normal. A vasculitis with or without thrombosis and local ischaemia has been implicated (Katoh et al. 1985; Lee 1986). In colonic biopsies not in the immediate vicinity of the ulcers, the appearances are entirely normal and this gives a clue to the diagnosis, especially if the patient also has oro-genital ulceration, iritis, arthritis and skin and nervous system involvement. It is well to remember, however, that similar systemic manifestations can occur in idiopathic inflammatory bowel disease.

In chronic granulomatous disease a colitis complete with granulomata which is indistinguishable from Crohn's disease can occur. The diagnostic feature, however, is the presence of PAS-positive lipofuscin-filled histiocytes in both mucusa and submucosa (Isaacs et al. 1985). Rarely Wegener's granulomatosis (Sokol et al. 1984; Haworth and Pusey 1984) and angioimmunoblastic lymphadenopathy (Rosenstein et al. 1988) have also been reported in the context of a presentation as inflammatory bowel disease, but their histological characterisation rarely poses a problem once the diagnosis is considered. Radiation-induced colitis has acute and chronic phases which have been described in detail by Berthrong and Fajardo (1981) and should not normally cause diagnostic difficulties.

References

Atherton LD, Leib ES, Kaye MD (1984) Toxic megacolon associated with methotrexate therapy. Gastroenterology 86:1583–1588

Baum CA, Bhatia P, Miner PB (1989) Increased cononic mucosal mast cells associated with watery diarrhoea and microscopic colitis. Dig Dis Sci 34:1462–1465

Berezin S, Schwarz SM, Glassman M, Davidian M, Newman LJ (1989) Gastrointestinal milk intolerance of infancy. Am J Dis Child 143:361–362

Berthrong M, Fajardo LF (1981) Radiation injury in surgical pathology. II. Alimentary tract. Am J Surg Pathol 5:153–178

Bo-Linn GW, Vendrell DD, Lee E, Fordtran JS (1985) An evaluation of the significance of microscopic colitis in patients with chronic diarrhea. J Clin Invest 15:1559–1569

Bosshardt RT, Abel ME (1984) Proctitis following fecal diversion. Dis Colon Rectum 27:605–607

Boyd JF (1985) Pathology of the alimentary tract in *Salmonella typhimurium* food poisoning. Gut 26:935–944

Cawthorn SJ, Gibbs NM, Marks CG (1983) Segmental colitis, a new complication of diverticular disease. Gut 24:500

Editorial (1989) Diversion colitis. Lancet I:764

Fishel R, Hamamoto G, Barbul A, Jiji V, Efron G (1985) Cocaine colitis: is this a new syndrome? Dis Colon Rectum 28:264–266

Frejou JF, Grimand JA, Molas G, Baviera E, Potet F (1984) Collagenous colitis: Ultrastructural study and collagen immunotyping of 1 to 4 cases. Arch Pathol Lab Med 108:977–982

Glotzer DJ, Glick ME, Goldman H (1981) Proctitis and colitis following diversion of the fecal stream. Gastroenterology 80:438–441

Green ES, Parker NE, Geller AR, Beck ER (1984) Campylobacter infection mimicking Crohn's disease in an immunodeficient patient B Med J 289:159–160

Gryboski JD (1967) Gastrointestinal milk allergy in infants. Pediatrics 40:354–362

Guss C, Larsen JG (1984) Group A beta-hemolytic streptococcal proctocolitis. Pediatr Infect Dis 3:442–443

Haworth SJ, Pusey CD (1984) Severe intestinal involvement in Wegener's granulomatosis. Gut 25:1296–1300

Herrerias JM, Muniain MA, Sanchez S, Garrido M (1983) Alcohol induced colitis. Endoscopy 15:121–122

Innes A, Rowe PA, Foster MC, Steiger MJ, Morgan AG (1988) Cyclosporin toxicity and colitis. Lancet II:957

Isaacs D, Wright VM, Shae DG, Raafat F, Walker-Smith JA (1985) Chronic granulomatous disease mimicking Crohn's disease. J Pediatr Gastroenterol Nutr 4:498–501

Jessurun J, Yardley JH, Lee EL, Vendrell DD, Schiller LR, Fordtran JS (1986) Microscopic and collagenous colitis: different names for the same condition? Gastroenterology 91:1583–1584

Jessurun J, Yardley JH, Giardiello FM, Hamilton SR, Bayless TM (1987) Chronic colitis with thickening of the subepithelial collagen layer (collagenous colitis). Hum Pathol 18:839–848

Jonas G, Mahoney A, Murray J, Gertler S (1988) Chemical colitis due to endoscope cleaning solutions: a mimic of pseudomembranous colitis. Gastroenterology 95:1403–1408

Kalkay MN, Ayanian ZS, Lahaf EA, Baldi A (1983) *Campylobacter*-induced toxic megacolon. Am J Gastroenterol 78:557–559

Katoh K, Matsunaga K, Ishigatsubo Y, Chiba J, Tani K, Kitamura H, Tani S, Handwerger BS (1985) Pathologically defined neuro-, vasculo-, entero-Behcet's disease. J Rheumatol 12:1186–1190

Kaufman HJ, Taubin HL (1987) Nonsteroidal anti-inflammatory drugs active quiescent inflammatory bowel disease. Ann Intern Med 107:513–516

Kingham JGC, Levison DA, Ball JA, Dawson AM (1982) Collagenous colitis. Gut 27:570–577

Korelitz BI, Cheskin LJ, Sohn N, Sommers SC (1984) Proctitis after fecal diversion in Crohn's disease and its elimination with reanastomosis: implications for surgical management. Report of four cases. Gastroenterology 87:710–713

Lake AM, Whitington PF, Hamilton SR (1982) Dietary protein-induced colitis in breast-fed infants. J Pediatr 101:906–910

Lazenby AJ, Yardley JH, Giardiello FM, Jessurun J, Bayless TM (1989) Lymphocytic ("microscopic") colitis: a comparative histopathologic study with particular reference to collagenous colitis. Hum Pathol 20:18–28

Lee RG (1986) The colitis of Behcet's syndrome. Am J Surg Pathol 10:88–893

Levine MM (1987) *Escherichia coli* that cause diarrhoea: enterotoxigenic, enteropathogenic, enteroinvasive, enterohemorrhagic, and enteroadherent. J Infect Dis 155:377–389

Lillemoe KD, Romolo JL, Hamilton SR, Pennington LR, Burdick JF, Williams GM (1987) Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. Surgery 101:267–272

Lindstrom CG (1976) "Collagenous colitis": with watery diarrhoea: new enitity: Pathol Eur 11:87–89

Loss RW Jr, Mangla JC, Pereira M (1980) *Campylobacter* colitis presenting as inflammatory bowel disease with segmental colonic ulcerations. Gastroenterology 79:138–140

Lusk LB, Reichen J, Levine JS (1984) Aphthous ulceration in diversion colitis. Clinical implications. Gastroenterology 87:1171–1173

Martin DM, Goldman JA, Gilliam J, Nasrallan SM (1981) Gold-induced eosinophilic enterocolitis. Response to Cromolyn Sodium. Gastroenterology 80:1567–1570

Murray FE, O'Brien MJ, Birkett DH, Kennedy SM, LaMont JT (1987) Diversion colitis. Pathologic findings a resected sigmoid colon rectum. Gastroenterology 93:1404–1408

Ona FV, Boger JM (1985) Rectal bleeding due to diversion colitis. Amer J Gastroenterol 80:40–41

Orchard JL, Lawson R (1986) Severe colitis induced by soap enemas. South Med J 79:1459–1460

Pearson DJ, Stones NA, Bentley SJ, Reid H (1983) Proctocolitis induced by salicylate and associated with asthma and recurrent nasal polyps. Br Med J 287:1675

Price AB, Davies DR (1977) Pseudomembranous colitis. J Clin Pathol 30:1–12

Rhodes JM, Cockel R, Allan RN, Hawker PC, Dawson J, Elias E (1984) Colonic Crohn's disease and use of oral contraception. Br Med J 288:595–596

Rocca JM, Hecker R, Pieterse AS, Rich GE, Rowland R (1984) *Clostridium difficile* colitis. Austr NZ J Med 14:606–610

Rosenstein ED, Rickert RR, Gutkin M, Bacay A, Kramer N (1988) Colonic involvement in angioimmunoblastic lymphadenopathy resembling inflammatory bowel disease. Cancer 61:2244–2250

Ruppin H, Domschke S (1984) Acute ulcerative colitis: rare complication of sulfasalazine therapy. Hepato-gastroenterology 31:192–193

Sladen GE, Filipe MI (1984) Is segmental colitis a complication of diverticular disease. Dis Colon Rectum 27:513–514

Smith HR, Rowe B, Gross RJ, Fry NK, Scotland SM (1987) Haemorrhagic colitis and vero-cytotoxin-producing *Escherichia coli* in England and Wales. Lancet I:1062–1065

Sokol RJ, Farrell MK, McAdams AJ (1984) An unusual presentation of Wegener's granulomatosis mimicking inflammatory bowel disease. Gastroenterology 87:426–432

Steadman C, Teague C, Kerlin P, Harris O, Jourigan K, Sampson J (1987) Collagenous colitis: clinical and histological spectrum in ten patients. J Gastroenterol Hepatol 2:459–466

Sweeney JL, Hewett P, Riddell P, Joffmann DC (1986) Rectal gangrene: a complication of phosphate enema. Med J Austr 144:374–375

Tanner AR, Raghunath AS (1988) Colonic inflammation and nonsteroidal anti-inflammatory drug administration. Digestion 41:116–120

Teglbjaerg PS, Thaysen EH, Jensen HH (1984) Development of collagenous colitis in sequential biopsy specimens. Gastroenterology 87:703–709

Wang KK, Perrault J, Carpenter HA, Schroeder KW, Tremaine WJ (1987) Collagenous colitis: a clinicopathologic correlation. Majo Clin Proc 62:665–671