Inflammation in ileal reservoirs: ‘pouchitis’

Unlike conventional ileostomies, ileal faecal reservoirs often become inflamed. The first reservoirs were continent ileostomies and follow up studies soon showed histological features of mucosal inflammation.1 Similar changes were found when pelvic ileal pouches were examined.2 The clinical entity caused by mucosal inflammation in a pouch was first recognised in continent ileostomies3 and later in pelvic ileal pouches.4

Clinical ‘pouchitis’ has been widely recognised since.5,6,7,8 It is characterised by diarrhoea, sometimes and have features of ileostomies. Unlike conventional ileostomies, found become inflamed.9 The clinical entity caused by mucosal inflammation in a pouch was first recognised in continent ileostomies3 and later in pelvic ileal pouches.4

Defining the pathology of pouchitis

The proportion of patients described as developing clinical pouchitis after continent ileostomy ranges from 16% to 30%15,16 while even larger variations (7% to 33%) have been described in pelvic pouch patients.8,16 These wide differences reflect the need for a uniform diagnostic standard, a requirement which was partly satisfied by the development of an endoscopic and a histological scoring system for pouchitis.17–19 These workers assessed endoscopic pouchitis by defining signs of acute and chronic inflammation separately in order to obtain a numerical grade for endoscopic inflammation. They also scored acute and chronic histological changes separately. Only severe acute histological inflammation was consistently associated with sigmoidoscopic abnormalities.17 Extensive acute inflammatory cell infiltration and crypt abscesses occurred only in pelvic pouches with clinical and sigmoidoscopic pouchitis.18 In a similar study acute inflammation was found in biopsies from five of six patients with symptomatic pouchitis in a continent ileostomy or a pelvic pouch;19 there was no inflammation in asymptomatic pouches, nor in conventional ileostomies. An earlier study20 had reported, however, that acute inflammation did not correlate with continent ileostomy function, and it is relevant that some degree of acute inflammation is common in pelvic pouches and was found in 69% of 54 by Moskowitz21 and 38% of 13 patients by Nasmith.22

Studies separating acute and chronic histological inflammatory changes have shown that pouch function is unaffected by the chronic inflammation, shortening and broadening of villi and colonic metaplasia which normally occur.5,10,17,20,21 Two recent histological studies of pelvic pouches10,20 have confirmed this point: over 90% of 53 pelvic pouches biopsied by Moskowitz et al and 62% of the 13 examined by Nasmith et al (but only one of 10 ileostomies) showed some chronic inflammatory changes. Villous atrophy occurred in pouch mucosa but not in normal ileum or in conventional ileostomies.20 Similar changes have been found in continent ileostomy pouches, where the villi became shorter and broader, while the crypts became deeper.1 Whether a pelvic pouch is constructed for ulcerative colitis or familial polyposis, the pouch mucosa often secretes colonic rather than ileal type mucus. Mucin stains showed this change in half of a series of 32 patients20 while colonic metaplasia developed in nine of 20 patients with ulcerative colitis.19 There, however, are two studies which have not identified chronic inflammation as a feature of ileal pouches. Luukonen reported no difference in chronic inflammatory cell infiltration and villous atrophy between 15 conventional ileostomies, 15 continent ileostomies and, 15 pelvic pouches20 nor did Kelly find a difference between continent ileostomies with and without pouchitis, and conventional ileostomies.18 Some of the differences between these various studies are probably because of the way in which patients were selected and to different histological definitions of chronic inflammation.

Thus nearly all pelvic ileal pouches develop histological features of chronic inflammation and colonic metaplasia occurs in approximately half. Acute inflammatory changes are less common, however, and when severe are accompanied by clinical pouchitis.

Diagnostic criteria

It is hard to interpret or compare existing studies of pouchitis because they define the condition in different ways. Standard diagnostic criteria are required. The clinical problem of pouchitis is dominated by diarrhoea, and the number of stools per day correlates well with both endoscopic and histological features of acute inflammation.17–19 For an unequivocal diagnosis, diarrhoea should therefore be accompanied not only by endoscopic features of acute inflammation but also by histological evidence of a prominent polymorphonuclear cell exudate.17 The endoscopic and histological components of this diagnostic triad are important because outlet obstruction, an ischaemic pouch and Crohn’s disease can mimic the pouchitis syndrome. However, the endoscopic changes of pouchitis are often patchy so sampling errors can complicate the histological diagnosis. It is also of interest that a few severely inflamed and ulcerated pouches cause no symptoms.

Prevalence

Pouchitis appears confined to patients operated on for ulcerative colitis, whether the pouch is placed in the pelvis15,23,24 or constructed as a continent ileostomy.18 Only a few poorly documented cases have been reported in patients who have had the identical operation for familial adenomatous polyposis.24 Pouchitis is more likely in colitic patients presenting with extensive colitis than with left sided involvement.15

Bacteria and bacterial metabolites

A bacterial aetiology for pouchitis is suggested by the many anecdotal reports of its response to metronidazole and other antibiotics.6,10,17,18–21,24–26 No intestinal pathogen, however, has been clearly incriminated. Attention has been focused
on the pattern of bacterial species associated with inflammation in pelvic pouches and continent ileostomies. The first of these studies was performed before pouchitis had been recognised, and indicated that pouches with chronically inflamed mucosa on biopsy contained equal proportions of anaerobes and aerobes, unlike a conventional ileostomy in which anaerobes normally predominate. Three subsequent studies confirmed that pouches of patients with or without symptoms and past or current pouchitis contained similar aerobe and anaerobe counts. A group of patients with jejunal (not ileal) overgrowth of both aerobes and anaerobes was identified, but they did not have pouchitis, merely diarrhoea. At present the evidence for a direct bacterial cause for pouchitis rests solely on its apparent response to antibiotic treatment. If bacteria do not cause pouchitis directly, might they act by changing the pouch contents? Some intestinal bacteria such as Bacteroides spp produce volatile fatty acids by digesting carbohydrate and alterations in volatile fatty acid levels have been linked to mucosal inflammation. Volatile fatty acids seem to have a trophic effect on terminal ileal cells in rats. Absence of fecal volatile fatty acids seems to be the cause of the colitis which may occur in bypassed human colon, because addition of volatile fatty acids to a defunctioned, colitic segment reverses the colitis. Low levels of both volatile fatty acids and Bacteroides spp in pouch faeces correlate with mucosal villous atrophy, a marker of chronic inflammation. A failure of volatile fatty acid metabolism in colonic mucosal cells (not a lack of substrate volatile fatty acids) may play a role in the pathogenesis of ulcerative colitis because the mucosa metabolises the volatile fatty acid butyric acid more slowly than normal mucosa. In summary, these findings show that a healthy mucosa needs both normal luminal levels of volatile fatty acids and the ability to metabolise these products. They do not suggest that reduced levels of bacterial metabolites cause either ulcerative colitis or pouchitis. Might bacterial metabolism of bile acids cause pouchitis? Bile acids are conjugated with taurine or glycine before being secreted into bile. Bacteria in the terminal ileum and colon (or in an ileal pouch) then hydrolyse them to their original unconjugated form. In a different reaction, the primary bile acids are metabolised by bacteria in the secondary bile acids. Loss of hydroxyl groups makes these compounds more lipophilic than their corresponding primary bile acids and experimentally they damage the lipid structure of cell membranes more than the parent compound. One such secondary bile acid, deoxycholic acid, causes a progressive increase in water and salt permeability followed by cell death in the rat colon, while the sulphated conjugate exerts a protective effect. Bacterial deconjugation might therefore convert this bile acid to a toxic form. Could secondary and deconjugated bile acids produced by pouch bacteria cause pouchitis? Bile acids and pouch bacteria have been compared in three groups of patients; those with ulcerative colitis with pouchitis, with ulcerative colitis without pouchitis, and in patients with polyposis. Bacterial counts of 19 different organisms did not correlate with mucosal inflammation, but concentrations of both total conjugated bile acids and tauroconjugated bile acids were lower in pouchitis patients. This suggests increased bacterial deconjugation in pouchitis, an avenue which deserves further investigation.

Pouch emptying
Although pouch stasis seems an obvious possible cause for pouchitis, no correlation between poor emptying and pouchitis has been found in studies using an isotopically labelled enema or porridge.

Treatment and response
Frequent defecation in a patient with a pouch is not usually due to pouchitis and in the absence of another specific cause it will generally respond to an antidiarrhoeal drug such as codeine or loperamide. Moreover, a proportion of patients with inflamed pouches have an acceptable stool frequency and need no treatment. The treatment of symptomatic, endoscopically proven pouchitis is empirical. First, pouchitis has been treated like ulcerative proctitis, with enemas containing steroids or salicylic acid derivatives followed by a short course of oral steroids if enemas cannot be retained. Alternatively an antibacterial agent has been given, usually metronidazole. Each approach is usually combined with an antidiarrhoeal drug. Obviously the use of such combinations makes it impossible to assess the effectiveness of the individual agents. Ancodotial support for an antibacterial agent active against anaerobes is, however, so substantial that some authors actually use a therapeutic response as a diagnostic test or even administer metronidazole prophylactically to all patients after pouch construction.

Animal study
Luukonen interposed an ileal pouch between the proximal rectum and the anus in piglets. Although 10 of the 12 piglets developed mucosal ulceration in the pouch, this was only associated with a mild polymorphonuclear cell infiltrate and no crypt abscesses, unlike human pouchitis where both these features are prominent. The most striking ulceration occurred in two pouches with outlet strictures. The chronic inflammatory changes were similar to those seen in human pouches, with villous atrophy and a chronic inflammatory cell infiltrate. The relevance of this model to human pouchitis is not clear, as the piglets did not have colitis and there are histological differences between their pouchitis and its human equivalent.

Theories on pathogenesis
The cause of pouchitis is unknown. Acute inflammatory changes affect a minority of pouch patients, while the chronic changes occur in almost all. Acute changes, particularly when severe, are significantly commoner in ulcerative colitis than in polyposis patients. Moreover, unequivocal pouchitis has only been diagnosed in colitis patients. This suggests that it is disease-related and not simply due to the construction of the pouch. Whether it represents 'ulcerative colitis' in the small intestine is not known but it may be that ulcerative colitis and pouchitis have the same aetiology.

The second clue relates to the anecdotal yet extensive evidence that pouchitis responds to antibacterial treatment. This suggests that human pouchitis requires both previous colitis and subsequent exposure of the pouch to faecal organisms, or their metabolites distinct from those in a conventional ileostomy.

Pouchitis remains an important clinical problem and a fascinating model for the study of the aetiology of ulcerative colitis. Further work is clearly needed to unravel this ileal enigma.

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