Pouchitis – What's new in etiology and management?

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RJ NICHOLLS. Pouchitis – What's new in etiology and management? Can J Gastroenterol 1995;9(1):17-22. Pouchitis requires a clear clinicopathological definition. There are many conflicting data concerning etiology. It is linked to an initial diagnosis of ulcerative colitis by clinical association and occurrence of extra-alimentary manifestations, histologically and by macrophage types and inflammatory mediators. Evidence for a bacteriological cause comes from response to metronidazole, increased counts of intramucosal bacteria in pouchitis and the possible association of hypochlorhydria. Most studies have, however, shown no specific bacterial pathogen or luminal bacterial count differences in pouches with or without pouchitis. Abnormal fecal bile salt concentrations have been reported. Stasis and evacuation efficiency of the pouch are not associated with pouchitis in most studies. Reduced mucosal bloodflow may be associated perhaps leading to increased permeability to toxins causing activation of interleukin-1, platelet-activating factor (PAF) and tumour necrosis factor (TNF). PAF may be increased in pouchitis. Pouchitis may respond to allopurinol. Volatile short chain fatty acids (VSFA) may be reduced in ileal reservoirs compared with straight ileoanal segments and in pouchitis. The response of pouchitis to administered VSFA is, however, variable. Glutamine administration may help. There is evidence that intraepithelial T lymphocytes are reduced. Crypt cell turnover is higher in colitic than in polypotic pouches. Mucosal morphological changes of villous atrophy and inflammation occur early after relapsing polychondritis and may predict future susceptibility to pouchitis. Early mucosal biopsy appears to have prognostic value. Metronidazole and antibiotics (amoxicillin/potassium clavulanate, ciprofloxacin) may be effective although in a controlled trial of the former there was little advantage over placebo. The results of treatment using VSFA, glutamine, allopurinol sucralfate and anti-inflammatory agents, including aminosalicylic acid (5-ASA) and steroids, is reviewed. Assessment of efficacy is difficult because the definition of pouchitis is not standardized, there may be more than one clinical type and studies may not be controlled. Failure of medical treatment may require surgical defunctioning or removal of the pouch. (*Pour résumé, voir page 18*)

Key Words: *Pouchitis, Restorative protocolectomy, Ulcerative colitis*

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POUCHITIS IS A CLINICAL condition associated with inflammation of the ileal reservoir. It was recognized first in continent ileostomies by Kock et al (1) and subsequently in ileoanal ileal reservoirs by Handelsman et al (2). Histological changes in ileal reservoirs of a chronic inflammatory or atrophic type had been reported in both types of reconstruction by Philipson et al (3) and Nicholls et al (4). Subsequently it was appreciated that pouchitis occurs predominantly in ulcerative colitis and only rarely (if at all) in familial adenomatous polyposis. Various possible causes, including stasis, bacterial flora and biochemical factors (for example short chain fatty acids [SCFA] or bile salts), have been studied. Various treatments from antibiotics to bile salts, SCFA, xanthene oxidase inhibitors and conventional anti-inflammatory medication have been tried.

One is left with a somewhat confusing picture, due in part to ignorance concerning the etiopathology of inflammatory bowel disease (IBD), in part to a variable interpretation of diagnosis and in part to the possibility that acute inflammation may be due to various agents. The term pouchitis implies inflammation. It cannot be diagnosed solely by the presence of symptoms or, indeed, by endoscopic appearances. There has to be histopathological evidence of acute inflammation. Several studies have not used histopathology to make the diagnosis and as a result some

Pouchite – Quoi de neuf en matière d'étiologie et de traitement?

RÉSUMÉ : La pouchite requiert une définition clinicopathologique claire. Il existe plusieurs données conflictuelles à l'égard de son étiologie. Elle est liée à un diagnostic initial de colite ulcéreuse sur la base des signes cliniques, des manifestations extra-alimentaires, des signes histologiques et des types de macrophages et de médiateurs de l'inflammation. Les indices d'une cause bactériologique proviennent de sa réponse au métronidazole, de l'augmentation de la numération bactérienne intramuqueuse et de la possible association d'hypochlorhydrie. La plupart des études n'ont toutefois démontré aucun pathogène bactérien spécifique ni aucune différence de la numération bactérienne luminale dans les réservoirs, qu'il y ait ou non inflammation. Des concentrations anormales de sels biliaires dans les selles ont été rapportées. La stase ou l'efficacité de l'évacuation ne sont pas associés à la pouchite dans la plupart des études. Le ralentissement de la circulation sanguine dans la muqueuse peut être associé à une augmentation de la perméabilité aux toxines qui activent l'interleukine 1, le facteur d'activation plaquettaire et le facteur de nécrose tumorale. Le facteur d'activation plaquettaire peut être augmenté dans la pouchite. La pouchite peut répondre à l'allopurinol. Les acides gras en chaînes courtes volatils peuvent être réduits dans les réservoirs iléaux en comparaison avec les segments iléoanaux droits, et dans la pouchite. La réponse de la pouchite à l'administration d'acides gras en chaînes courtes est toutefois variable. L'administration de glutamine peut aider. Il y a des signes à l'effet que les lymphocytes-T intra-épithéliaux soient réduits. Le renouvellement des cellules des cryptes est plus rapide dans les réservoirs en présence de colite qu'en présence de polypes. Les modifications morphologiques de la muqueuse, comme l'atrophie des villosités et l'inflammation, se produisent tôt après la rechute d'une polychondrite et peuvent fragiliser le sujet à l'égard de la pouchite. Les biopsies muqueuses précoces semblent avoir une utilité pronostique. Le métronidazole et les antibiotiques (amoxycilline/clavulanate de potassium, ciprofloxacine) peuvent être efficaces, bien qu'un essai contrôlé sur le premier lui ait trouvé peu d'avantages en comparaison avec le placebo. Les résultats du traitement par acides gras en chaînes courtes, glutamine, sucralfate d'allopurinol et anti-inflammatoires, y compris l'acide aminosalicylique (5-AAS) et les corticostéroïdes, sont passés en revue. L'efficacité est difficile à évaluer parce que la définition de la pouchite n'est pas normalisée; il peut en exister plus d'un type clinique et les études ne peuvent être contrôlées. L'échec du traitement médicamenteux peut exiger une ablation chirurgicale.

patients deemed to have pouchitis may not have had this condition. There are various causes of frequency of defecation and other bowel symptoms that may be confused with pouchitis. These include physical factors, for example a small reservoir or emptying difficulties, intrinsic bowel motility, psychological factors, partial small bowel obstruction and extramural inflammation. To diagnose pouchitis, it is generally accepted that there must be inflammation present. There is a reasonable correlation between the severity of the histological inflammation based on a semi-objective grading system and symptoms (5).

RESERVOIR HISTOPATHOLOGY

Histopathological examination of the ileal pouch mucosa shows several different abnormalities which may variably be represented and overlap.

Chronic inflammation and villous atrophy: Almost all functioning pouches show some mucosal abnormality. These are common to patients with ulcerative colitis and familial adenomatous polyposis. They may vary in their severity but are qualitatively similar (6). The changes are characterized by an increase in the presence of chronic inflammatory cells within the lamina propria. These include lymphocytes, plasma cells and sometimes eosinophils. In addition, there is villous atrophy to a varying degree from individual to individual and within the same pouch. The degree of villous atrophy is associated with crypt hyperplasia.

These changes appear to occur early after restoration of the fecal stream (3,7,unpublished data). They appear to be confined to the reservoir and only rarely extend into the proximal ileum, as noted by Shepherd et al (6), who demonstrated more severe changes in the posterior than the anterior aspect of the lower part of the reservoir. Setti-Caffaro et al (8), in a study of 57 patients having four biopsies taken from the pouch at 5 cm intervals from distal to proximal, identified three groups of patients. These included patients in whom none of the biopsies showed any acute inflammation (n=8), those in whom all biopsies showed acute inflammation (n=25) and those in whom there was a gradient of decreasing inflammation from distal to proximal (n=26).

These changes may be the result of an alteration in milieu due to the presence of increased numbers of fecal bacteria compared with the normal ileostomy effluent. These may lead to changes in colonic intraluminal carbohydrate fermentation of dietary fibre with the increased production of SCFA and changes in bile salt concentration and type. The mucosal dynamics in response to this alteration in microenvironment are unknown, as are the factors responsible. Nasmyth et al (9) have, however, presented data suggesting that the degree of villous atrophy is inversely related to the concentration of butyrate in the pouch feces. The degree of villous atrophy is also related to crypt cell turnover as determined immunohistochemically using the monoclonal antibody Ki-67 (10). A similar result was obtained by Martelli and coworkers (unpublished data) who demonstrated an increase in labelling index within the ileal mucosa in patients with ulcerative colitis after pouch construction. There was no change in patients with familial adenomatous polyposis.

COLONIC METAPLASIA

Histologically the presence of severe villous atrophy and crypt hyperplasia

resembles colonic mucosa. When inflammation is present they look like ulcerative colitis (10,11). Studies have shown colonic type mucin in ileal pouches irrespective of the original diagnosis. Using Alcian blue staining techniques and the monoclonal antibody PR3A5, which is thought to be specific for colon type mucin, the presence of sulphated mucin has been demonstrated in ileal pouch mucosa (11,12). A similar result has been reported using a S_{35}-H_3 glucosamine labelling technique (13).

These changes are, however, not complete. For example the pouch mucosa retains certain properties of small intestinal enterocytes with preservation of disaccharidase activity and the activity to absorb vitamin B_{12}, xylose and bile acids (12). It is unknown whether colonic metaplasia is a prerequisite for pouchitis (6).

'DIVERSION' CHANGES

In defunctioning pouches, that is before closure of the ileostomy, histological abnormalities have been reported in some patients (14). These include villous atrophy, chronic inflammation with eosinophil predominance and acute inflammation. The changes are not typical of ischemia or Crohn's disease, and those authors speculated on the possibility that they may represent a form of diversion ileitis analogous to that described in the rectum (15,16).

POUCHITIS

Pouchitis is characterized by the presence of acute inflammation. This is correlated with the severity of chronic inflammation (5,8,11,12). The appearance of pouchitis is similar to ulcerative colitis in an active phase. Polymorphs appear to be located predominantly through the epithelium with crypt abscess formation, and aggregates are seen in the lamina propria but are often focal. Ulceration is present. There may be evidence of colonic metaplasia but sometimes small intestinal sialomucins predominate (11). Perhaps this is similar to the appearance of sialomucins in cases of acute ulcerative colitis (17). In contrast with celiac disease, intraepithelial lymphocyte counts in ileal pouches are low and do not increase in pouchitis (18).

Pouchitis is essentially confined to patients with ulcerative colitis. While case reports of its occurrence in familial adenomatosis have been reported, it is rare and histological confirmation is not always obtained. In 37 polyposis patients followed for a mean of five years, no case was reported (19).

The timing of these morphological changes is unknown in detail. Some information is, however, available from a long term histopathological study of 60 pouch patients with an original diagnosis of ulcerative colitis biopsied over a median period of 97 months (range 90 to 173) (8). On the basis of histological grade of severity of acute and chronic inflammation, the patients can be divided into three groups. In the first group (n=27) were patients whose changes were minor, with acute changes never seen. Patients in the second group (n=25) had chronic changes that were more severe and had transient episodes of acute inflammation. In the third group (n=8), severe chronic and severe acute inflammation were constantly present. Pouchitis never occurred in the first group and was constantly present in the third group. Patients were allocated to a group within six months of closure of the ileostomy and remained in that group indefinitely.

If these data are true, patients at risk of developing pouchitis can be identified on biopsy at an early stage in the postoperative course (8). Verres et al (20) made similar observations. They reported that dysplasia occurred, albeit rarely but exclusively, in the third group (constant presence of severe chronic and severe acute inflammation).

POSSIBLE EVOLUTION

On the basis of histopathological observations, a hypothetical sequence of events can be suggested. On construction of an ileal reservoir with defunctioning ileostomy, some cases will develop an inflammation in the mucosa associated with low intraluminal SCFA levels. This will be abolished with closure. The presence of feces containing bacterial counts similar to normal colonic feces then leads to chronic inflammation and villous atrophy. The degree of this will be variable according to the individual but is generally less in familial adenomatous polyposis patients than in those with ulcerative colitis. Stasis is always present to some degree in an ileal reservoir whether it is in a continent ileostomy or ileoanal construction.

As villous atrophy progresses, crypt hyperplasia occurs and mucin changes into colonic type. Colonic metaplasia can occur in both ulcerative colitis and familial adenomatous polyposis. It appears to be variable in its distribution and not complete in that some small intestinal function is preserved.

Colonic metaplasia then renders the mucosa susceptible to the underlying pathological process. With ulcerative colitis this results in inflammation, with familial adenomatous polyposis in the induction of adenoma formation.

POSSIBLE ETIOLOGICAL FACTORS

Bacteria: Bacterial counts in ileal reservoir feces are greater than in ileostomy effluent and approximate those in normal feces. In addition there is a relative rise in the anaerobic count. The anaerobe:aerobe ratio in pouches is 100:1 compared with about 4:1 in ileostomy effluent (21). These changes are likely to be due to stasis in the reservoir. In both Kock and ileoanal reservoirs, stasis is present compared with a constantly acting ileostomy. In both, total counts and increase in anaerobes have been reported (4,9,22).

While these changes may lead to mucosal alterations, for example chronic inflammation and villous atrophy, there is no evidence that stasis per se is responsible for pouchitis. A study assessing the efficiency of evacuation of the pouch has not shown any difference in patients with or without pouchitis (5,23).

Pouchitis is not related to the type of reservoir. Its incidence is no different in patients with S reservoirs needing to be catheterized compared with J reservoirs in which evacuation was not

impeded (5). Fleshman et al (24) presented evidence that pouch inflammation was more likely in the presence of an ileoanal stricture, although pouchitis could still occur without it. Furthermore, there is no correlation between the number or species of bacteria and the presence or absence of pouchitis. No specific pathogenetic bacteria have consistently been found to be associated with pouchitis (22,23,25). Onderdonk et al (26), in an electron microscopic study of pouch mucosa combined with bacterial culture techniques, showed significantly greater total counts for aerobic bacteria associated with the mucosa in patients with pouchitis.

There is, however, much evidence (mostly anecdotal) that metronidazole improves pouch inflammation. The most objective comes from a recent study by Kmiot and colleagues (27) employing ^{111}In-labelled granulocyte scanning in six patients with pouchitis. These authors showed a reduction in granulocyte migration to the pouch, associated with endoscopic and histological improvement, one month after metronidazole was started. In another study, Dube and Heyen (28) identified 15 cases of pouchitis in 70 patients. Ten patients responded to metronidazole. Six patients, including three responders and three nonresponders, had gastric function studies. Fasting gastric pH was 1.3 or less in the responders and 4.2 or more in the nonresponders. This suggests an effect by metronidazole on fecal flora. Metronidazole does not always work, however. In a double-blind crossover trial in 11 patients with chronic unremitting pouchitis, there was only a slight diminution in the frequency of defecation and no significant change in histological grade or C reactive protein (29).

METABOLIC EFFECTS OF ALTERED FECAL FLORA

SCFA: SCFA are produced by the fermentation of carbohydrate in dietary fibre by colonic anaerobic bacteria. They are an important source of energy to the colonic epithelium and their lack may cause diversion colitis. Nasmyth et al (9) reported higher SCFA concentrations in stool from ileal reservoirs than in normal ileostomy stool, and concentrations similar to normal feces. They also observed a relationship between butyrate concentrations and the degree of villous atrophy: the higher the concentration, the lower the atrophy. This implied a protective influence of SCFA on limiting chronic changes. Clausen and associates (30) showed that SCFA concentrations were markedly lower in six patients with pouchitis than in 28 without, with levels of 56.2±13.3 mmol/L and 139.0±8.5 mmol/L, respectively. There was no change in the ratios of acetate:butyrate:propionate in either group. Those authors produced evidence to indicate that this difference is due to lack of substrate rather than to the difference in the capacity of the flora to produce SCFA because in vitro production of SCFA of fecal homogenates in patients with pouchitis can be restored with the addition of saccharides. This suggested the possibility that pouchitis is due to a reduction of substrate available, leading to low SCFA. Wischmeyer et al (31) demonstrated SCFA concentrations in stool of 11 pouchitis patients to be 25% of the level in 13 nonpouchitis patients. Further evidence indicating that SCFA may be important in influencing the state of the mucosa comes from a study of 14 patients in whom frequency of defecation was inversely related to the stool SCFA concentration (32). Pouchitis did not respond to the installation of SCFA into the pouch by enema (33).

In contrast, benefit of SCFA was found in a study by Wischmeyer et al (34). Patients who had had pouch operations for ulcerative colitis were recruited on the basis of a diagnosis of 'chronic pouchitis'. (It is unclear whether this was confirmed histologically.) Ten patients completed a trial of L-glutamine (1 g) given by suppository and six patients had no recurrence of symptoms. Nine patients completed a trial of sodium butyrate (40 mmol) given by suppository and three had no recurrent symptoms. There is, however, no long term follow-up of this study and no detailed statement of the criteria for improvement (34).

BILE SALTS

Hill and Owen (35) reported high levels of deconjugated and secondary bile acids in the ileal reservoir compared with ileostomy effluent. Deconjugated bile acids can, through their detergent effect, damage membranes (36) and may therefore be a factor in pouchitis. The significant difference in total bile acid conjugates in six patients with pouchitis – 20 with ulcerative colitis without pouchitis and seven with familial adenomatous polyposis of 0.52 mg/feces, 2.68 mg/feces and 1.56 mg/feces, respectively – requires further work for its corroboration (35). Hulten (37) reported that cholestyramine was not helpful in pouchitis.

IMMUNE MECHANISM

The association of pouchitis with ulcerative colitis suggests a common etiopathogenesis. Clinically the conditions both show a natural history of exacerbations and remissions, either with resolution or with persisting chronic mucosal damage. Both are associated with an activity-related polyarthropathy. In pouchitis this is more likely to occur if it was present preoperatively (38). Histologically there are close similarities, including the low numbers of intra-epithelial lymphocytes, crypt abscesses and chronic cell infiltrate in the lamina propria. Increased immunoglobulin (Ig) G and IgA secreting plasma cells have been shown in the lamina propria in pouchitis in densities similar to those seen in ulcerative colitis (39). Merrett et al (40) studied biopsies from rectal mucosa and compared the findings with original colitic rectal mucosa in seven cases. Ig-containing cells were identified by immunohistochemistry. The total counts and profile of cells containing IgG, IgA, IgM and IgG1-4 were similar. De Silva et al (10) demonstrated increased numbers of RFD9+ macrophages in the mucosa, again a feature of noninfective IBD. Gionchetti et al (41) confirmed this finding and showed RFD9+ macrophages to be present in significantly higher proportions in pouchitis, compared with nonpouchitis, patients.

Mediators and inflammation have been shown to be increased in ileal

pouches. Products of arachidonic acid metabolism, for example prostaglandin E_2 and leukotriene B_4, are present in mucosa and the lumen of ulcerative colitis patients (42). In the pouch patients, Gertner and co-workers (43) have shown increased release of leukotriene B_4 in biopsies of patients with ulcerative colitis compared with those with polyposis. In addition, there was no difference in leukotriene B_4 released from biopsies taken from defunctioning colitic pouches compared with properly functioning ones. Steroids, which stabilize cell membranes, and acetylsalicylic acid, which inhibits prostaglandin synthesis, may have beneficial effects in pouchitis via a mechanism similar to that in ulcerative colitis. Chaussade et al (44) have shown higher levels of platelet activating factor in the stool of pouch patients with pouchitis than in those without. Overall density of cell immunoreactivity to tumour necrosis factor-alpha is increased in ulcerative colitis and Crohn's disease and is confined to the lamina propria (mainly in subepithelial macrophages) in the flora (45). In pouch mucosa, tumour necrosis factor-alpha is also present as determined by in situ hybridization of mRNA (46).

ISCHEMIA

Hosie et al (47), using laser Doppler bloodflow estimations, have suggested that ischemia may be a factor in pouchitis. Histopathological examination of pouches has not shown changes typical of this pathology, however (48), and the intermittent relapsing and remitting nature of pouchitis is against ischemia.

Based on a possible ischemic etiology, allopurinol has been used in patients with acute (n=8) and chronic (n=14) pouchitis. It is important to note that the diagnosis was based on symptoms and not on histopathological confirmation. Four patients with acute pouchitis and seven of those with chronic pouchitis responded, but no data on long term follow-up were given (49). Further studies of appropriate placebos are required.

SUMMARY

Pouchitis is a man-made disease that appears clinically to resemble ulcerative colitis. It also appears to occur on a background of chronic inflammation, villous atrophy and colonic metaplasia. Histopathological confirmation of the diagnosis is essential. Patients at risk may be identified at an early stage after pouch construction by histopathological examination of a mucosal biopsy. Treatment using antibiotics, anti-inflammatory drugs, SCFA, xanthene oxidase inhibitors and cholestyramine is empirical. Like ulcerative colitis there is no specific cure. Further research studying the evolution of mucosal changes at a cellular and molecular level is the most likely way to increase understanding of the etiopathology and therefore the therapy.

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