Seminars in Colon and Rectal Surgery 28 (2017) 121–125

Contents lists available at ScienceDirect

Seminars in Colon and Rectal Surgery

journal homepage: www.elsevier.com/locate/yscrs

Etiology and pathogenesis of pouchitis

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A B S T R A C T

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the preferred surgery for ulcerative colitis (UC) and familial adenomatous polyposis (FAP). While this surgical therapy is effective and results in good clinical outcomes and quality of life, patients experience complications, the most common of which is pouchitis. While most pouchitis is considered idiopathic, there is mounting evidence that pouchitis results from aberrant immune response to the bacterial populations found in the pouch in a genetically predisposed patient. Dysbiosis and decreased diversity of the microbiota seem to contribute to this process. Risk factors for pouchitis including inflammatory bowel disease and obesity provide further clues to the etiology of pouchitis. In conclusion, we seek to understand the pathogenesis of pouchitis as both a post-operative complication and a form of inflammatory bowel disease (IBD).

Pouchitis is defined as inflammation of the surgically created intestinal reservoir or pouch.[1] The main surgical pouches created after proctolectomy performed today are the IPAA (ileal pouch anastomosis) in the form of a J, and less commonly the S or W pouch, and the Koch pouch (continent ileostomy). Up to 60% of patients with J pouch will experience pouchitis, with 5–28% with chronic pouchitis.[2–4] Specifying the nature of pouchitis is defined by reporting:[5] (1) etiology: idiopathic vs. secondary; (2) activity: active vs. in remission; (3) chronicity: acute less than 4 weeks or chronic; (4) interval: infrequent (less than four episodes a year) vs. relapsing (greater than four times a year times) vs. continuous; (5) response to antibiotic therapy: responsive vs. refractory.

The most commonly reported pouchitis is idiopathic and this review will focus on this entity primarily. Secondary causes include infections, autoimmune, structural, medication related and inflammatory including as Crohn's disease. While the etiology of pouchitis is not fully understood, evidence suggests that this represents a dysfunctional interaction between the mucosal immune system and the flora in genetically susceptible host. Our understanding of some of the identified secondary causes of pouch dysfunction may also provide insight into the pathways of classic, so-called idiopathic pouchitis.

Histologic and mucosal changes after pouch creation

Creation of a pouch involves forming a new organ with the primary role of storage from ileal mucosa, of which the original function was absorption. The mucosa of the pouch is well known to undergo histologic changes from that of the native ileum. This process is commonly described as colonic metaplasia. These adaptive changes probably allow the success of this surgical procedure but the morphologic change may impact the pathogenesis of pouchitis. Of interest, these histologic changes occur almost always after the diverting ileostomy is reversed. The changes in the environment of the pouch compared to the ileum are presumed to contribute cause this morphologic change. The shift in microbiota detailed in subsequent sections and fecal stasis are presumed to have impact. Bile concentrations within the ileal pouch are higher than those found reported in the ileostomy and of different composition than that colonic stool, which has higher concentrations of secondary bile acids while the IPAA has higher percentages of primary bile acids.[6] The histologic changes noted include crypt hyperplasia and villous atrophy, chronic inflammatory cell infiltrate including lymphocytes, eosinophils and histiocytes, and pyloric gland metaplasia.[7] Villous atrophy with chronic inflammation with neutrophils is described in the adapted mucosa even within asymptomatic pouches. Etorre et al. found that biopsies from the pouch body of 92% of pouch patients studied revealed histologic changes that were read as inflammatory, which include polymorphonuclear cell infiltration, ulceration, villous atrophy, and chronic inflammatory cell infiltration. There was no correlation between histology and symptoms of pouchitis.[8] Intraepithelial lymphocytosis has also been reported in both UC and FAP pouch biopsies and is found to have no correlation to presence of celiac disease or other pathology.[10] Other morphologic changes in pouch mucosa that were identified include increase in crypt cell proliferation compared to native ileum, expression of antigens such as PR3-A5 that are expressed only in the colon, and a change to expression of sulfomucin (colonic) mucin. In contrast to true

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http://dx.doi.org/10.1053/j.scrs.2017.05.003
1043-1489/

colonic tissue, biopsies from 50% of patient demonstrated preservation of sucrose–isomaltase activity which is expressed in the ileum but not found in the colon.[6,7] The adapted ileum also fails to demonstrate in increase in glycoprotein synthesis. The higher levels of glycoprotein found in the normal colon compared to the ileum are considered to be protective.[9] Mucosal permeability has been suspected to be part of pathogenesis of pouchitis by perpetuating exposure that results in activation of inflammatory pathways. It is reported that with the cellular changes in the ileal mucosa after the ileostomy closure, in fact the permeability of the mucosa does decrease to Cr-EDTA assay, presenting a more colonic defense, with the exception of pouchitis when the permeability increases.[11] Conversely, with mature pouches, an increase in bacterial permeability is noted over time even in the absence of pouchitis.[12] The transition from a largely absorptive mucosa to one with storage function is associated with chronic low-grade inflammation and morphologic changes. Coffey et al.[13] hypothesized that as the ileal mucosa undergoes colonic metaplasia, it becomes again susceptible to the inflammatory process that impacted the colon in UC patient and this may contribute to the pathogenesis of pouchitis. In contrast, we might hypothesize that the incomplete transition from ileal to colonic mucosa allows the function of the pouch but renders the mucosa less protected than fully colonic mucosa to the insults the distal intestinal tract endures, suggesting that identifying means to further this adaptation such as increase in glycoprotein expression might reduce the rate of pouchitis. Both of these concepts merit further investigation.

Genetic factors

The fact that patients with preexisting inflammatory bowel disease are far more likely to experience pouchitis than those with FAP lead to suspicion for genetic predisposition. Several genes have been identified as possible risk factors for pouchitis. A total of 109 patients with history of UC underwent genotyping and an association with interleukin-1 receptor antagonist gene allele 2 and pouchitis was found with a relative hazard was 3.1 [95% confidence interval (CI): 1.2–7.8; $P = 0.02$].[14] This allele was originally associated with UC and studies suggest it may impact mucosal down regulation of inflammation with reduced expression of interleukin-1 receptor antagonist. NOD2/CARD 15 mutations have been extensively studied for association with IBD and was the first gene polymorphism to be associated with a higher risk of Crohn's disease.[15] This gene product is involved with host response to bacterial peptidoglycan. The normal function of this gene product is to activate a cascade of cytokine response to facilitate bacterial clearance. Seghal et al. studied polymorphisms of this gene in patients with IPAA. They found that 8.5% of normal controls, 5.4% of asymptomatic IPAA patients, 67% of patients with severe pouchitis and 14.3% of patients with Crohn's-like complications of the pouch carried NOD2/CARD 15 mutations. Of patients with mild pouchitis, 18% were carriers.[16] These findings led to hypothesis that defects in host protection against bacteria result in lack of efficacy of antibiotics in patients with severe pouchitis. Additional studies of small nucleotide polymorphisms (SNP) found against an association with NOD2 and severe pouchitis, along with *TNFSF15*, an antiangiogenesis factor that is also associated with severe colitis.[17] Further analysis has identified specific polymorphisms as a risk, most prominently NOD2insC.[18] In a study of 150 Italian patients who had undergone IPAA for UC, dual alleles *TLR9*-1237C and *CD14*-260T synergistically increased the risk of pouchitis. These SNP in other studies are associated with higher levels of CD14 in the blood in IBD patients and increased levels of CD14 on macrophage membranes.[18] CD14 is part of a complex that participates in lipopolysaccharide (LPS) identification and works in conjunction with Toll-like receptors (TLR) 2 and 4. TLR9 interacts with identification of CgA methylated repeats in bacterial DNA. In summary, efforts have been made to determine if genetic variants increase the risk for pouchitis after IPAA may be identified. In a manner similar to other areas of inflammatory bowel disease, polymorphisms to genes that impact the innate immune system have been identified that seem to increase the risk of pouchitis or Crohn's-like complications of the pouch. Of note, all of these studies in pouchitis made use of sequences already implicated in other forms of IBD. These data do support the hypothesis that pouchitis occurs via immune dysfunction or dysregulation in a genetically predisposed host given that most of the polymorphisms identified are related in immunologic function.

Impact of the microbiota of the pouch

The interaction between the microbiota of the pouch and the mucosal immune system is obviously important and complex. There is a clear shift in the populations within the pouch from that of the native ileum. The fact that antibiotic therapy is highly efficacious for acute pouchitis and required for chronic antibiotic responsive pouchitis (CARP) points clearly to the impact of bacteria on this disorder. A reduction in diversity of the intestinal microbiome and dysbiosis, or altered populations compared to healthy individuals is implicated in the pathogenesis of both pouchitis and inflammatory bowel disease in general.

There is clearly a change in the microbiota within the pouch from that of the ileum. Again this seems to be an adaptation toward composition more commonly found in the colon. The contents of the IPAA have 10% of the counts found in colonic stool, compared to 0.1–1% found in the native ileum or ileostomy content. An increase anaerobic compared to aerobic is reported.[6] The bacterial shifts may increase sulfate reduction, change bile salt composition and impact the generation of short chain fatty acids.[13] Studies making use of terminal restriction fragment length polymorphism (T-RFLP) analysis comparing the microbiota of patients with IPAA for UC and normal controls showed a transition over time to bacteria more common to the colon.[19] Further analysis suggests that the changes occurred over the first year after ileostomy closure with little change after that. There was increase in anaerobic species and including species considered colonic such as *Clostridium coccoides*, *Clostridium leptum*, *Bacteroides fragilis*, and *Atopobium* with a progressive decrease in bacterial species more common to the ileum including *Lactobacillus.*[20]

Efforts have been made in attempt to map out the differences within the pouch microbiota with a focus on diversity and dysbiosis. Reshef et al. examined the species within the microbiota of 140 pouch patients. This included 131 UC patients and 9 FAP. Of interest, the α diversity was similar between patients with UC without surgery, FAP patients with pouch and UC pouch patients without pouchitis. While the diversity in all three of these groups was decreased compared to healthy controls. the α diversity of pouchitis patients was even further decreased compared to the other healthy pouch patients. Along with diversity, there was noted a decrease in *Bacteroides, Collinsella*, and 8 genera belonging to the *Lachnospiraceae* and *Ruminococcaceae* families, including *Faecalibacterium*, *Eubacterium*, and *Roseburia.* An increase in *Fusobacterium* was associated with pouchitis. The effect of pouch maturation was studied. It was found that the composition of the pouch bacteria did not change over time. While the diversity between UC healthy pouches and FAP was not different, one difference is that the mature FAP pouches did not demonstrate the reduction of *Faecalibacterium* that is noted in UC pouches. They detected an association between antibiotic treatment, but not