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Short- and long-term complications after restorative proctocolectomy with ileal pouch-anal anastomosis

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Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is a safe and effective operation. It eliminates chronic ulcerative colitis and the risk of colonic cancer. The patient experiences physical and psychological well-being after surgery and in the long run his quality of life (QoL) is comparable to that of the general population [1]. However, the construction of an ileal fecal reservoir profoundly alters ileal luminal ecology. The availability of the mucosal metabolic substrate is impaired and bacterial stasis alters the morphology of the epithelium and the cellular composition of the pouch wall.

In addition to these circumstances, the construction of the reservoir may be complicated by leakage or cuffitis and as a result of the alteration of the luminal milieu, irritable pouch syndrome (IPS) may develop. Some patients may develop bowel obstruction and pouch-related fistula. These complications are more frequent in women [2]. The most frequent long-term complication following IPAA is non-specific and idiopathic inflammation of the ileal mucosa of the pouch, commonly known as pouchitis. Pouchitis may also present early in the postoperative course. These complications have an adverse effect in the QoL of the patient.

Although the symptoms may be similar (increased stool frequency, urgency, and abdominal cramps), the treatment of these complications is different: patients with cuffitis respond to topical hydrocortisone or Mesalamine (Mesalazine), patients with IPS respond to antidiarrheal, anticholinergic, and/or antidepressant therapies [3]. Therefore, a differential diagnosis is important. Endoscopy and histological assessment is useful in discriminating pouchitis, cuffitis, Crohn's disease and normal pouches with IPS or normal pouch. Pouchitis Disease Activity Index (PDAI), based on clinical symptoms, endoscopic appearance and histologic findings, represents an objective and reproducible scoring system for pouchitis [4].

It is becoming increasingly clear that the pathogenesis of different forms of pouchitis varies. Patients with IPS have an increased visceral sensitivity even without pouchitis [5], patients with primary sclerosing cholangitis have increased risk of pouchitis and inflammation of the afferent limb (pre-pouch ileitis) [6]. In these patients autoimmune mechanisms are more relevant and immunosuppression is indicated. Cases with small bowel obstruction, in particular the afferent limb syndrome, need surgical therapy [7].

The frequency of a milder form of pouchitis increases with the years after the operation. In 1,885 patients with a preoperative diagnosis of chronic ulcerative colitis who underwent IPAA at the Mayo Clinic were followed-up over a 20-year period (mean follow-up 11 years). It was found that the 10-year rate of pouchitis was 48% in patients with chronic ulcerative colitis, 49% in those with indeterminate colitis and 56% in patients with Crohn's disease. This rate increased to 70% for chronic ulcerative colitis, 78% for indeterminate colitis and 83% for Crohn's disease within 20 years [1].

In this issue of the *Annals of Gastroenterology*, clinical investigators from the Evangelismos Hospital in Athens report their experience on the treatment of refractory pouchitis following IPAA with Infliximab [8]. This form of pouchitis occurs in about 5% of patients [9] but, as the authors describe, these patients are difficult to treat and apart from experiencing significant morbidity they are at a greater risk of either pouch excision or diversion. Therefore, Infliximab, which so far has been effective in the short- and mid-term in this condition, appears to offer significant progress in the treatment of these patients. However, medication had to be discontinued in a high number of patients in a multicenter Spanish study. Thirteen of 33 patients (39%) were withdrawn from treatment for different reasons [10]. This has also been reported in a recent Cochrane overview. Infliximab was associated with significantly higher risk of withdrawals due to adverse events compared to controls (OR 2.04, 95% CI 1.43-2.91; NNTH = 12, 95% CI 8-28) [11]. There is also concern for the long-term risk for malignancy and the occurrence of severe infection in the long-term use of biological therapy and consideration of the high cost of therapy.

These observations mean that we still do not have the ideal treatment of this condition and further studies into the pathogenesis are necessary. Pouchitis is considered to be recurrent ulcerative colitis in the ileal mucosa, or a novel form of recurrent inflammatory bowel disease. Apart from the factors mentioned above that are a consequence of the new anatomy created, it is accepted that the etiology of pouchitis is multifactorial, with both host and commensal microbiota playing critical roles. We now know that 99 IBD "susceptibility loci" have been identified, of which 18 seem to be unique to ulcerative colitis patients, and 28 unique to Crohn's disease patients [12,13]. However, the informa-

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tion on genetic markers determining the susceptibility to pouchitis after IPAA is limited. In England it was observed in 82 patients who had been followed prospectively after IPAA formation, that patients with pouchitis had a higher interleukin 1 receptor antagonist gene allele 2 carriage rate compared with those without pouchitis (72% vs. 45%) and Kaplan-Meier survival analysis showed that allele 2 carriers had a significantly increased incidence of pouchitis compared with non-carriers (log-rank test, 6.5) [14]. These observations have not been replicated in other studies in Italy and Holland.

Analysis of the three subgroups of IPAA patients (i.e. patients who never developed pouchitis, patients with infrequent pouchitis and patients with a chronic refractory form of pouchitis) revealed a positive association of allele *TLR9 -1237C* with the risk of developing chronic refractory pouchitis, once these patients developed pouchitis. Haplotype analysis showed that out of the four SNPs defining *TLR9* haplotypes, this allele was uniquely responsible for this finding. Carrier trait analysis revealed that an even stronger association was apparent with the combination of alleles *TLR9 -1237C* and *CD14 -260T* [15]. Larger studies are required to determine whether this allelic combination becomes a valuable predictive marker and functional studies are also required on the biological role of TLR9 and CD14 in pouchitis.

NOD2 mutations were found in 8.5% of healthy controls. *NOD2* mutations were significantly higher in the severe pouchitis group (67%) compared with both groups of asymptomatic IPAA patients (5.4%, P =.001) and IPAA patients with Crohn's disease-like complications (14.3%). Preoperative assessment of NOD2 in the equivocal IPAA candidate may predict severe pouchitis and might assist in preoperative surgical decision making [16]. Similar findings were seen by Meier et al, who found an 8% incidence of *NOD2* mutations in patients without pouchitis vs 24% in patients with more than 2 episodes of pouchitis per year [17].

These studies suggest that patients with severe pouchitis have an intrinsic defect in innate immunity against commensal pouch bacteria.

Among the factors supporting the role of microflora, is a decreased butyrate oxidation which was found in the ileal pouch mucosa of patients without active pouchitis. This was thought to be a consequence of changes in ecology and morphology. As a fecal stream through the pouch is "necessary" to cause ileal inflammation, there is probably an important role for intestinal bacteria or their metabolites. Butyrate seems to play a key role in the regulation of immunological mechanisms in the mucosa such as nuclear factor-κ (kappa) = NF-κB activation and also in the maintenance of the gut barrier [18]. In 2004, Lammers KM [19] suggested that "*pouchitis could be used as a model to study the pathogenesis of inflammation*" and this year Shen et al [5], while demonstrating visceral hypersensitivity in IPS have concluded: "*that the unique and selective anatomy, accessible to biomechanical, cellular, and molecular investigations, may serve as a human model for studying functional bowel disorders*". Further studies are necessary and screening programs for malignancy in long-term follow up of patients with chronically inflamed pouchitis is mandatory. Increasing reports of adenocarcinoma in pouches should stimulate us to identify patients with high risk for pouch adenocarcinoma [20,21].

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