Is Irritable Bowel Syndrome an Inflammatory Disorder?

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Histopathologic data demonstrate low-grade mucosal inflammation in a subset of patients with irritable bowel syndrome (IBS). This inflammatory infiltrate is mainly represented by increased numbers of T lymphocytes and mast cells lying in the lamina propria. The close apposition of immunocytes to gut nerves supplying the mucosa provides a basis for neuroimmune cross-talk, which may explain gut sensorimotor dysfunction and related symptoms in patients with IBS. A previous gastroenteritis (due to Campylobacter jejuni, Salmonella, Shigella, Escherichia coli, and, likely, viruses) is now an established etiologic factor for IBS (hence, postinfectious IBS). Other putative causes, such as undiagnosed food allergies, genetic abnormalities, stress, or bile acid malabsorption, may also promote and maintain a low-grade mucosal inflammation in IBS. The identification of mucosal inflammation in IBS has pathophysiologic implications and paves the way for novel therapeutic options.

Clinical and Experimental Evidence Supporting a Role for Inflammation in IBS
Several lines of evidence indicate that an immune activation/inflammatory response at the mucosal level may play a role in generating and perpetuating symptoms in patients with IBS [1,2,7]. This concept is based on clinical experience and experimental data from animal models of gut inflammation. Clinically, it is well known that patients with inflammatory bowel disease (especially during the remission phase) frequently develop symptoms overlapping those of IBS patients [8]. Following a bout of gastroenteritis (ie, Campylobacter jejuni, Shigella, or Salmonella infections), about one third of patients develop persistent IBS symptoms (leading to the term postinfectious IBS). Postinfectious IBS has a clear onset and a better prognosis over time than conventional IBS [9]. Finally, a low-grade inflammatory response, which is usually undetectable endoscopically and at routine histology, has been demonstrated in the intestinal mucosa of patients with either conventional or postinfectious IBS [2,7,9]. Studies on animal models of gut inflammation have been instrumental in exploring pathophysiologic aspects involved in

Introduction
The impact of gastrointestinal inflammation on altered digestive sensorimotor function has long been established in various commonly identified disorders: reflux esophagitis, celiac disease, acute infectious gastroenteritis, and inflammatory bowel disease [1]. Growing evidence now indicates that immune and inflammatory mechanisms contribute to the pathophysiology of a subset of functional bowel disorders, particularly irritable bowel syndrome (IBS) [2], one of the most common gastrointestinal disorders in clinical practice [3,4].

IBS accounts for 3% of visits to general practitioners and about 40% of all gastroenterology outpatient consultations [5]. Its symptoms include chronic or recurrent abdominal pain or discomfort associated with changes in bowel habits [6]. Patients with IBS are usually subdivided into three major subsets: diarrhea-predominant, constipation-predominant, or alternating diarrhea and constipation. The pathogenesis is multifactorial; major mechanisms that have been considered to contribute to IBS symptoms include psychosocial factors, gut dysmotility, and enhanced perception of sensory stimuli conveyed from the gut wall to the central nervous system via sensory nerve pathways [7]. In addition, novel data concerning genetics, gut infection, food allergy or intolerance, modifications of gut microbiota, abnormal gas handling, impaired epithelial permeability, neuroplastic changes, stress and related hormone release, and gut-wall immune activation have suggested that these factors may participate in symptom generation in subsets of IBS patients [7].

This review provides evidence for low-grade inflammation in patients with IBS, placing special emphasis on immunohistopathologic findings, which may contribute to symptom generation. The role of possible causes of minimal mucosal inflammation, such as infectious enteritis, is examined.
IBS, including inflammation-related changes of enteric neuromuscular function and sensory nerve function of the gastrointestinal tract [1,2]. These studies have provided the biologic basis for intestinal inflammation as a possible mechanism in the pathophysiology of a subset of patients with IBS and other functional disorders of the gut. Among animal models reminiscent of human functional bowel disorders, a model of postinfectious IBS has been proposed. Specifically, in susceptible strains of mice (eg, NIH Swiss), a transient Trichinella spiralis infection induced enteric muscle dysfunction lasting long after the parasite was expelled from the gut and the acute mucosal inflammatory response had subsided, thus resembling the clinical condition of postinfectious IBS [10]. Further work has clarified that long-term neuromuscular abnormalities were maintained by active synthesis within the neuromuscular layer of products derived from cyclooxygenase-2 [11]. Taken together, both clinical and experimental data provide a basis for inflammation as a mechanism underlying IBS symptoms.

Morpho-functional Correlates of Inflammation in IBS

Except for one study using full-thickness tissue samples to look at the inflammatory infiltrate in gut wall [12], studies dealing with IBS immunohistopathology have been based on colonic mucosal biopsies. Routine histologic examination of these biopsy specimens commonly has found no obvious abnormalities, but systematic approaches such as quantitative histopathology, immunohistochemistry, and (in some studies) electron microscopy have revealed alterations involving immunocytes, enteroendocrine cells, and (in some studies) electron microscopy have revealed alterations involving immunocytes, enteroendocrine cells, and nerve fibers supplying the gut mucosa [13–17].

Quantitative analysis of mucosal biopsy specimens from IBS patients has shown an increased number of immunocytes—mainly lamina propria T cells [14,18], intraepithelial lymphocytes (IELs) [14], and mucosal mast cells [17–20]—when compared with specimens from asymptomatic control subjects. A low-grade inflammatory response can be detected in about three quarters of patients with either conventional IBS [14,16,18] or postinfectious IBS [13,15,16,18]. The increases in mucosal lymphocytes span wide ranges, such as 20% to 100% for lamina propria T cells and up to 60% to 250% for epithelial lymphocytes. These ranges suggest that IBS patient subgroups are heterogeneous, that the sites of biopsy sampling along the colon vary, or perhaps both. In one study by Chadwick et al. [14], most of the mucosal T lymphocytes of 90% of IBS patients expressed CD25, a marker of immune activation and a component of the interleukin (IL)–2 receptor, regardless of the patient’s symptom profile or a previous bout of gastroenteritis. Nonetheless, the same study, the authors found that patients with diarrhea-predominant IBS had a greater increase in mucosal T cells than those with constipation-predominant IBS [14]. The pathophysiologic meaning of that association and the impact of increased activated mucosal T lymphocytes on IBS symptoms deserve further study.

Postinfectious IBS is an established cause of low-grade inflammation, at least in a subset of patients. Two weeks after the resolution of a C. jejuni gastroenteritis, rectal inflammatory cells were increased in patients who developed chronic IBS symptoms. Inflammatory changes (increased T lymphocytes in the lamina propria and IELs), although reduced, were detectable up to 3 months after the infection [13,21]. At 1 year of follow-up, mucosal inflammatory cells persisted in a small subset of these IBS patients. In addition, patients with postinfectious IBS [22,23] showed increased mucosal levels of the pro-inflammatory cytokine IL–1β mRNA, a finding that may help to explain the role of immune cells and related mediators in sensorimotor dysfunction in this disease. Pro-inflammatory cytokines such as IL–1β, IL–6, and tumor necrosis factor-α were recently found to be increased in peripheral-blood mononuclear cells of patients with IBS [24], whereas IL–6 and IL–8 levels were elevated in the serum [25]. These pro-inflammatory cytokines may contribute to IBS symptom perception, as they have been shown to generate visceral hyperalgesia via direct activation of sensory nerve pathways [26]. The cellular source of IL–1β in the rectal mucosa of patients with postinfectious IBS remains unknown; newly recruited calprotectin-positive macrophages are possible candidates [13]. Macrophages also may contribute to the synthesis and release of nitric oxide, a mediator playing a critical role in gut sensorimotor function [27,28]. Increased levels of inducible nitric oxide synthase mRNA have been detected in the colonic mucosa of patients with conventional IBS, particularly during stressful events [29].

More than 40 years ago, Hiatt and Katz [30], using full-thickness colonic biopsy samples, were the first to demonstrate mast-cell infiltration in the muscular layer of four patients with “spastic colitis.” Because full-thickness biopsies are not easy to obtain in patients with functional bowel disorders, these early results remained isolated evidence in the IBS literature. Nonetheless, this study paved the way for the concept that mast cells could play a role in the puzzling pathophysiology of IBS. Since that early demonstration, subsequent studies in patients with IBS have shown an increased number of mast cells in the lamina propria of the terminal ileum [20] and mucosa of the right colon [19] and left colon [18,31]. Data suggested a predominance of mucosal mast-cell infiltrate in patients with postinfectious IBS or the diarrhea-predominant subgroup of conventional IBS [22]; more recent data indicate no difference between patients with diarrhea-predominant IBS and those with constipation-predominant IBS in terms of mast-cell density [18,31]. Recent data provide evidence that mast cells may significantly affect sensorimotor function and therefore contribute to IBS symptoms [2,18,31]. In addition to increased concentration of these cells, muco-