Mast Cells and Intestinal Motility Disorders (Mastocytic Enteritis/Colitis)

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The quest for specific markers and potential therapeutic targets for patients with irritable bowel syndrome (IBS) has gained some momentum with the recognition of subtle morphologic changes that may be present in small and large intestinal biopsies. Amongst these, increased numbers of mast cells (MC), eosinophils, intraepithelial T-lymphocytes and serotonin-producing enterochromaffin cells have attracted the most attention [1, 2]. The traditional paradigm of IBS as a “functional” disorder may be changing with the possibility of an underlying neuro-immune interaction increasingly being considered.

Several studies have demonstrated an increase in MC in intestinal biopsies from patients with diarrhea predominant IBS (IBS-d) and post-infectious IBS (PI-IBS) [3–12]. More recently, a subset of IBS-d patients with increased intestinal MC identified in biopsy specimens have been reported to respond well to MC stabilizers termed “mastocytic enterocolitis” [13]. A handful of clinical trials have also reported symptomatic improvement in IBS treated with MC stabilizers [14–20]. The association between MC and diarrhea/abdominal cramps, is further highlighted by the fact that these symptoms are prevalent in patients with intestinal involvement by systemic mastocytosis [21, 22].

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The recognition of a potential role for MC in IBS-d has increased requests by gastroenterologists and pathologists for MC—specific staining of biopsy specimens.

A study by Bassotti et al. reports a significant increase of MC in resection specimens of obstructed/constipated IBS patients (IBS-c) compared to matched controls [23]. Increased MC were identified in all layers of the bowel wall, but especially in the mucosa and submucosa, where degranulated MC were often located close to enteric glial cells (ECG) and glial filaments. MC proximal to enteric nerves, previously reported in animal [24] and human studies [3, 8, 11], led to the hypothesis that psychological or physical stress may activate the enteric nervous system via the central nervous system subsequently attracting and potentially activating MC [25].

The study by Bassotti et al. [23] raises several questions, some methodological:

- First, were MC numbers selectively increased in patients with IBD-c or was this part of a global increase of inflammatory cells? Since other inflammatory cells (e.g. lymphocytes, macrophages, eosinophils) were not quantified, a global increase of inflammatory cells secondary to decreased transit/increased intraluminal pressure was not excluded.
- Second, is the increase in MC numbers specifically related to IBS-c or is it common to all disorders associated with constipation? Since the control group (patients with non-obstructed colorectal cancers) did not have documented constipation, this question also remains unanswered. Increased MC has been reported in motility disorders such as Hirschsprung’s disease and Chagas disease [26, 27].
- Third, is there a plausible pathophysiological basis for MC in the pathogenesis of IBS-c? The diarrhea predominant form of IBS can be readily explained

(MC mediators, e.g., tryptase and histamine activate enteric neurons leading to abnormal secretomotor function and visceral hypersensitivity [28, 29]), but a pathogenic role for MC in constipation is less clear. The concept that MC activation underlies constipation—and diarrhea-predominant forms of IBD seems implausible. In the current and their corresponding previous study [30] the authors seem to suggest that the increase in MC in IBS-c and other motility disorders such as Hirschsprung's disease may be a compensatory mechanism (an "attempt to overcome neuroenteric damage in these patients"). Indeed it is possible that MC activation is secondary to constipation rather than its cause.

The final questions relate to the role of MC in IBS in general. How strong is the evidence that MC play a role the pathogenesis of IBS-d? How reliable are the data that MC stabilizers are effective in these patients? Should MC quantification of mucosal biopsies from patients with IBS be routine?

The presence of MC within the muscularis propria was first described by Hiatt and Katz [12] in 1962 in four patients with "spastic colitis," although it wasn't until the early 1990s that an increase of MC was recognized in terminal ileal and colonic biopsies of IBS patients [3, 8, 11, 31]. The presence of increased MC alone may not however be sufficient; MC in IBS patients may be activated since some have reported that MC is degranulated [3, 8] with increased spontaneous release of tryptase and histamine [8]. Reports of an increase in the number of mucosal nerve fibers [11], increased proximity between nerve fibers and MC [3, 11, 29], lymphocytes [32, 33], and lymphocytic infiltration and neuronal degeneration of the myenteric plexus [34] in IBS have provided a morphologic basis for a neuro-immune interaction. MC have been singled out as a possible "gut target" of the "brain–gut axis," a bi-directional communication between the enteric nervous system of the gut and the central nervous system [35, 36].

MC are also encountered in the gastrointestinal tract in systemic mastocytosis (SM), a condition characterized by the abnormal proliferation of MC in several extracutaneous sites. Gastrointestinal symptoms are second only to pruritus as a major cause of morbidity in these patients. The most frequent symptoms in SM are diarrhea and abdominal cramps, thus overlapping somewhat with IBS-d. Nevertheless, patients with SM also frequently experience nausea and vomiting, weight loss and dyspepsia, and sometimes malabsorption and hypoalbuminemia. Increased systemic levels of MC mediators are likely to be important in the genesis of gastrointestinal symptoms since not all symptomatic patients with SM have increased MC numbers in the gastrointestinal tract. Treatment of SM is aimed

primarily at providing symptomatic relief by controlling mediator release by stabilizing MC with cromolyn (an inhibitor of MC degradation) and, by blocking the effects of histamine via H1 and H2 antihistamines [37, 38], whereas systemic chemotherapy regimens (e.g. interferon- α) have not been consistently effective [39, 40].

Treating IBS patients with a similar MC targeted approach however has had limited success.

Apart from the uncontrolled study by Jakate et al. [13], demonstrating symptomatic improvement with H1 and H2 antihistamines in a subset of IBS-d patients, only a handful of other studies have attempted to assess the effect of MC targeted therapies in IBS-d patients. Short-term administration of the "MC stabilizer" sodium cromoglycate in combination with or without an elimination diet has yielded inconsistent results, with some authors reporting symptomatic improvement and others failing to observe any [14–19]. Only two of these studies were randomized and double-blinded [16, 17], with one evaluating only IBS-d patients ($n = 20$) [16] and the second including patients with chronic unexplained diarrhea ($n = 40$) [17]. An 8-week treatment with sodium cromoglycate significantly improved symptoms in the first study [16], but only about 30 % of patients reported a significant decrease of stool frequency after a 4-week regimen in the second study, with no improvement in the placebo group [17]. The largest uncontrolled study ($n = 409$) compared a 1-month course of sodium cromoglycate with an elimination diet, reporting comparable results with both interventions in decreasing IBS related symptoms [18]. Response rates in both groups may have been better for patients with positive skin tests for dietary antigens; however, the lack of a placebo group limits interpretation of these data. A more recent placebo controlled, double-blind randomized trial ($n = 60$) utilizing ketotifen, a MC stabilizer and antihistamine (H1) receptor antagonist, demonstrated significant improvements in symptoms and reduction in visceral hypersensitivity compared to controls [20]; however, an associated decrease in MC degranulation or density within the rectal mucosa was not observed in patients who improved with treatment, raising the possibility that H1 receptor blockade may be responsible for the reported symptomatic improvement.

Serotonin receptor (5-HT₃) antagonists have also provided symptomatic relief in IBS although safety concerns (rare cases of intestinal ischemia) have restricted their use [41, 42]. These agents slow small bowel transit, decrease colonic tone and intestinal secretion, and delay colonic transit [43–45]. Alosetron, the best studied 5-HT₃ receptor antagonist, relieves IBS associated symptoms in specific patient subsets according to large clinical trials [46–51]. Since 5-HT₃ receptor antagonists target the splanchnic afferent nerve system directly, it is no surprise that alosetron administration reduces MC degranulation [52, 53]. In addition to MC, enterochromaffin cells (also reportedly

increased in mucosal biopsies from IBS subjects) provide a further source of serotonin, although the relative contributions of MC and enterochromaffin cells remains to be defined.

Given these clinical observations, is routine staining for MC of pathology specimens from IBS-d patients justified? First, the mean MC/hpf in “normal” colonic endoscopic biopsies has not yet been validated in large patient cohorts with no universally accepted threshold for what constitutes an increase in MC. Second, methodology for counting of MC (including special stains used, number of fields counted and field diameters used) has varied widely in the literature. Third, subtle increases in MC are difficult to detect using routine (haematoxylin and eosin, H&E) stains. Accurate counting therefore requires supplementary histochemical (e.g. Giemsa, toluidine blue) or preferably immunohistochemical (mast cell tryptase and CD117) stains, which substantially increases cost. Until strong evidence from appropriately designed, controlled and appropriately statistically powered research studies are available supporting this practice, there is no justification for such evaluations to be performed in routine pathologic assessment of suspected IBS.

In summary, routine quantification of the number of MC in mucosal biopsies obtained from IBS-d or IBS-c patients, and the potential of MC and their released factors as therapeutic targets, though intriguing, remains to be defined. There is a major need for well designed, adequately powered placebo-controlled studies to determine whether there is any therapeutic basis for MC-targeted medications. Until then, it is very difficult to justify routine evaluation of MC numbers in IBS-d biopsies outside of the research setting.

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