

Mastocytic Enterocolitis

Increased Mucosal Mast Cells in Chronic Intractable Diarrhea

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• **Context.**—In some adult patients with chronic intractable diarrhea, the diagnosis remains elusive even after detailed evaluations, and colonic or duodenal biopsy specimens may appear unremarkable on routine hematoxylin-eosin staining.

Objectives.—To assess the concentration of mast cells in colonic or duodenal biopsy specimens by immunohistochemical analysis for mast cell tryptase from patients with chronic intractable diarrhea and to evaluate their response to drugs affecting mast cell function.

Design.—Mast cells per high-power field were assessed in biopsy specimens from 47 patients with chronic intractable diarrhea, from 50 control subjects, and from 63 patients with other specific diseases that cause chronic diarrhea (inflammatory bowel disease, celiac disease, collagenous colitis, and lymphocytic colitis). Patients with chronic intractable diarrhea who had more than 20 mast cells per high-power field were administered drugs affecting mast cell mediator function and release.

Results.—The mean \pm SD concentration of mast cells in

the 50 control subjects was 13.3 ± 3.5 cells per high-power field; hence, patients with more than 20 mast cells per high-power field were considered to have increased mast cells. Thirty-three (70%) of 47 patients with chronic intractable diarrhea had increased mast cells, and symptoms were controlled by drug therapy in 22 (67%) of the 33 patients. No patient had systemic or cutaneous mastocytosis. No increase in mast cells was seen in patients with other common causes of chronic diarrhea.

Conclusions.—In chronic intractable diarrhea, colonic or duodenal biopsy specimens may appear unremarkable on routine hematoxylin-eosin staining, but increased mast cells may be demonstrated by immunohistochemistry for mast cell tryptase, with the novel term *mastocytic enterocolitis* describing this condition. Similar increases in mast cells are not apparent in control populations or in patients with other specific diseases that cause chronic diarrhea. The cause of the increased mast cells remains to be elucidated.

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Chronic diarrhea, defined as the production of liquid or loose stools for more than 4 weeks, has an approximate prevalence of 5% among the US population.¹ The causes of chronic diarrhea vary widely by age and by socioeconomic status of the population surveyed. The most frequent diagnoses in patients with chronic diarrhea in developed countries include irritable bowel syndrome (IBS), inflammatory bowel disease, malabsorption syndrome (including celiac disease or gluten-sensitive enteropathy), chronic infections, and idiopathic secretory diarrhea.¹ Most of these conditions can be diagnosed by following the guidelines for evaluation recommended by the American Gastroenterological Association,² which include a detailed 14-point history, physical examination, routine laboratory tests, therapeutic trials, stool analysis, and further evaluations such as culture studies, radiography, en-

doscopy, and biopsies. Management strategies also include concurrent testing and empiric treatment.³ However, in some patients, no cause is clinically apparent even after these guidelines are followed, and the diagnosis remains indeterminate and the treatment frustrating.

Mucosal mast cells are key regulators of intestinal sensory and motor function and may be involved in chronic functional diarrhea. We observed increased mast cells in the gut mucosa as the principal morphologic abnormality in a subset of patients with chronic functional diarrhea. We consider this a distinctive morphologic disorder that is revealed by immunohistochemical analysis for mast cell tryptase (MCT) and term this condition *mastocytic enterocolitis*. The increase in mast cells is not associated with systemic or cutaneous mastocytosis. Most patients with this condition respond to drugs affecting mast cell mediator function and release such as histamine H₁ and H₂ receptor antagonists and granule membrane stabilizing agents. An increase in enterocolonic mucosal mast cells is postulated to be a reactive and gut-specific phenomenon resulting from unknown stimuli. This increase is presumed to enhance mast cell mediator release, which results in diarrhea and abdominal pain through paracrine interaction with the enteric nervous system and its effector motor response. In our affected patients, no consistent underlying clinical determinants were obvious, and many cases would be classified as diarrhea-predominant IBS for

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lack of a more specific diagnosis. To calibrate the increase in mast cells, we determined the baseline concentration of mast cells in adult colonic and duodenal mucosa in incidentally biopsied tissue from control subjects. To estimate the specificity of increased mast cells in chronic intractable diarrhea, the mucosal concentration of mast cells was investigated in other common disorders that cause chronic diarrhea, such as inflammatory bowel disease, gluten-sensitive enteropathy, collagenous colitis, and lymphocytic colitis.

MATERIALS AND METHODS

Forty-seven patients (32 women and 15 men; age range, 21-78 years) were diagnosed as having chronic persistent diarrhea of unknown cause at our institution between 2000 and 2004. All patients underwent the investigational protocol recommended by the American Gastroenterological Association. A comprehensive history was obtained that included the onset, pattern, and duration of symptoms, as well as the presence or absence of fecal incontinence, abdominal pain, weight loss, medication use, recent travel, diet, and stress. A physical examination was conducted to assess the extent of fluid loss, as well to evaluate rashes, flushing, oral ulcers, edema, perianal skin, anal sphincter tone, abdominal masses, and ascites. Complete blood counts and a basic metabolic panel (serum sodium, potassium, chloride, carbon dioxide, glucose, calcium, urea nitrogen, and creatinine) were performed. A stool analysis assessed the type and severity of diarrhea and the presence of ova and parasites. In addition, the patients underwent full colonoscopy (22/47 patients), upper endoscopy (20 patients), or both (5 patients), with random biopsy samples taken from the colon and from the second part of the duodenum. The random colonic biopsies included 4 to 10 pieces taken from the right and left colon and submitted in one container, and the random duodenal biopsies included 2 to 5 pieces taken mainly from the second part of the duodenum and submitted in one container. The colonic and duodenal biopsy specimens were processed for routine histologic examination with standard formalin fixation and paraffin embedding, and 5- μ m-thin sections were stained with hematoxylin-eosin. In addition, all sections were immunohistochemically stained for MCT as follows: 4- μ m-thin sections were cut, dried, and deparaffinized before placing them on the Ventana NexES autostainer (Ventana Medical Systems Inc, Tucson, Ariz), where they were treated with protease 1 for 4 minutes and then incubated with monoclonal mouse anti-human MCT (clone AA1, code M 7052; DAKO, Carpinteria, Calif; dilution 1:1600) for 32 minutes. A recommended negative control was used. Visualization was performed using the iView DAB detection kit (Ventana Medical Systems Inc).

To establish the baseline concentration of mucosal mast cells, similar immunohistochemical staining was performed on 50 incidentally obtained duodenal ($n = 25$) and colonic ($n = 25$) biopsy specimens from patients with conditions unrelated to diarrhea (such as duodenal biopsies for gastroesophageal reflux, *Helicobacter gastritis*, gastric fundic gland polyps, and mucosa adjacent to duodenal adenomatous polyps; and colonic biopsies for melanosis and mucosa adjacent to adenomatous polyps). The baseline concentration was presumed to be the distribution of mast cells in a control population of comparable age and sex (age range, 24-77 years; female-male ratio, 27:23) as the study population. The sources of the control biopsy specimens included the duodenal bulb, second part of the duodenum, random or unspecified duodenum, random colon, right colon, left colon, descending colon, sigmoid, and rectum. In addition, biopsy specimens from 63 patients with chronic diarrhea caused by the following specific diseases were immunostained for MCT: collagenous colitis (4 patients), lymphocytic colitis (3 patients), Crohn colitis (9 patients), ulcerative colitis (12 patients), and gluten-sensitive enteropathy (35 patients). Endoscopic mucosal biopsies in these patients were initial diagnostic specimens demonstrating

active inflammation and were not posttherapeutic or surveillance samples.

Mast cells (representing ≥ 2 separate biopsy pieces and random parts of the mucosa that filled the entire visual field) were counted per high-power field (original magnification $\times 400$, objective $\times 40$, and eyepiece $\times 10$) and were averaged per 10 high-power fields. Muscularis mucosa and submucosa were excluded from mast cell counts. In the duodenum, only the closely arranged villi that filled the entire visual field were included. In addition, only the intact mast cells with visible nuclei and darkly staining cytoplasm were counted. Wisps of extracellular, apparently degranulated tryptase were excluded from counts. In 40 of 47 study patients, concurrent toluidine blue staining was used to demonstrate metachromasia in mast cells. Levels of serum tryptase were determined in 3 of 47 patients.

Among the 47 patients with chronic intractable diarrhea, 33 patients had increased mast cells (> 20 mast cells per high-power field) and were administered a 2-week regimen of 10 mg/d of cetirizine hydrochloride (an H_1 receptor antagonist) and 300 mg twice a day of ranitidine hydrochloride (an H_2 receptor antagonist). In 8 of the 33 patients, a third drug, 200 mg (in 10 mL) of cromolyn sodium (a mast cell mediator release inhibitor) was given 4 times daily for 4 to 6 weeks. The patients were followed up for resolution, improvement, or persistence of symptoms. The patients who did not have increased mast cells were not given these drugs.

RESULTS

All 47 study patients had chronic diarrhea of unknown cause, and no specific underlying disorder could be identified after conducting the recommended history, physical examination, routine laboratory tests, and stool analysis. Twenty-one of the 47 patients also had variable and intermittent abdominal pain and were diagnosed as having possible diarrhea-predominant IBS, based on Rome II diagnostic criteria.⁴ No patient had documented systemic or cutaneous mastocytosis. Assessment of serum tryptase levels in the 3 patients analyzed showed no elevation. On endoscopy, the colon and duodenum were described as being normal in 43 of 47 patients and as showing mild edema in the other 4 patients. In 34 of 47 patients, the colonic and duodenal mucosa appeared normal on routine hematoxylin-eosin staining (Figure 1) or showed a mild and focal increase in mixed inflammatory cells in the lamina propria (Figure 2). In the other 13 patients, there was a mild increase in eosinophils in the lamina propria, without any other abnormality (Figure 3). In particular, there were no specific pathologic features such as crypt distortion or mucin depletion, cryptitis, crypt abscesses, granulomas, thickened collagen band, excessive eosinophils, increased intraepithelial lymphocytes, shortened duodenal villi, parasites, or viral inclusions.

In the 40 samples stained with toluidine blue, 30% to 60% fewer mast cells were highlighted than with MCT, because only the heavily granulated mast cells showed metachromasia. Hence, the results of toluidine blue staining were eliminated from the analysis. Immunostaining for MCT revealed intracytoplasmic brown staining that was highly specific for mast cells. The staining was so consistently strong that it was read as positive or as negative for mast cells, without assessing the intensity of staining. The mean \pm SD concentration of mucosal mast cells in the control population was 13.3 ± 3.5 cells per high-power field (colon, 13.6 ± 3.1 cells; and duodenum, 13.2 ± 3.7 cells) (Figure 4). When other tissue such as duodenal bulb, stomach, and ileum was included with colon or duodenum, the variation in mast cell counts was no

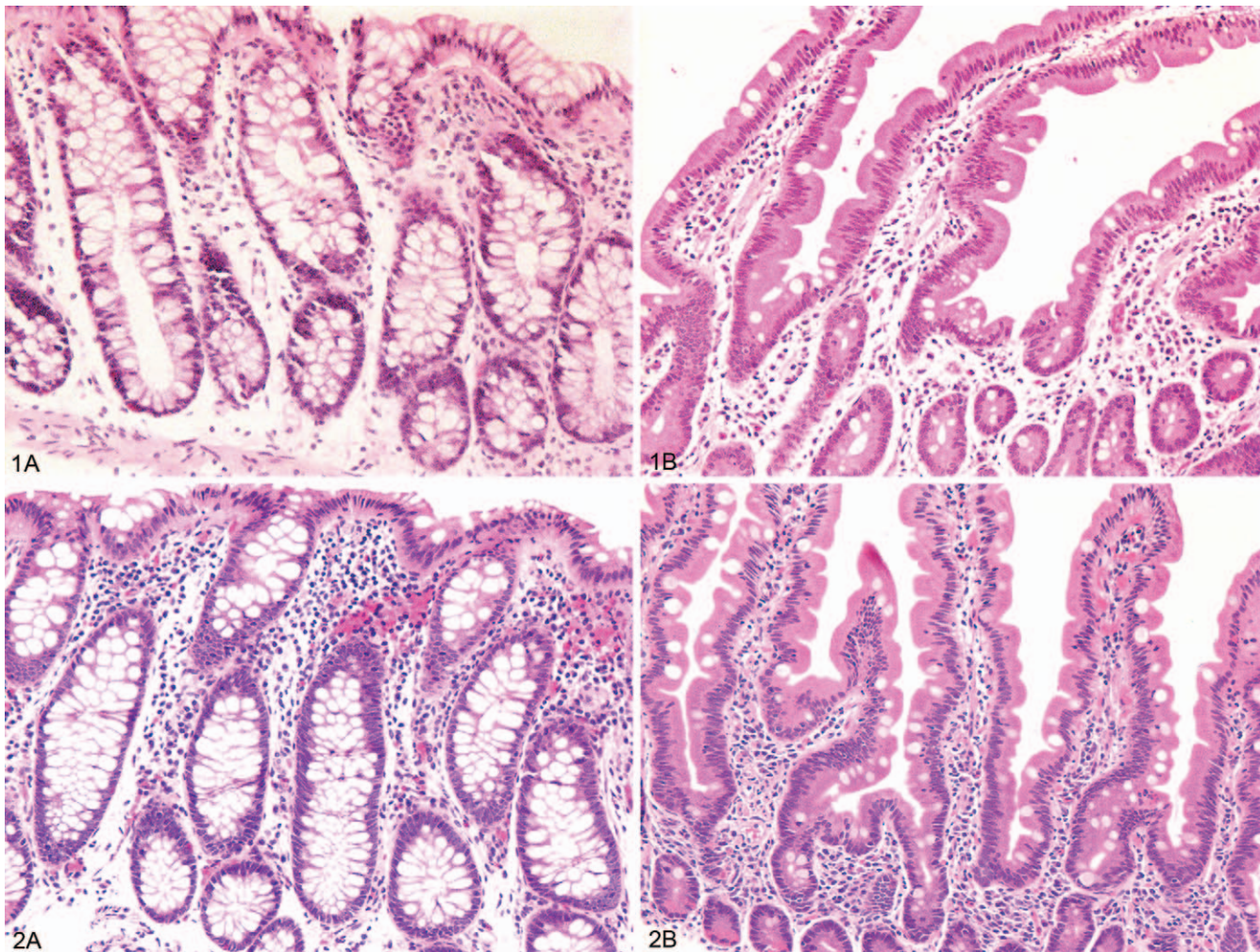


Figure 1. Histologically normal-appearing colonic (A) and duodenal (B) mucosa (hematoxylin-eosin, original magnification $\times 200$).

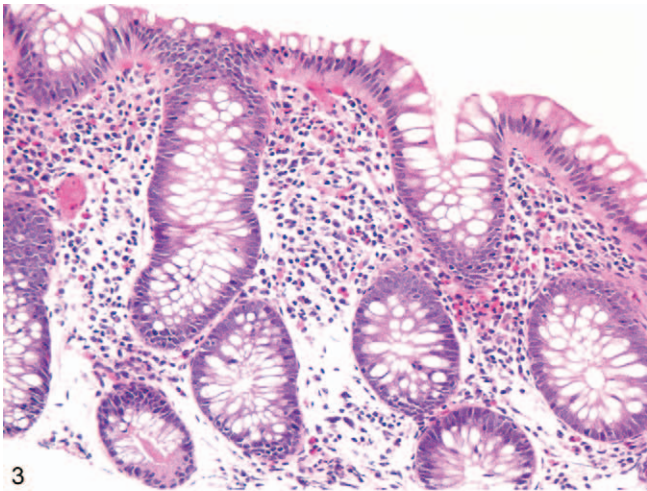
Figure 2. Mild nonspecific increase in mixed inflammatory cells in the lamina propria of colonic (A) and duodenal (B) mucosa (hematoxylin-eosin, original magnification $\times 200$).

greater than 2 SD. However, only the colonic and duodenal tissue counts were considered baseline values for comparison with colonic and duodenal samples in the study patients with chronic intractable diarrhea. The presence of more than 20 mast cells per high-power field was considered an increase in mast cells because this represented 2 SD beyond the normal values for colon and duodenum. Among the 63 samples from patients with other specific diseases that cause chronic diarrhea, the mean \pm SD mast cell count of 12.4 ± 2.3 cells per high-power field was close to that of the control population. Thirty-three (70%) of 47 study patients with chronic intractable diarrhea had increased mast cells (mean \pm SD, 25.7 ± 4.5 cells per high-power field) (Figure 5). Figure 6 illustrates the mean \pm SD concentrations of mast cells in the control subjects, in the patients with diarrhea caused by specific diseases, and in the study patients with chronic intractable diarrhea. Among the 5 patients who underwent both colonic and duodenal biopsies, the increase in mast cells observed in 3 patients was seen in both organs, suggesting a diffuse enterocolonic mucosal increase. Among all biopsy samples in which there was an increase in mast cells, the increase was generally diffuse in the mucosa, with little elevation in the concentration of submucosal mast cells (Figure 7),

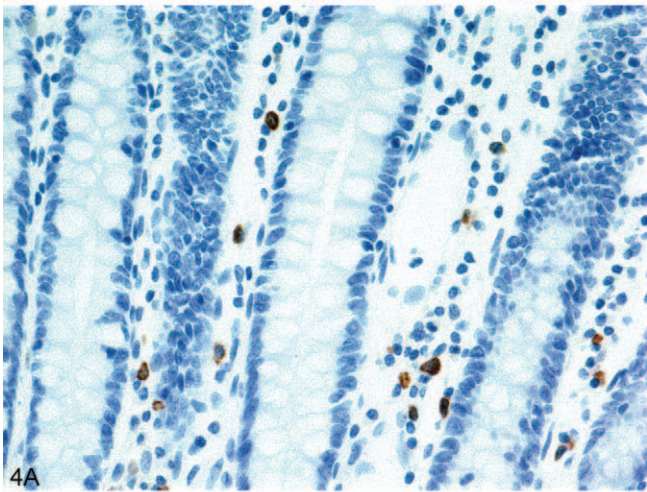
with no sex differences observed in the control versus the affected populations. At follow-up, 22 (67%) of 33 study patients who received H_1 and H_2 receptor antagonists with or without mast cell mediator release inhibitor showed cessation of diarrhea or significant reduction in diarrhea (defined as $\geq 50\%$ reduction in stool frequency or as $\geq 50\%$ improvement in stool consistency).

COMMENT

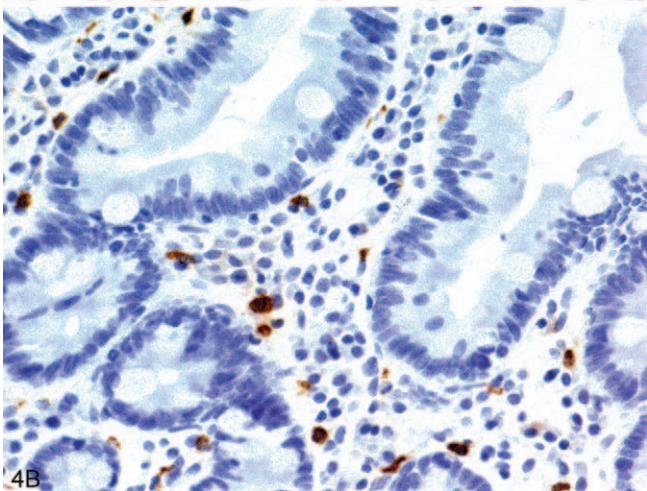
Mast cells, functionally and morphologically distinct cells of hematopoietic origin, are distributed throughout many tissues⁵ and are rich in gastrointestinal mucosa, enabling their immune function in response to a diversity of environmental substances in the gut lumen. Mast cells are unique granulocytes because they are absent in peripheral blood and develop in situ from CD34-positive or c-Kit-positive progenitor cells.⁶ Within the gut, the following 2 distinct subpopulations of mast cells are distinguishable by their neutral protease content: (1) the mucosal "reactive" mast cells, which may increase dramatically in response to immune stimuli and are dependent on T lymphocytes (termed the *T mast cell* phenotype because it contains tryptase) and (2) the submucosal "constitutive" mast cells, which are more static, are related to angiogenesis



3



4A

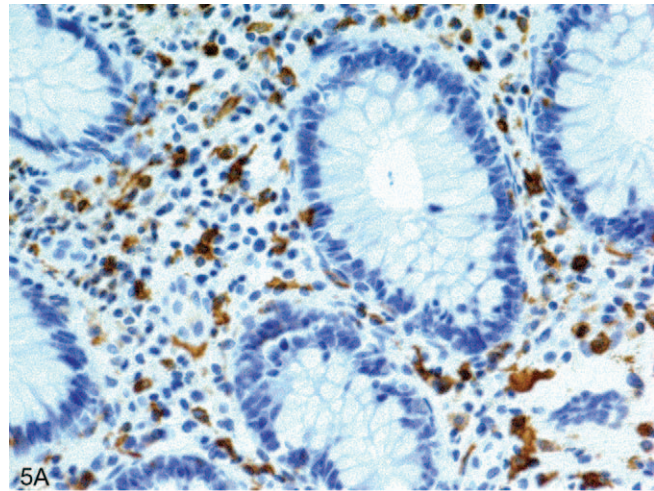


4B

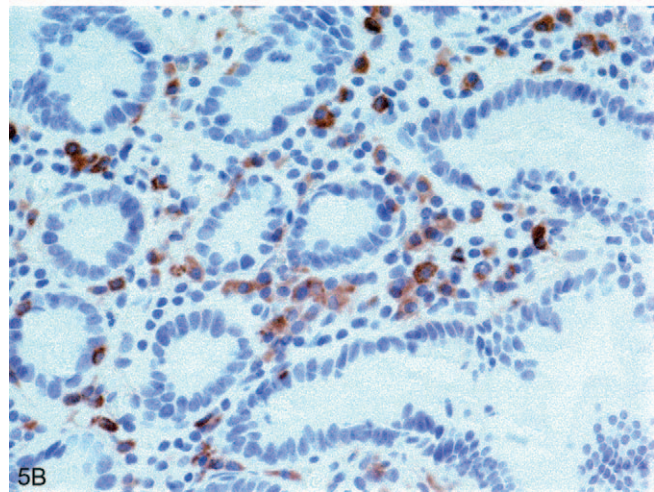
Figure 3. Mild increase in eosinophils in the lamina propria of colonic mucosa (hematoxylin-eosin, original magnification $\times 200$).

Figure 4. Distribution of mast cells visualized by immunohistochemical staining for mast cell tryptase in control samples in colonic (A) and duodenal (B) mucosa (original magnification $\times 400$).

and tissue remodeling, and are unrelated to the immune system (termed the *TC mast cell* phenotype because it contains tryptase and chymase).^{7,8} Mast cells are best known for their classic role in the allergic hypersensitivity type I reaction, in which binding of multivalent allergen to mem-



5A



5B

Figure 5. Increased mast cells visualized by immunohistochemical staining for mast cell tryptase in patients with chronic intractable diarrhea in colonic (A) and duodenal (B) mucosa (original magnification $\times 400$).

brane-bound immunoglobulin E causes activation and release of stored inflammatory mediators in secretory granules, including histamine, neutral proteases, cytokines, lipid mediators, and others. However, mast cells may have an equal or greater role in the gastrointestinal tract in immune response to complement components⁹ against various microbial and other agents, in excitability on central nervous system stimuli such as stress,¹⁰ and as strategic connector between the gut lumen and the integrated enteric nervous system.¹¹ The contribution of mast cells to gastrointestinal symptoms is exemplified by the frequency of gastrointestinal complaints in systemic mastocytosis (commonly abdominal pain and diarrhea and less frequently nausea and vomiting).¹²⁻¹⁴ Patients with systemic mastocytosis have shown abnormally increased visceral sensitivity to rectal balloon distension, which may explain diarrhea, urgency, and fecal incontinence.¹⁵ Mast cell degranulation has been shown to mediate postoperative ileus in a murine model,¹⁶ indicative of the role of mast cells in hypomotility and hypermotility of the gut.

In many gastrointestinal diseases that may cause chronic diarrhea, the role of mast cells and their mediators is being investigated, although with increasing controversy. There have been several reports of increased, normal, or

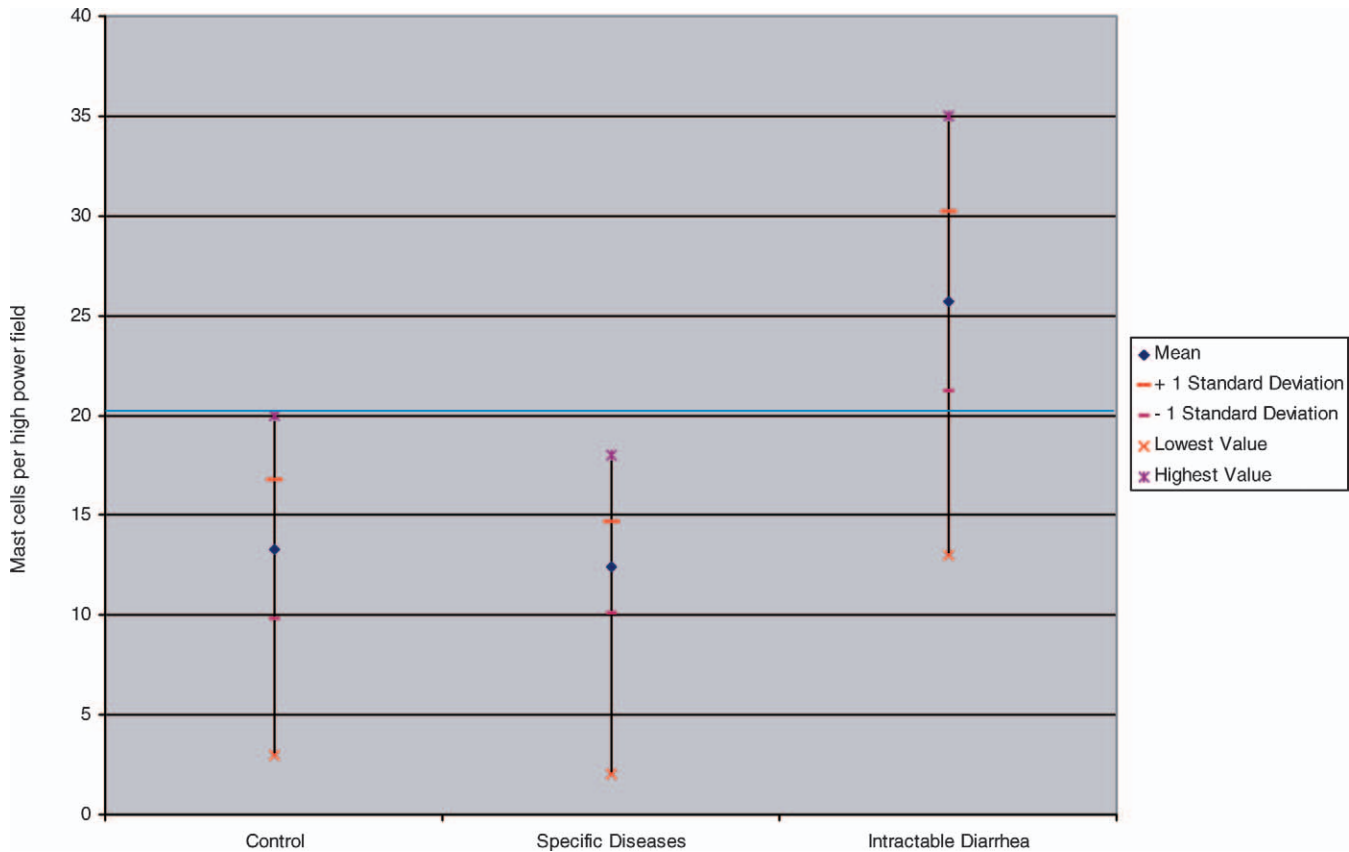


Figure 6. Chart illustrating the distribution of mast cells in control subjects, patients with diarrhea caused by specific diseases, and patients with chronic intractable diarrhea.

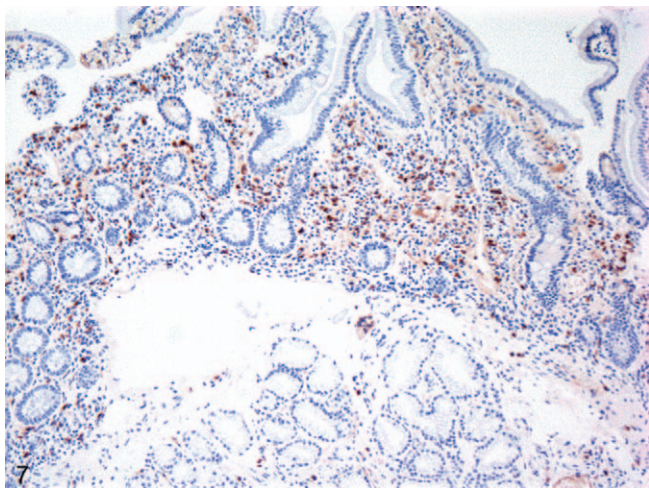


Figure 7. Microphotograph showing preferential mucosal increase of mast cells compared with the static submucosal mast cells in the duodenum (immunohistochemical staining for mast cell tryptase, original magnification $\times 100$).

decreased concentrations of mast cells in inflammatory bowel disease,^{17–20} increased MCT secretion in ulcerative colitis,²¹ mast cell-mediated ion transport in inflammatory bowel disease,²² increased mast cell activation in collagenous colitis,^{23,24} and increased or decreased mast cell concentrations in gluten-sensitive enteropathy.^{25–27} Some contribution of mast cells in the pathogenesis of these diseases appears inevitable by virtue of their diffuse residence in

the gastrointestinal mucosa, their role as potent mediators, and their close collaboration with the enteric nervous system. Among the gastrointestinal diseases that may cause chronic diarrhea, IBS is intriguing because the diagnosis is based on symptoms and on exclusion of other diseases. Irritable bowel syndrome has an overall prevalence in the United States of about 2.9% among the adult population, and the symptoms include pain, constipation, or predominant diarrhea.²⁸ Predominant diarrhea is the least frequent of the 3 symptoms, with no published incidence rates, but probably comprising fewer than 20% of IBS cases. Twenty-one (45%) of our 47 study patients had abdominal pain and were initially presumed to have diarrhea-predominant IBS. In patients with IBS, increased mast cells have been demonstrated in the cecum,²⁹ terminal ileum,³⁰ and colon.³¹ Although mast cells may be altered in all forms of IBS, patients with presumed diarrhea-predominant IBS are more easily evaluated, as more of these patients undergo endoscopy and biopsy compared with patients with other forms of presumed IBS.

Herein, we describe a group of patients with clinically intractable chronic diarrhea and the sole abnormality of an increase in mast cells observed on immunohistochemical staining for MCT. Unlike urticaria pigmentosa or cutaneous mastocytoma, in which dense collections of mast cells are easily visualized on routine hematoxylin-eosin staining, the enterocolonic mucosa in mastocytic enterocolitis appears unremarkable. This is because the increased mast cells are diffusely scattered and are masked by the usual population of histiocytes, lymphocytes, and

plasma cells within the lamina propria. Histologically, this increased mast cell population is of the mucosal reactive T mast cell phenotype because there is no simultaneous increase in the submucosal constitutive TC mast cell phenotype. This fortuitous mucosal diffuse distribution perfectly suits the type of tissue sample obtainable on random endoscopic biopsy specimens.

Increased mast cells may produce symptoms through an increase in mast cell mediator release and local or paracrine signals to the enteric nervous system.¹¹ Although the cause of increased mast cells in chronic intractable diarrhea is unknown, mast cell mediator release is a typical response to adaptive and innate immunologic stimuli and to brain-gut interactions. Recognition of the released mast cell mediators by sensory neurons and interneurons of the enteric nervous system activates a programmed stereotypic defense reaction from the motor neurons (resulting in hypersecretion and power propulsion) and from the effector systems (causing diarrhea and abdominal pain).

We propose the novel term *mastocytic enterocolitis* to describe the increased gut mucosal mast cells that are revealed by immunohistochemical demonstration of MCT in patients with chronic intractable diarrhea. This term is not meant to imply a specific diagnosis but rather to reflect the clinical setting of chronic intractable diarrhea with negative results on laboratory workup, unremarkable histologic appearances on routine staining, and more effective treatment availability compared with diarrhea-predominant IBS. Drugs affecting mast cell function are commonly prescribed and are widely used for conditions such as allergies and peptic ulcer but are not ordinarily prescribed for diarrhea. The primary objective of this study was to assess the concentration of mast cells in colonic or duodenal biopsy specimens from patients with chronic intractable diarrhea, and evaluation of the clinical and therapeutic aspects of the disease will require additional research. Physicians managing patients with chronic intractable diarrhea are encouraged to incorporate endoscopy, random colonic or duodenal mucosal sampling, and MCT immunostaining as part of their investigational protocol, and if increased mast cells are found, they should consider therapeutic options that alter mast cell mediator release and function. Because the mast cell population can demonstrate dynamic fluctuations, investigations are best performed during periods of active symptoms and before treatment. Although MCT, a neutral serine protease, is the most abundant mediator stored in mast cell granules,³² serum tryptase level measurement may not be diagnostic in chronic intractable diarrhea because the effect of mast cell mediator release is immediately local or paracrine. Further studies in this area should elucidate clinical subclasses of disorders with distinct immunologic or central nervous system triggers for mucosal mast cell proliferation and mediator release.

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