Mast Cells in Gastrointestinal Disease

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Abstract: The function of mast cells in allergic inflammatory reactions is well documented in the literature. Mast cells also play an important role in the regulation of gastrointestinal visceral sensitivity and vascular permeability. Several studies have noted an increased number of mast cells in the mucosa of patients with gastrointestinal diseases such as irritable bowel syndrome, mastocytic enterocolitis, and systemic mastocytosis. The role of mast cells in the symptomatology of these and other diseases has only recently been fully appreciated and could provide avenues for new therapeutic opportunities. This paper examines studies that have evaluated the role of mast cells in various gastrointestinal diseases.

Mast cells have an important immunoregulatory function, particularly at the mucosal border between the body and the environment. Due to the gastrointestinal tract's large interface with the environment, mast-cell overproduction or overactivation can lead to gastrointestinal disorders.[1] These cells have been found to play an increasingly important role in the pathophysiology of gastrointestinal diseases. This changing paradigm may lead to new therapeutic opportunities for several chronic digestive conditions.

Immunology of Mast Cells

Mast cells express surface receptors for fragment crystallizable portions of immunoglobulin (Ig)E and certain classes of IgG that enable the binding of antibodies to the cell surface. The introduction of an antigen causes a mast-cell granulated release of numerous inflammatory mediators such as histamine and serotonin. Several enzymes are also released, including cytokines and proteases, which are crucial to allergic reactions and anaphylactic-type responses. Once a genetically susceptible individual is sensitized to a given allergen and an IgE antibody forms, subsequent exposure to this allergen induces the manifestation of atopic disease. This reaction may be attenuated by the use of medications that inhibit the release

of mast-cell mediators, called mast-cell stabilizers, or the actions of mediators such as antihistamines.[2]

As mast cells have an important function in innate immunity, they are able to respond to bacterial and parasitic infections via secretion of their mediators and thus achieve optimal induction of inflammatory and adaptive immune responses. Recent evidence has found that mast cells may play a role in the last-phase response and chronic remodeling of mucosal tissue, as histamine and tryptase have been shown to stimulate fibroblast growth in vitro and in vivo.[2]

Mast cells can be found throughout normal connective tissue, often next to blood vessels or nerves or beneath epithelial surfaces, where these cells are exposed to the environment via the respiratory and gastrointestinal tracts. For example, mast cells located next to venules could influence the entry of foreign substances due to their fast response. Histamine and lipid mediators also affect vascular permeability, enabling a local influx of plasma proteins such as complement and immunoglobulins. Within these different anatomical sites, mast cells can vary widely in terms of their ability to respond to stimuli, responsiveness, and mediator content.[3]

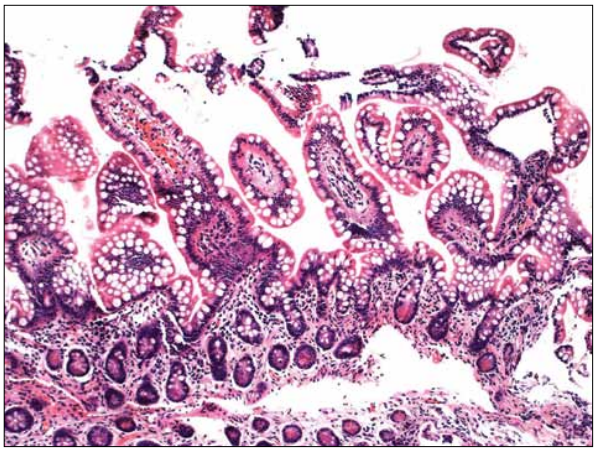

Figure 1. A 50-year-old white woman had a 20-year history of chronic diarrhea that had been diagnosed as medically refractory irritable bowel syndrome. Tests for inflammatory bowel disease, celiac disease, lactose intolerance, and fructose intolerance were negative, and a colonoscopy revealed grossly normal findings. A hematoxylin and eosin stain of random biopsies of the colon and terminal ileum (shown above) was normal.

Gastrointestinal Physiology and Mast-Cell Function

The number of mast cells at a given site can vary, depending upon the location and immunologic status of the host.[2,4] Mast cells comprise 2–5% of mononuclear cells in the lamina propria of the normal gastrointestinal tract, representing an average of 13 cells per high-power field in the duodenum and colon.[5,6] Previous studies have documented an increased number of mast cells in gastrointestinal mucosa tissue samples from patients with gastrointestinal diseases such as irritable bowel syndrome.[7,8]

Mast cells are preferentially located next to nerve terminals in the lamina propria, where they are activated by secreted neuropeptides such as substance P. When stimulated by substance P, these mast cells release inflammatory mediators, such as serotonin and proteases, as well as proinflammatory cytokines. Other mediators are important for the function and regulation of the gastrointestinal tract. For example, the release of histamine and prostaglandin D2 is important for chloride and water secretion as well as control of intestinal motility.[5]

Due to their location, mast cells may play a role in visceral sensitivity. Reaction from motor neurons secondary to degranulation can result in hypersecretion and power propulsion, causing diarrhea and abdominal pain.[9] Mediators released by mast-cell degranulation also sensitize silent nocireceptors in the large intestine. This mechanism has been demonstrated in animal models in which degranulation of mast cells resulted in a reduced threshold for pain, with rectal distension that could be prevented by treatment with mast-cell stabilizing drugs.[10] Receptors for mast-cell mediators are also found on vagal and spinal sensory afferent neurons, which could likewise contribute to abdominal pain.[11,12]

Mast cells are also affected by both acute and chronic stress. Anatomic connections between mast cells and enteric nerve fibers have been demonstrated in human gastrointestinal mucosa and are known to increase with inflammation.[13] The mast cell–enteric nerve association provides a physiologic means for bidirectional communication between the central nervous system and intestinal tract through which stress may influence gastrointestinal function. As stress has been shown to induce mast-cell activation, mediators released secondary to an external stressor may affect motility, visceral sensitivity, and gut barrier function.[7]

Diagnostic Evaluation

Histologic evaluation, determination of enzyme activity, and allergy testing may aid in the investigation of conditions with a suspected mast-cell etiology. Endoscopic biopsies of the stomach, small bowel, and colon can help to determine whether the number of mast cells in the mucosa has increased. Except for urticaria pigmentosa

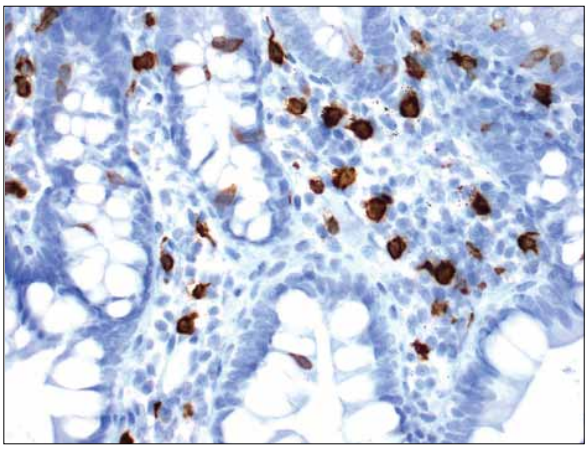

Figure 2. A CD117 immunohistochemical stain (bronze coloring) for mast cells was obtained in the chronic diarrhea patient discussed in Figure 1. The stain (shown above) revealed more than 20 mast cells per high-power field in both the colon and terminal ileum, a finding consistent with the diagnosis of mastocytic enterocolitis. (The same cells can also be highlighted with Giemsa stain or mast-cell tryptase.) The patient experienced an immediate, sustained response to cetirizine hydrochloride (Zyrtec, McNeil) antihistamine therapy.

(fixed reddish brown maculopapular lesions) and cutaneous mastocytosis, mast-cell biopsy findings are difficult to identify via standard hematoxylin and eosin staining (Figure 1), and in many cases, specific pathologic features such as crypt distortion, mucin depletion, cryptitis, abscesses, granulomas, thickened collagen bands, shortened villi, or excessive eosinophils/lympocytes are not seen in mast cell–related disease.[6] Consultation with a pathologist is essential to ensure that an appropriate evaluation is performed. The excess of mast cells can be evaluated via immunohistochemical analysis for CD117, mast-cell tryptase, or Giemsa staining (Figure 2). We believe that many patients with mast cell–induced gastrointestinal disease may be missed if these stains are not used.

As the role of mast cells in the pathology of gastrointestinal disease is still evolving, no specific criteria currently exist for diagnosis. One study suggested a cutoff of 20 mast cells per high-power field within the lamina propria, as this value is 2 standard deviations above the normal value found in the general population; however, other studies have not supported this cutoff.[6,14] Criteria for the diagnosis of systemic mastocytosis specify a value of 15 mast-cell aggregates in an extracutaneous organ, as mast cells are often found in confluent sheets and aggregates of over 100 cells per high-power field. Other studies have suggested that the number of appreciated cells can be affected by the fixing or staining technique.[15-17] In addition to sheets of mast cells in the lamina propria, other gastrointestinal findings in systemic mastocytosis include eosinophil infiltrates and architectural changes such as the broadening and flattening of villi in the small bowel and changes in crypt size, shape, and space in the colon.[18]

The presence of serum tryptase levels persistently over 20 ng/mL may also aid in the diagnosis of mast-cell disease. This value is a minor criterion for diagnosis of systemic mastocytosis due to the usual increase in tryptase levels in systemic disease; however, this enzyme may not be as elevated in focal gastrointestinal conditions such as irritable bowel syndrome.[15] Jejunal aspirates have been evaluated for increased levels of tryptase in patients with various numbers of mucosal mast cells, but no correlation has been found between the number of mucosal mast cells and the levels of luminal tryptase detected.[7]

Allergy assessment with skin prick tests or radioallergosorbent tests (RASTs) followed by an exclusion diet based upon these results is warranted for suspected IgE-mediated gastrointestinal symptoms.[5] However, these tests can often be misleading due to their significant number of false-positive and false-negative results. In a study of symptomatic patients with endoscopically proven mucosal changes to certain food allergens, only 46% of patients had positive skin tests and only 50% had positive RASTs.[19]

Mast Cells in Gastrointestinal Disease

Gastrointestinal Food Allergy

Mast cells are important in food allergies. Sensitivity to glycoproteins in food is caused by a series of interactions among T cells, B cells, antigen-presenting cells, and mast cells. Infection or inflammatory processes in the gastrointestinal tract can lead to increased intestinal permeability, which causes antigens to bypass the normal route of presentation to columnar intestinal epithelial cells and allows for allergic sensitization as antigens reach IgE antibodies bound to mast cells. These reactions lead to symptoms such as shock, rash, angioedema, pruritus, vomiting, and diarrhea. Endoscopic observation has revealed local vasodilatation, edema, mucus secretion, and petechial hemorrhage. One such study evaluated patients with food allergies 30 minutes after placing a known allergen on gastric mucosa. These patients had a significant number of hyperemic and edematous patches of thick gray mucus and scattered petechiae at this site. An IgE-mediated mechanism was suggested for this reaction. Studies have demonstrated the presence of food-specific IgE antibodies and an increased number of intestinal mast cells compared to normal controls prior to the challenge; following the food challenge, a

decreased number of stainable mast cells and a decreased amount of tissue histamine were observed.[19]

Diarrhea-Predominant Irritable Bowel Syndrome

The prevalence of irritable bowel syndrome in the adult population ranges from 3% to 20%.[20] Although the prevalence of this condition is rising, its etiology remains unclear. Diagnosis of irritable bowel syndrome depends upon the presence of altered bowel habits and abdominal pain as well as the exclusion of other conditions. Treatment is predominately based upon symptom control. Studies such as the one conducted by Jakate and associates highlight the possibility that a subset of patients with diarrhea-predominant irritable bowel syndrome may have increased numbers of mast cells.[6] This finding could theoretically transform the paradigm of diarrhea-predominant irritable bowel syndrome.

Increased numbers of mast cells have been found in the cecum, terminal ileum, and jejunum of patients with irritable bowel syndrome in several studies.[7,8,21] However, other studies have demonstrated normal numbers of mast cells in irritable bowel syndrome patients; Hahn and Hornick evaluated the concentration of mast cells in 16 patients with irritable bowel syndrome and did not find a significant increase in 20 terminal ileal and colonic biopsies.[14] If the number of mast cells is increased, the effect of mast-cell mediators on the gastrointestinal tract could explain the symptomatology of diarrhea-predominant irritable bowel syndrome. Animal studies have shown that increased numbers of intestinal mast cells are associated with intestinal hypermotility caused by food allergies.[22]

Mast-cell mediators released after degranulation can also sensitize nociceptors in the intestine. Mast-cell tryptase and histamine can activate enteric nerves, resulting in neuronal hyperexcitability.[22] The sensitization of nociceptors due to mast-cell degranulation could play a role in abdominal pain among patients with irritable bowel syndrome.[9] Psychological factors appear to play a role in increased colonic mast-cell concentration. Human studies have shown increased mast-cell colonic concentration in irritable bowel syndrome patients with high depression and fatigue scores.[23] This finding suggests that mast cell–inducing psychological factors may play a causal role in symptoms of irritable bowel syndrome.

Although not accepted by all gastroenterologists, the term mastocytic enterocolitis was coined by Jakate and coworkers to describe an increase in mucosal mast cells in patients with chronic diarrhea.[6] The researchers assessed mucosal mast cells in 47 patients with chronic functional diarrhea and normal-appearing biopsies via hematoxylin and eosin stains. Biopsy samples were obtained from the colon (22/47 patients), duodenum (20/47 patients), or both (5/47 patients). Samples were compared to 50 control patients who underwent biopsies to evaluate gastroduodenal complaints not involving diarrhea. In addition, specimens were compared to biopsies from 63 patients with specific gastrointestinal conditions causing diarrhea (eg, collagenous colitis, Crohn's colitis, celiac disease). All biopsies were stained for mast-cell tryptase by immunohistochemical analysis. The mean standard deviation of the concentration of mast cells per high-power field in the control patients was 13.3±2.5, compared to 25.7±4.5 in the study group and 12.3±2.3 in the group with specific diarrheal conditions. Increased numbers of mast cells were found in 33 of the 47 patients with chronic functional diarrhea (70%). Symptoms were controlled in 22 of the 33 patients treated with antihistamine H1 blockers.[6] Similarly, a case report of a young woman with bloody diarrhea who had increased numbers of mucosal mast cells in colonic biopsies was cited in the allergy literature. Her symptoms improved with oral cromolyn and balsalazide therapy, though she was later lost to follow-up.[24] Both this case study and the study by Jakate and colleagues indicate that the predominant symptoms were diarrhea and abdominal pain. In the study conducted by Jakate and associates, 21 of the 47 patients (45%) experienced abdominal pain.[6]

Although the exact cause of increased numbers of mast cells in chronic diarrhea is unknown, it is thought to be a response to immunologic stimuli causing a brain-gut interaction. Jakate and colleagues measured serum tryptase levels in 3 patients and found no elevation, which implied localized mucosal mast-cell infiltration rather than systemic mastocytosis. The diagnosis of mastocytic enterocolitis was not made with routine hematoxylin and eosin or Toluidine blue staining. Immunostaining for mast-cell tryptase revealed intracytoplasmic brown stains highly specific for mast cells.[6] The authors concluded that all patients with unexplained diarrhea, abdominal pain, normal endoscopies, and unremarkable biopsies via hematoxylin and eosin stains may benefit from further evaluation for mastocytic enterocolitis. Additional evaluation will be required to confirm mastocytic enterocolitis as a true entity separate from diarrhea-predominant irritable bowel syndrome.

Systemic Mastocytosis

Mastocytosis is caused by the proliferation of mast cells in various extracutaneous organs. The most commonly involved sites are the liver, spleen, bone marrow, and gastrointestinal tract. Most cases of mastocytosis are associated with a C-KIT mutation and up to 93% involve codon 816 (C-KIT D816V).[25]

Symptoms result from the infiltrated organ and mast-cell mediator release and can affect the respiratory, diges-

tive, neuropsychiatric, and hematologic systems. Urticaria pigmentosa is commonly seen in mastocytosis. Mast-cell infiltration can result in organ dysfunction in aggressive systemic mastocytosis (ASM). Gastrointestinal symptoms are present in 60–80% of cases. The most frequent digestive symptoms are abdominal pain and diarrhea. Due to increased histamine production in systemic mastocytosis, symptoms can also include esophagitis, gastric ulcer disease, and intestinal malabsorption.[16]

Diagnosis of mastocytosis is based upon criteria developed by the World Health Organization. In order to fulfill this criteria, 1 major and 1 minor criterion, or 3 minor criteria, must be met. An example of a major criterion is the presence of more than 15 mast cells per high-power field in an extracutaneous organ. Examples of minor criteria are spindle-shaped cells comprising over 25% of mast-cell infiltrates, detection of the C-KIT D816V mutation, expression of CD2 and CD25 on CD117 mast cells, and a serum tryptase level higher than 20 ng/mL.[15]

Management of systemic mastocytosis includes avoidance of triggers (eg, alcohol, nonsteroidal anti-inflammatory drugs) and control of symptoms related to mast-cell mediator release. Cytoreductive therapy is reserved for patients with ASM.

Potential Therapies

Treatments are aimed at stabilizing mast cells and controlling mediator release to prevent symptoms. Therapies to prevent mast-cell infiltration (such as fludarabine and interferon) have been used in ASM. Newer treatments with tyrosine kinase inhibitors have also been discussed to target the C-KIT mutation associated with ASM.

Antihistamines H2 antihistamines are targeted to decrease hypersecretion of gastric acid and can be helpful for treating the gastrointestinal symptoms of diarrhea and abdominal cramping. Ranitidine 150 mg orally every 12 hours or famotidine 10 mg orally every 12 hours can be used. H1 antihistamines can control flushing and pruritis.[26] Patients evaluated in the study by Jakate and coworkers showed significant symptom improvement with H1 and H2 antihistamines.[6]

Cromolyn An inhibitor of mast-cell degradation, cromolyn can be used at a dose of 100–200 mg orally 4 times per day. Small studies have shown improvement in gastrointestinal symptoms with cromolyn therapy.[26,27] In a large multicenter trial evaluating 428 diarrhea-predominant irritable bowel syndrome patients, oral cromolyn was compared to elimination diet. Symptom improvement was seen in 67% of patients treated with oral cromolyn sodium (1,500 mg/day) for 1 month compared to 60% of patients treated with elimination diet.[28]

Antileukotriene Drugs Although antileukotriene drugs such as montelukast may cause abdominal pain, they have shown improvements in pruritus and flushing.[29]

Budesonide If the aforementioned, targeted therapies fail, 9 mg daily of oral budesonide can be used as an alternative treatment.[16]

Exclusion Diet As food allergies have been proposed in the pathogenesis of irritable bowel syndrome, patients with mast-cell infiltration may benefit from allergy testing and exclusion diets.[21] The role of non-IgE delayed type 4 reaction is unclear in gastrointestinal food allergies. Diagnosing specific gastrointestinal food allergies is difficult, as IgE immediate type 1 reaction is rare. Methods such as skin prick tests and RASTs for IgE suggest that sensitization to certain allergens may develop. However, a positive test implies a food allergy without a clinical reaction.[30,31]

A 2-week diet excluding certain foods should be adequate to assess response. Gradual reintroduction of foods accompanied by the development of symptoms suggests the presence of trigger foods. A meta-analysis reviewing 7 studies of elimination diets in patients with irritable bowel syndrome suggested that milk, wheat, eggs, and foods high in salicylates or amines consistently exacerbated symptoms.[32] Desensitization injections have been evaluated as a possible treatment, but inadequate evidence exists in IgE-medicated reactions to support their effectiveness.

In conclusion, the authors believe that mast cells may play a common but, heretofore, underappreciated role in gastrointestinal diseases and thus recommend that patients with chronic unexplained diarrhea undergo colonoscopic biopsies with special mast-cell stains.

References

1. Miner PB Jr. The role of the mast cell in clinical gastrointestinal disease with special reference to systemic mastocytosis. *J Invest Dermatol.* 1991;96:40S-43S; discussion 43S-44S.
2. Paul WE, ed. *Fundamental Immunology.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:22-23.
3. Kasper DL, Braunwald E, Hauser S, Longo D, Jameson JL, Fauci AS, eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York, NY: McGraw-Hill; 2005:1947-1949.
4. Koyasu S, Minowa A, Terauchi Y, Kadowaki T, Matsuda S. The role of phosphoinositide-3-kinase in mast cell homing to the gastrointestinal tract. *Novartis Found Symp*. 2005;271:152-161; discussion 161-165, 198-199.
5. Feldman M, Friedman L, Brandt L, eds. *Gastrointestinal and Liver Disease.* 8th ed. Philadelphia, PA: Saunders; 2006:31.
6. Jakate S, Demeo M, John R, Tobin M, Keshavarzian A. Mastocytic enterocolitis: increased mucosal mast cells in chronic intractable diarrhea. *Arch Pathol Lab Med.* 2006;130:362-367.

7. Guilarte M, Santos J, de Torres I, et al. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut.* 2007;56:203-209.
8. Weston AP, Biddle WL, Bhatia PS, Miner PB Jr. Terminal ileal mucosal mast cells in irritable bowel syndrome. *Dig Dis Sci.* 1993;38:1590-1595.
9. Wood JD. Enteric neuroimmunophysiology and pathophysiology. *Gastroenterology*. 2004;127:635-657.
10. Coelho AM, Fioramonti J, Bueno L. Mast cell degranulation induces delayed rectal allodynia in rats: role of histamine and 5-HT. *Dig Dis Sci.* 1998;43:727-737.
11. Kirkup AJ, Jiang W, Bunnett NW, Grundy D. Stimulation of proteinase-activated receptor 2 excites jejunal afferent nerves in anaesthetised rats. *J Physiol.* 2003;552(pt 2):589-601.
12. Jiang W, Kreis ME, Eastwood C, Kirkup AJ, Humphrey PP, Grundy D. 5-HT(3) and histamine H(1) receptors mediate afferent nerve sensitivity to intestinal anaphylaxis in rats. *Gastroenterology.* 2000;119:1267-1275.
13. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology.* 2004;126:693-702.
14. Hahn HP, Hornick JL. Immunoreactivity for CD25 in gastrointestinal mucosal mast cells is specific for systemic mastocytosis. *Am J Surg Pathol*. 2007;31:1669-1676.
15. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res*. 2001;25:603-625.
16. Sokol H, Georgin-Lavialle S, Grandpeix-Guyodo C, et al. Gastrointestinal involvement and manifestations in systemic mastocytosis. *Inflamm Bowel Dis*. 2010;16:1247-1253.
17. Braverman DZ, Dollberg L, Shiner M. Clinical, histological, and electron microscopic study of mast cell disease of the small bowel. *Am J Gastroenterol.* 1985;80:30-37.
18. Kirsch R, Geboes K, Shepherd NA, et al. Systemic mastocytosis involving the gastrointestinal tract: clinicopathologic and molecular study of five cases. *Mod Pathol.* 2008;21:1508-1516.
19. Reimann HJ, Lewin J. Gastric mucosal reactions in patients with food allergy. *Am J Gastroenterol.* 1988;83:1212-1219.
20. Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment: an update for health-care practitioners. *J Gastroenterol Hepatol.* 2010;25:691-699.
21. O'Sullivan M, Clayton N, Breslin NP, et al. Increased mast cells in the irritable bowel syndrome. *Neurogastroenterol Motil.* 2000;12:449-457.
22. Traver E, Torres R, de Mora F, Vergara P. Mucosal mast cells mediate motor response induced by chronic oral exposure to ovalbumin in the rat gastrointestinal tract. *Neurogastroenterol Motil.* 2010;22:e34-43.
23. Piche T, Saint-Paul MC, Dainese R, et al. Mast cells and cellularity of the colonic mucosa correlated with fatigue and depression in irritable bowel syndrome. *Gut*. 2008;57:468-473.
24. Ogilvie-McDaniel C, Blaiss M, Osborn FD, Carpenter J. Mastocytic enterocolitis: a newly described mast cell entity. *Ann Allergy Asthma Immunol.* 2008;101:645-646.
25. Bains SN, Hsieh FH. Current approaches to the diagnosis and treatment of systemic mastocytosis. *Ann Allergy Asthma Immunol.* 2010;104:1-10; quiz 10-12, 41.
26. Worobec AS. Treatment of systemic mast cell disorders. *Hematol Oncol Clin North Am*. 2000;14:659-687.
27. Horan RF, Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. *J Allergy Clin Immunol.* 1990;85:852-855.
28. Stefanini GF, Saggioro A, Alvisi V, et al. Oral cromolyn sodium in comparison with elimination diet in the irritable bowel syndrome, diarrheic type. Multicenter study of 428 patients. *Scand J Gastroenterol.* 1995;30:535-541.
29. Tolar J, Tope WD, Neglia JP. Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. *N Engl J Med.* 2004;350:735-736.
30. Heizer WD, Southern S, McGovern S. The role of diet in symptoms of irritable bowel syndrome in adults: a narrative review. *J Am Diet Assoc*. 2009;109:1204-1214.
31. Park MI, Camilleri M. Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? A systematic review. *Neurogastroenterol Motil.* 2006;18:595-607.
32. Niec AM, Frankum B, Talley NJ. Are adverse food reactions linked to irritable bowel syndrome? *Am J Gastroenterol.* 1998;93:2184-2190.