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A Clinicopathologic Study of 24 Cases of Systemic Mastocytosis Involving the Gastrointestinal Tract and Assessment of Mucosal Mast Cell Density in Irritable Bowel Syndrome and Asymptomatic Patients

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Abstract

Counting mast cells in gastrointestinal (GI) mucosal biopsies is becoming an increasingly common practice. The primary reason for this exercise is to evaluate for possible involvement by systemic mastocytosis (SM). However, the features of mastocytosis in GI biopsies are not well described. In addition, recent studies have suggested that increased mast cells may be involved in the pathogenesis of some cases of diarrhea-predominant irritable bowel syndrome (IBS); the term “mastocytic enterocolitis” has been proposed for such cases. As the baseline mast cell density in colonic biopsies from normal patients has not been established in large cohorts, there is no widely accepted threshold for what constitutes increased mucosal mast cells. The aims of this study were (1) to determine the utility of GI biopsies for the diagnosis of SM, (2) to characterize the clinical, histologic, and immunohistochemical features of mastocytosis in the GI tract, (3) to determine mast cell density in normal colonic mucosa from a large cohort of asymptomatic patients, and (4) to compare these findings with those from patients with diarrhea-predominant IBS. Twenty-four patients with SM involving the GI tract, 100 asymptomatic patients, and 100 patients with IBS (the latter 2 groups with histologically normal colonic biopsies) were included. For the mastocytosis group, 107 biopsies (70 involved by mastocytosis; 67 mucosal, 3 liver) from 20 women and 4 men were evaluated (median age 59 y). The most commonly involved site was the colon (19 patients, 95%), followed by ileum (86%), duodenum (80%), and stomach (54%). In 16 cases (67%), the first diagnosis of SM was made on the basis of GI biopsies. Seventeen patients

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had documented cutaneous mastocytosis. Fifteen of 17 patients who underwent bone marrow biopsy had marrow involvement by SM. Eighteen patients had indolent disease, and 6 had aggressive disease (including all 3 with liver involvement). The most common GI symptom was diarrhea, followed by abdominal pain, nausea, weight loss, bloating, vomiting, or reflux. Liver disease presented with hepatomegaly and ascites. Endoscopic abnormalities (observed in 62%) included erythema, granularity, and nodules. Histologically, involved biopsies were characterized by infiltrates of ovoid to spindle-shaped mast cells in aggregates or sheets in the lamina propria, sometimes forming a confluent band underneath the surface epithelium; 25% of biopsies had only focal involvement (single aggregate). Prominent eosinophils were seen in 44% of involved colonic/ileal biopsies and 16% of duodenal biopsies. Mast cells were highlighted by diffuse membranous staining for KIT and CD25. In the nonmastocytosis groups, all biopsies contained singly dispersed mast cells with no aggregates. The mean highest mast cell counts (in a single high-power field) for asymptomatic patients and IBS patients were 26 (range, 11 to 55) and 30 (range, 13 to 59), respectively. In summary, GI (especially colonic) biopsies can establish a diagnosis of SM in patients with GI symptoms. GI involvement is usually subtle and is often associated with prominent eosinophils, which may obscure the mast cell infiltrate. KIT and CD25 are invaluable markers for the diagnosis. Mast cell density in colonic mucosa from asymptomatic patients is highly variable. Although patients with diarrhea-predominant IBS on average have mildly increased mast cells, the overlap in range with that of control patients is too great for this difference to be clinically useful. These findings argue against the utility of counting GI mucosal mast cell in patients with chronic diarrhea.

Keywords

gastrointestinal tract; liver; mast cells; mastocytosis; mast cell activation syndrome; irritable bowel syndrome; urticaria pigmentosa; KIT

Mastocytosis is a clonal neoplastic proliferation of mast cells that involves one or more organ systems. Mastocytosis encompasses a group of clinically and pathologically heterogeneous disorders, with different subtypes recognized by distribution of disease and clinical manifestations. Mastocytosis most commonly involves the skin, which typically takes the form of urticaria pigmentosa (UP), and much less commonly telangiectasia macularis eruptiva perstans, diffuse cutaneous mastocytosis, or solitary mastocytoma. Of extracutaneous sites, bone marrow is most frequently involved. Gastrointestinal (GI) tract involvement is increasingly recognized because of increasing awareness among pathologists and physicians involved in the care of patients with mastocytosis, as well as the availability of sensitive and specific immunohistochemical markers to detect neoplastic mast cells.

Many patients with mastocytosis, even without apparent GI involvement, have significant GI symptoms, such as abdominal pain, nausea, and diarrhea, which are thought in most cases to be due to the release of mast cell mediators such as histamine and leukotrienes. In patients with involvement of the GI tract, symptoms may also be due to direct infiltration of the mucosa by mast cells, with resultant malabsorption and/or enhanced local effects of mediator release. The frequency of GI symptoms in patients with systemic mastocytosis (SM) is estimated at 70%¹ and in patients with UP (without known GI involvement), 25%.²

However, although not all patients with GI symptoms have GI involvement by mastocytosis, data are limited in this regard, as many patients do not undergo endoscopic biopsy unless they have long-standing, persistent, or changing symptoms. Therefore, the true frequency of GI involvement by mastocytosis in patients with GI symptoms and disease presumed to be limited to the skin has not been established.

The major diagnostic criterion for SM is the presence of mast cell aggregates (defined as 15 mast cells) in bone marrow or extracutaneous organs, including the GI tract. Minor diagnostic criteria include coexpression of CD25 by neoplastic mast cells, 25% of mast cells having spindle-shaped or atypical morphology, the presence of an activating point mutation at codon 816 of *KIT*, and serum total tryptase > 20 ng/mL.³ A diagnosis of SM is made on the basis of 1 major and 1 minor or 3 minor criteria. In general, most patients undergo bone marrow biopsy when there is a clinical suspicion for systemic disease.⁴ However, endoscopic GI biopsies may be a reasonable alternative to establish a diagnosis of SM in selected patients.

The diagnosis of mastocytosis in GI mucosal or liver biopsies has significant therapeutic and prognostic implications, in that it defines SM, and it may sometimes be associated with aggressive disease. To date, clinical and pathologic descriptions of mastocytosis in GI biopsies have chiefly been limited to case reports and small series.^{5–12} More recently, the clinical GI manifestations of a larger cohort of patients with mastocytosis were described, of whom 23 had undergone GI biopsies.¹³

Recent studies have suggested that mast cells are involved in the pathogenesis of some cases of diarrhea-predominant irritable bowel syndrome (IBS). The term “mastocytic enterocolitis” has been proposed to describe a subset of such patients with increased mucosal mast cells and symptomatic improvement after treatment with histamine receptor antagonists and an inhibitor of mast cell mediator release (cromolyn).^{14,15} However, the baseline mast cell density in colonic biopsies from normal patients has not been established in large cohorts, and there is no widely accepted threshold for what constitutes increased mucosal mast cells. The aims of this study were: to determine the utility of GI biopsies for the diagnosis of SM; to characterize the clinicopathologic features of mastocytosis in the GI tract in a large series of patients; to determine mast cell density in normal colonic mucosa from a large asymptomatic patient cohort; and to compare the findings with those from patients with diarrhea-predominant IBS and mast cell activation syndrome, a recently described disorder defined by clinical criteria (including IBS-like symptoms), evidence of mast cell mediator release, and responses to anti-mast cell mediator therapy.¹⁶

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Brigham and Women's Hospital. Twenty-four patients with mastocytosis involving the GI tract and liver were identified from the surgical pathology files of Brigham and Women's Hospital. In addition, 100 patients with diarrhea-predominant IBS were identified by searching the surgical pathology files between January 2010 and August 2013 for patients with chronic diarrhea, a clinical diagnosis of IBS, and histologically normal colonic biopsies. A control group of 100

asymptomatic patients undergoing screening colonoscopy between January 2010 and October 2013 was also selected. Ten patients with well-defined mast cell activation syndrome who underwent colonoscopic biopsy were also evaluated.

For patients with mastocytosis, clinical details including documentation of prior skin disease and other sites of involvement by mastocytosis, presence of D816V *KIT* mutation, GI symptoms, and endoscopic findings were obtained. Treatment and clinical outcome data were documented when available. Representative hematoxylin and eosin–stained slides and immunohistochemical slides (see below) were reviewed for all biopsies to document the presence or absence of involvement by mastocytosis. World Health Organization diagnostic criteria for SM were applied.³ Additional histologic features, including extent and distribution of involvement, mast cell morphology, mast cell density (highest mast cell count in 1 high-power field [HPF] using a $\times 40$ objective and a $\times 10$ ocular lens; field size 0.25 mm^2), and the presence of an associated eosinophilic infiltrate, were evaluated. Immunohistochemical analysis for KIT, CD25, mast cell tryptase, and CD30 was performed on biopsies with available material.

For patients with IBS and mast cell activation syndrome and for the asymptomatic control group, the mean mast cell density per HPF was determined by counting KIT-positive cells in 5 contiguous HPFs (field size 0.25 mm^2) in the colonic lamina propria in areas with greatest density of mast cells; the highest mast cell count (in a single HPF) was also calculated. The Student *t* test and the Fisher exact test were used, as appropriate; $P < 0.05$ was considered significant. Clinical history was reviewed for all asymptomatic control patients and patients with IBS to identify those with allergic disorders (allergic rhinosinusitis, asthma, eczema, urticaria).

The antibodies, clones, dilutions, pretreatment conditions, and sources are listed in Table 1. Appropriate positive and negative controls were used throughout.

RESULTS

Clinical and Endoscopic Features of Patients With SM

The clinical features are summarized in Table 2. In total, 107 biopsies (102 GI mucosal biopsies and 5 liver biopsies) from 20 women and 4 men with mastocytosis were evaluated. The median patient age at the time of GI biopsy was 59 years (range, 18 to 77 y). Three patients underwent upper GI (esophagus, stomach, and duodenum) endoscopy and biopsy only, 8 underwent lower GI (colon and terminal ileum) endoscopy and biopsy only, 12 underwent both upper and lower GI endoscopy and biopsy, and 1 patient underwent liver biopsy only (the remaining 4 liver biopsies were from patients who also had endoscopic biopsies). All included patients had 1 or more biopsy showing involvement by mastocytosis. In total, 67/102 (66%) mucosal biopsies were involved by mastocytosis, and liver involvement was identified in 3/5 liver biopsies. Of the total biopsies, mastocytosis was seen in 42/52 (81%) colonic, 6/7 (86%) ileal, 12/18 (67%) duodenal, and 7/20 (35%) gastric biopsies. All 5 esophageal biopsies were uninvolved. Per patient, the most commonly involved site within the GI tract was the colon (19/20 patients, 95%), followed by ileum (6/7, 86%), duodenum (12/15, 80%), and stomach (7/13, 54%).

Seventeen patients had documented cutaneous mastocytosis before undergoing endoscopic biopsy—UP in all 17, of whom 2 also had telangiectasia macularis eruptiva perstans and solitary mastocytoma. The median interval from the time of diagnosis of skin disease to the time of documented GI involvement was 10 years (range, 0.8 to 50 y). GI symptoms included diarrhea (n = 18), abdominal pain (n = 9), nausea (n = 6), weight loss (n = 4), and bloating, vomiting, or reflux (2 each). Two patients were asymptomatic, and GI mastocytosis was only detected during screening colonoscopy for colorectal cancer. Liver disease presented with hepatomegaly and ascites in 2 cases each, including 1 patient who also had upper GI bleeding secondary to varices. Endoscopic abnormalities were observed in 62% of biopsies involved by mastocytosis and included mucosal erythema/congestion, granularity, or nodularity (Fig. 1). The remaining involved GI tract biopsies were taken at random from normal-appearing mucosa. In total, 93% of biopsies obtained from endoscopically abnormal mucosa showed involvement by mastocytosis, compared with 63% of biopsies taken from endoscopically normal mucosa. Serum tryptase measurements at the time of GI biopsy were available for 16 patients; the median value was 79.5 ng/mL, ranging from 16 to 1609. Thirteen patients had documented D816V *KIT* mutation.

Five patients had associated clonal hematologic non-mast cell lineage disorders: 2 chronic myelomonocytic leukemia, 1 essential thrombocythemia with *JAK2* mutation, 1 chronic eosinophilic leukemia associated with a *PDGFRA* rearrangement (as well as *KIT* D816V), and 1 refractory anemia with excess blasts-1.

Histologic Features of Biopsies Involved by Mastocytosis

Histologically, mucosal biopsies involved by mastocytosis were characterized by infiltrates of ovoid to spindle-shaped mast cells in aggregates or sheets in the lamina propria (Fig. 2). There were 3 biopsies that contained scattered single mast cells with expression of both *KIT* and *CD25*, determined to represent minimal involvement by mastocytosis, as concurrent biopsies showed obvious histologic involvement. In most cases the mast cell aggregates showed a predominantly subepithelial distribution (Fig. 2), with the greatest density directly under the surface epithelium. This feature was less frequent in the upper GI tract, where the aggregates tended to be scattered throughout the lamina propria. Mast cell morphology ranged from rounded cells with moderate amounts of pale, eosinophilic cytoplasm to, more commonly, ovoid or spindle cells with more limited cytoplasm (Fig. 3). Mast cell density was highly variable and ranged from 20 to 278/HPF (mean 116; median 109). Twenty-five percent of involved biopsies had only focal infiltration by mastocytosis, defined as a single discrete aggregate of mast cells (Fig. 4). In addition, 21% (14/67) of involved biopsies showed multifocal involvement within biopsies taken from the same region, with some biopsy fragments showing no or minimal involvement, and other fragments showing obvious sheets or aggregates of mast cells (Fig. 5). In 21% (4/19) of involved upper GI biopsies and 6% (3/48) of involved lower GI biopsies, the mast cell infiltrate extended into the muscularis mucosae.

Prominent eosinophilic infiltrates were seen in 44% of involved colonic/ileal biopsies (Fig. 6) and 16% of duodenal biopsies but not in any of the involved gastric biopsies. Other histologic findings were observed in 28% (19/67) of biopsies involved by mastocytosis:

architectural distortion in 4 colonic biopsies, chronic duodenitis in 3 biopsies, villous blunting in 4 small intestinal biopsies, and chronic inactive gastritis in 3 biopsies. One patient with coexisting ulcerative colitis showed chronic active colitis in 2 biopsies also involved by mastocytosis. Mastocytosis involved the lamina propria of adenomas in 4 cases and a hyperplastic polyp in 1 case (Fig. 7).

Liver biopsies involved by mastocytosis (n = 3) showed mast cell infiltrates in both a portal and a sinusoidal distribution. The sinusoidal component was usually subtle histologically, highlighted by KIT staining (Fig. 8). The mast cells in the liver were predominantly spindled. One case also had an admixed eosinophilic infiltrate. Two biopsies showed periportal fibrosis, and 1 showed bridging fibrosis. There was no steatosis or evidence of hepatoportal sclerosis.

Immunohistochemical Features of Biopsies Involved by Mastocytosis

Neoplastic mast cells were highlighted by diffuse membranous staining for KIT and CD25 in all cases evaluated (Figs. 2–8). In contrast, expression of mast cell tryptase was more variable; of 24 involved biopsies stained with tryptase, 19/24 (79%) showed positive staining in only a subset of neoplastic mast cells (Fig. 9). CD30 expression was evaluated in 7 patients; reactivity for CD30 was identified in 1 of 2 patients with aggressive disease and 2 of 5 patients with indolent disease.

Outcome Data of Patients With Mastocytosis

In 16 cases (67%), the first diagnosis of SM was established on the basis of endoscopic GI or liver biopsy findings (Table 2). Eighteen patients had indolent disease per the current World Health Organization definition, and 6 had aggressive disease (including all 3 patients with liver involvement). Aggressive clinical features included signs of liver dysfunction (hepatosplenomegaly, portal hypertension, bleeding varices), transfusion-dependent anemia, and malabsorption with severe weight loss/cachexia. Of the 6 patients with aggressive disease (4 female and 2 male), 1 initially had indolent disease at the time of diagnosis of SM but subsequently progressed to aggressive disease, and 4 had cutaneous disease (UP).

In total, 17 of the 24 patients included in this study underwent bone marrow biopsy. Only 6 patients had documented bone marrow involvement before the time of GI biopsy. Of the 16 patients in whom the first diagnosis of systemic disease was made on the basis of the GI biopsy findings, 11 patients subsequently underwent bone marrow biopsy; 9 of those patients had bone marrow involvement. Medical treatment included mast cell stabilizers such as cromolyn, proton pump inhibitors, and antihistamines. In advanced, resistant or aggressive cases, steroids and/or midostaurin, a multikinase inhibitor, were used with variable clinical responses. Imatinib was administered to 1 patient (*KIT* mutation status unknown) with little to no effect. One patient (with *KIT* D816V) was treated with dasatinib, with no clinical benefit. Outcome data were available for 18 patients, with a median duration of 25 months since the first diagnosis of systemic disease (range, 5 to 312 mo). One patient with aggressive disease died of SM, whereas the remaining 17 patients were alive with disease at last follow-up.

Mast Cell Density in Biopsies From Patients With IBS and MCAS and From Asymptomatic Controls

The IBS group consisted of 82 female and 18 male patients, with a mean age of 43 years (range, 18 to 78 y). The control group consisted of 58 female and 42 male patients, with a mean age of 56 years (range, 24 to 77 y). The mast cell activation syndrome group consisted of 9 female and 1 male patient, with a mean age of 41 years (range, 22 to 58 y). All biopsies were histologically unremarkable and contained singly dispersed mast cells with no aggregates (Fig. 10). The mast cell data are summarized in Table 3. The mean mast cell counts per HPF (ie, average of 5HPF counted) for asymptomatic patients, IBS patients, and mast cell activation syndrome patients were 19 (range, 7 to 39), 23 (range, 9 to 45), and 20 (range, 12 to 31), respectively (controls vs. IBS, $P < 0.001$; controls vs. mast cell activation syndrome, not significant). If a cutoff of 25 mast cells per HPF (1SD above the mean for controls) was considered “increased,” 16% of normal, 38% of IBS, and 30% of mast cell activation syndrome patients would qualify (controls vs. IBS, $P < 0.001$; controls vs. mast cell activation syndrome, not significant). The mean highest mast cell counts in a single HPF for control patients, IBS patients, and mast cell activation syndrome patients were 26 (range, 11 to 55), 30 (range, 13 to 59), and 28 (range, 14 to 48), respectively (controls vs. IBS, $P < 0.001$; controls vs. mast cell activation syndrome, not significant). There was no significant association between allergic disorders and mast cell density in either the control group or the IBS group.

DISCUSSION

In this study, of the 24 patients with SM, the first diagnosis of systemic disease (ie, extracutaneous disease) was made on the basis of involvement of GI endoscopic biopsies in two thirds of patients. The diagnosis of systemic disease has significant prognostic implications. SM is further divided into indolent or aggressive categories, and patients with aggressive disease typically have rapid progression and survival of only a few years, whereas patients with indolent SM usually have a normal life expectancy.^{17–19} Diagnostic criteria for aggressive disease include bone marrow dysfunction, liver dysfunction (hepatomegaly, abnormal liver function tests, ascites, portal hypertension), pathologic fractures, splenomegaly/hypersplenism, and malabsorption with weight loss due to mast cell infiltrates within the GI tract.³ In this study, most patients did not fulfill criteria for aggressive disease, and thus GI mucosal involvement in the absence of malabsorption and weight loss does not appear to correlate with aggressive disease. Prior studies have shown an association between CD30 expression and advanced disease.²⁰ Although the number of cases examined was small, we did not find an association between CD30 expression by neoplastic mast cells in the GI tract and aggressive disease, as expression was detected in 2 of 5 cases with an indolent clinical course and 1 of 2 aggressive cases.

Three patients in this study had cutaneous mastocytosis diagnosed in infancy, one of whom subsequently developed aggressive systemic disease; the remaining patients with skin disease were diagnosed in adulthood, which is known to be highly associated with SM.²¹ Systemic disease is rare in children who develop cutaneous mastocytosis, and most cases regress by puberty.^{4,22} In the vast majority of cases, adult-onset mastocytosis is associated

with somatic point mutations in codon 816 of *KIT*, which results in ligand-independent activation and autophosphorylation of *KIT*.²³ However, this mutation results in a conformational change in *KIT* that renders it resistant to the effects of imatinib, a tyrosine kinase inhibitor effective in the treatment of chronic myeloid leukemia and GI stromal tumor, such that imatinib is not effective in the treatment of most patients with mastocytosis.^{24,25}

The diagnosis of mastocytosis in mucosal biopsies can be difficult for several reasons; involvement can be very focal and subtle, making recognition of the infiltrate challenging. Because of this, we recommend that for patients with a clinical history of mastocytosis involving skin or other organ sites, it is helpful to have a low threshold for using *KIT* immunohistochemistry as a screening tool to detect subtle aggregates of mast cells, which if present can be further evaluated for CD25 expression to confirm the diagnosis. In addition, as demonstrated by several cases in this study, involvement within the GI tract is often multifocal (as opposed to diffuse), and therefore inadequate sampling may miss involved areas. For the endoscopist, it is therefore advisable to take multiple random biopsies at different sites, as approximately 40% of involved biopsies in our study did not show corresponding endoscopic abnormalities. In our practice, if a patient with diarrhea is suspected to have mastocytosis, we will perform colonoscopy and take random biopsies placed in separate jars from the ileum, right and left colon, and rectum as well as any visibly abnormal areas. Finally, mastocytosis is often associated with prominent eosinophils, which may obscure the mast cell infiltrate. Two cases in the current series were initially diagnosed as eosinophilic colitis on the basis of the dense eosinophilic infiltrate that obscured the mast cell infiltrate. Most cases of eosinophilic gastroenteritis, an immune-mediated disorder of unknown etiology, involve multiple parts of the GI tract, including lower and upper GI tract, and in general do not contain increased numbers of mast cells.⁹ Furthermore, mast cells in this disorder do not express CD25.

In this study, we also found that mast cell density in colonic mucosa from asymptomatic patients is highly variable, with highest counts ranging from 11 to 55 in a single HPF. Recent studies suggesting that mast cell density in GI mucosa may be increased in diarrheal disorders^{14,15} have led to increasing requests by gastroenterologists and other clinicians for pathologists to count mast cells in histologically normal biopsies. The term “mastocytic enterocolitis” has been proposed for those patients with intractable diarrhea, histologically normal endoscopic biopsies, “increased” mast cells by immunohistochemistry, and responses to antihistamines or inhibitors of mast cell mediator release.¹⁴ However, the total number of colonic biopsies (study and control groups) examined in these prior reports was relatively small.^{14,15} We were prompted to undertake this portion of our study in part after reviewing multiple consult cases (both pathology consultations and referrals to our Mastocytosis Center based on outside pathology reports suggesting increased mast cells); our previously published data⁹ and subsequent experience have indicated that the range of mast cell counts in normal colonic mucosa is much broader than suggested in some other studies. Indeed, although patients with diarrhea-predominant IBS on average had mildly increased mucosal mast cell density compared with asymptomatic patients in our current study, the overlap in range with that of control patients is too great for this difference to be

clinically useful. These findings argue against the utility of routine mast cell enumeration in patients with chronic diarrhea. Some of the patients in the study by Jakate et al¹⁴ showed a marked response to treatment with histamine receptor antagonists (with or without cromolyn, an inhibitor of mast cell mediator release); it is possible that such patients may in fact fulfill criteria for mast cell activation syndrome, a disorder characterized by signs and symptoms attributable to inappropriate mast cell mediator release, not a proliferation of mast cells (ie, mast cell density in colonic mucosa is normal).¹⁶

We found that within the GI tract, neoplastic mast cells show somewhat variable expression of mast cell tryptase, with many cases showing positivity in only a limited number of cells, compared with KIT and CD25, which showed diffuse expression in all cases. This is unlikely to be due to technical or antibody-related issues; we have not observed this finding in neoplastic mast cells in bone marrow or skin in our practice. Variable tryptase expression may reflect differences in the composition of mast cell granules at this site but is a significant potential pitfall and highlights the superior diagnostic utility of KIT and CD25, which are therefore more reliable markers for mast cells in suspected cases of GI mastocytosis. This finding was not documented in another large study of endoscopic biopsies from patients with mastocytosis.¹³ Prior studies have established the utility of CD25 in the evaluation of mast cell infiltrates at different anatomic sites; aberrant expression of CD25 is seen in neoplastic mast cells but not in non-neoplastic mast cells, and thus expression of CD25 on mast cells confirms that the infiltrate represents a neoplastic process.^{9,26–29} CD25 is a low-affinity receptor for interleukin-2; it is important to note that CD25 is also expressed normally on some T lymphocytes. Distinction between mast cells and T cells is afforded by coexpression of KIT on mast cells, stronger CD25 staining on lymphocytes, and more abundant cytoplasm in mast cells.⁹ Given the subtlety of involvement in some biopsies, the use of KIT and CD25 was essential in confirming the diagnosis.

Previous studies have reported GI tract involvement by mastocytosis in small numbers of patients.^{10,13} However, in contrast to these prior reports, in our current series more biopsies showed focal or limited involvement, possibly because of the greater number of biopsies evaluated. Kirsch and colleagues noted that many patients do not have skin disease at the time of diagnosis, which can add to the difficulty of appreciating the mast cell infiltrate in the absence of a suggestive clinical history of mastocytosis, similar to our findings. In general, endoscopic correlation with mast cell infiltration is variable; mucosal nodularity is a common appearance,^{10,11} but other findings include erythema³⁰ and granularity, as seen in several patients in our study. However, almost half of the patients did not have endoscopic abnormalities, and therefore random and systematic biopsies are needed to detect disease involvement, as noted above.

In general, the histologic differential diagnosis of mastocytosis in the GI tract is limited; perhaps the most difficult differential diagnosis is with normal colonic mucosa, followed by eosinophil-rich disorders. In addition to primary eosinophilic gastroenteritis, as discussed above, increased numbers of lamina propria eosinophils are often seen in association with parasitic infections and chronic inflammatory bowel disease (IBD). Mast cells are often slightly increased in parasitic infection but do not show coexpression of CD25, which can

help in the differential diagnosis with mastocytosis.⁹ In general, mucosal mast cells are only mildly, if at all, increased in IBD; however, aggregates of mast cells are not observed.^{9,13} It is noteworthy that mastocytosis can also involve the lamina propria of adenomas or hyperplastic polyps, where it may easily be overlooked. Other histologic changes associated with mastocytosis are generally mild and include mild chronic gastritis and villous blunting in small intestinal biopsies, as well as architectural distortion in colonic biopsies, which may mimic chronic IBD.⁶ Clinical history and other histologic features of IBD can readily discriminate between SM and IBD.

In summary, this study shows that GI mucosal (especially colonic) biopsies can establish a diagnosis of SM in patients with GI symptoms and may be a helpful alternative to bone marrow biopsy for this purpose. Because involvement is often multifocal and is frequently not associated with endoscopic abnormalities, taking multiple biopsies at different sites throughout the colon (or other sites in the GI tract) is the optimal approach at the time of endoscopy. GI involvement is usually subtle histologically and is often associated with prominent eosinophils, which may obscure the mast cell infiltrate. Our findings also demonstrate the wide spectrum of disease involvement in GI mucosal biopsies, particularly those cases with minimal involvement by mastocytosis, which may only be recognized by the presence of more obvious involvement in other biopsies and/or a clinical history of mastocytosis, in conjunction with aberrant expression of CD25. GI involvement does not necessarily correlate with aggressive disease, as many patients with GI involvement follow an indolent clinical course. Mast cell tryptase has more limited utility in identifying neoplastic mast cell infiltrates in the GI tract compared with KIT and CD25, which are invaluable markers for the diagnosis. Finally, mast cell density in colonic mucosa is highly variable in both asymptomatic patients and those with diarrhea-predominant IBS, with significant overlap even at the high end of the spectrum, arguing against the utility of counting GI mucosal mast cells in patients with chronic diarrhea. Instead, the presence of aggregates or sheets of mast cells is the key diagnostic finding, which should prompt confirmation of mastocytosis by documenting aberrant expression of CD25.

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FIGURE 1. Endoscopic images from the right colon of 2 patients with systemic mastocytosis, one showing nodular mucosa (A) and the other showing erythema (B).

FIGURE 2.

A, Colonic mucosa with a sheet-like infiltrate of mast cells in the superficial lamina propria. The mast cells show diffuse expression of KIT (B) and CD25 (C).

FIGURE 3.
Neoplastic mast cells in the mucosa typically contain ovoid or spindle-shaped nuclei and abundant pale cytoplasm.

FIGURE 4.

A, A very subtle single aggregate of mast cells in the tip of a villus in the duodenum was the only evidence of involvement in biopsies from this site. B, The aggregate is more easily appreciated on the KIT immunostain.

FIGURE 5.

Multifocal involvement of biopsies from the left colon. A, Some fragments show a hypercellular lamina propria, corresponding to the presence of the mast cell infiltrate, whereas other fragments are unremarkable. B, The variable distribution of mast cells is highlighted by KIT. Note the band-like infiltrate underneath the surface epithelium.

FIGURE 6.
Prominent lamina propria eosinophils are common in colonic biopsies involved by systemic mastocytosis and may mask the mast cell infiltrate.

FIGURE 7.
Involvement of an adenoma by systemic mastocytosis. A, The neoplastic mast cells infiltrate around adenomatous crypts. B, KIT immunostain.

FIGURE 8. Liver involvement by systemic mastocytosis: ovoid mast cells infiltrate portal tracts and sinusoids (A) and are highlighted by staining for KIT (B).

FIGURE 9.
Patchy expression of mast cell tryptase (A), in comparison with diffuse KIT expression (B)
in colonic systemic mastocytosis.

FIGURE 10. Normal colonic mucosa from the right colon of an asymptomatic patient undergoing screening colonoscopy (A), showing numerous singly dispersed KIT-positive mast cells in the lamina propria (B).

TABLE 1

Panel of Antibodies Used in This Study

Antigen	Clone	Dilution	Antigen Retrieval	Source
KIT (CD117)	Polyclonal	1:200	None	Dako, Carpinteria, CA
CD25	4C9	1:200	EDTA+steamer	Novocastra, Newcastle-upon-Tyne, UK
Mast cell tryptase	AA1	1:500	Trypsin	Dako
CD30	Ber-H2	1:200	Pressure cooker	Dako

TABLE 2
Clinicopathologic Features of 24 Patients With Mastocytosis Involving the GI Tract

Case	Age at Positive GI Biopsies	Sex	Skin Involvement? (Age at Diagnosis)	GI Sites of Disease	First Diagnosis of SM Based on GI Biopsies?	Other Sites of Involvement	GI Symptoms (Duration)	Indolent or Aggressive	Disease Status (Follow-up Duration; Months Since Diagnosis of SM)
1	49	F	UP (6 mo)	Upper and lower GI tract	Yes	Bone marrow	Intermittent nausea, diarrhea, abdominal pain (3y)	Indolent	AWD; 108
2	61	F	UNK	Upper and lower GI tract	UNK	UNK	UNK	UNK	UNK
3	38	F	UP (28 y)	Lower GI tract	Yes	No (negative bone marrow biopsy)	Diarrhea, abdominal pain (several years)	Indolent	AWD; 312
4	52	F	UP (25 y)	Lower GI tract	Yes	No (no bone marrow biopsy performed)	Abdominal pain, bloating, diarrhea (several years)	Indolent	AWD; 144
5	70	M	UNK	Lower GI tract	No	Bone marrow	UNK	UNK	UNK
6	40	F	UP (3 mo)	Upper and lower GI tract, liver	No	Bone marrow, liver	Ascites, diarrhea (4 mo)	Aggressive (malabsorption, hepatosplenomegaly)	AWD; 90
7	53	F	UP (50 y)	Upper GI tract	No	Bone marrow	UNK	Indolent	Lost to follow-up after 3mo
8	73	F	No	Lower GI tract	Yes	Bone marrow	Diarrhea, cramps	Indolent	AWD; 18
9	64	F	No	Liver	No	Bone marrow (AHNMD-RAEB1), liver	Anemia	Aggressive (hepatosplenomegaly, GI bleeding from varices)	DOD; 10
10	75	M	No	Upper GI tract, liver	Yes	Bone marrow, liver, lymph nodes	Diarrhea, weight loss (6 mo)	Aggressive	Lost to follow-up after 5mo
11	78	F	UP (60 y)	Lower GI tract	Yes	Bone marrow (AHNMD-CMMIL)	Diarrhea (1 y)	Aggressive (weight loss, splenomegaly, anemia)	AWD; 26
12	58	F	UP (56 y)	Lower GI tract	Yes	Bone marrow	Worsening diarrhea (3 mo); history of ulcerative colitis	Indolent	AWD; 30
13	64	F	UP (43 y)	Upper and lower GI tract	No	Bone marrow	Epigastric pain, nausea, diarrhea (several months)	Indolent	AWD; 156
14	54	F	TMEP and UP (age unknown)	Lower GI tract	Yes	Bone marrow	Asymptomatic; screening	Indolent	AWD; 3

Case	Age at Positive GI Biopsies	Sex	Skin Involvement? (Age at Diagnosis)	GI Sites of Disease	First Diagnosis of SM Based on GI Biopsies?	Other Sites of Involvement	GI Symptoms (Duration)	Indolent or Aggressive	Disease Status (Follow-up Duration; Months Since Diagnosis of SM)
15	64	F	UP (57 y)	Upper and lower GI tract	Yes	Bone marrow (AHNMD-CEL with <i>PDGFRA</i> rearrangement)	Intermittent diarrhea, nausea (several years)	Indolent	AWD; 84
16	34	F	UP (age unknown)	Upper GI tract (lower GI biopsies ND)	Yes	No (no bone marrow biopsy performed)	Nausea, abdominal pain, diarrhea (5 y)	Indolent	AWD; 24
17	69	F	No	Lower GI tract	Yes	Bone marrow	Intermittent diarrhea (1 y)	Indolent	AWD; 24
18	19	M	Mastocytoma (5 mo); UP (9 y)	Lower GI tract	Yes	No (no bone marrow biopsy performed)	Abdominal pain, intermittent diarrhea (5 y)	Indolent	AWD; 18
19	47	F	UP (36 y)	Lower GI tract (upper GI biopsies ND)	Yes	Bone marrow	Diarrhea, weight loss, nausea, vomiting (2 mo)	Aggressive (cachexia, resumed liver and spleen involvement)	AWD; 36
20	60	F	UP (48 y)	Upper GI tract (lower GI biopsies ND)	Yes	No (no bone marrow biopsy performed)	Epigastric pain, reflux, intermittent diarrhea	Indolent	AWD; 3
21	61	M	UP (60 y)	Upper and lower GI tract	No	Bone marrow, lymph nodes, spleen	Diarrhea, nausea, vomiting	Aggressive	AWD; 24
22	75	F	No	Upper and lower GI tract	No	Bone marrow (AHNMD-CMML)	Watery diarrhea, weight loss	Indolent	AWD; 5
23	51	F	UP (48 y)	Lower GI tract (upper GI biopsies ND)	Yes	No—negative bone marrow (AHNMD-ET with <i>JAK2</i> mutation)	Asymptomatic; screening	Indolent	AWD; 12
24	51	F	UP (38 y)	Upper and lower GI tract	Yes	No (no bone marrow biopsy performed)	Diarrhea, abdominal pain	Indolent	AWD; 12

AHNMD indicates associated clonal hematologic non–mast cell lineage disorder; ANED, alive with no evidence of disease; AWD, alive with disease; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; DOD, died of disease; ET, essential thrombocythemia; ND, not done; RAEB, refractory anemia with excess blasts; TMEP, telangiectasia macularis eruptiva perstans; UNK, unknown.

TABLE 3

Mucosal Mast Cell Density in Normal Colonic Biopsies From Asymptomatic Patients, Patients With Diarrhea-predominant IBS, and Patients With Mast Cell Activation Syndrome

Patient Group (n)	Mean Highest Mast Cell Count in a Single HPF (Range)	SD	Mean Mast Cell Count per HPF, When 5 HPF Were Counted (Range)	SD
Asymptomatic (100)	26 (11–55)	8.5	19 (7–39)	6.1
Diarrhea-predominant IBS (100)	30 (13–59)*	9.0	23 (9–45)*	6.7
Mast cell activation syndrome (10)	28 (14–48) [†]	9.0	20 (12–31) [†]	5.4

* $P < 0.001$ compared with asymptomatic patients.

[†] Not significant compared with asymptomatic patients.

HPF indicates high power field; IBS, irritable bowel syndrome; SD, standard deviation.