

Gastrointestinal Involvement in Mast Cell Activation Disorders



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KEYWORDS

- Systemic mastocytosis • Mast cell activation syndrome
- Mast cell activation disorder • Gastrointestinal symptoms • Mast cell disease
- Monoclonal mast cell activation syndrome • Monoclonal mast cell activation disorder

KEY POINTS

- Gastrointestinal involvement in systemic mastocytosis is considered common, and gastrointestinal symptoms may be more likely to be triggered by mast cell–derived mediators compared with pathologic mast cell infiltration of gastrointestinal tissues.
- Both the presence of gastrointestinal symptoms and a response of gastrointestinal symptoms to anti–mast cell mediator therapy is considered qualifying criteria in the current diagnostic schema of the idiopathic mast cell activation syndrome.
- A variety of anti–mast cell mediator therapies have been proposed to alleviate the gastrointestinal symptoms attributed to systemic mastocytosis and the idiopathic mast cell activation syndrome.

INTRODUCTION

Gastrointestinal (GI) symptoms have long been recognized in patients with systemic mastocytosis. The attribution of GI symptoms in patients with clonal or monoclonal mast cell activation syndromes (MMCAS) or the evolving syndrome or constellation of symptoms attributed to the idiopathic mast cell activation syndrome (MCAS) is largely inferred from the presence of well-documented GI symptoms and GI involvement in patients with systemic mastocytosis. It is important to recognize that in systemic mastocytosis, especially in mastocytosis patients with biopsy-proven disease fulfilling current World Health Organization diagnostic criteria, the mast cells are intrinsically abnormal; that is, the mast cells have the activating KIT D816V or other KIT

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mutations and/or a variety of other somatic cell mutations that may influence mast cell survival, proliferation, activation, and function.^{1,2} It cannot be automatically assumed that patients with clonal or MMCAS (with a presumably lower level or total body load of abnormal mast cells) or with the idiopathic MCAS (where the mast cells have to date been largely identified to have a normal immunophenotype and normal cytology and c-KIT genetics) would necessarily have the same symptom complex involving any organ system, including the GI tract, as patients with systemic mastocytosis. Because GI involvement with systemic mastocytosis has been the subject of several thorough reviews,³⁻⁶ this article briefly reviews the GI involvement with systemic mastocytosis to serve in comparison with GI involvement reported in patients with mast cell activation disorders, such as the MMCAS, and those symptoms attributed to the idiopathic MCAS.

GASTROINTESTINAL INVOLVEMENT IN SYSTEMIC MASTOCYTOSIS

The occurrence of GI symptoms in patients with systemic mastocytosis has been documented since the 1960s and the frequency of GI symptoms in patients with mastocytosis ranges from 20% to 100%, with the early mastocytosis case series documenting fewer GI-related symptoms and studies in the last 20 years or so reporting more GI symptomatology; in some studies the frequency of GI symptoms is as high as skin manifestations.⁵⁻¹⁶ The symptoms can be severe and debilitating and are associated with a decreased quality of life.⁸ A large number of GI symptoms have been attributed to systemic mastocytosis (**Table 1**). The occurrence of GI symptoms does not seem to differ based on age of onset.^{8,17}

There are at least two pathophysiologic mechanisms proposed by which mastocytosis leads to GI symptoms: direct mast cell infiltration of the GI tract, and the downstream effect of mast cell mediators on the gut. Direct involvement of the GI tract by abnormal mast cells could certainly be responsible for GI symptoms and is a likely factor in some number of patients.^{18,19} However, recent studies suggest that the frequency of GI symptoms apparently does not seem to correlate with the presence of the KIT D816V mutation, the absolute value of serum tryptase, or histologic findings of mast cell infiltration in the GI biopsies.⁸ Indeed, there may even be an inverse correlation between the presence of the KIT D816V mutation and a high diarrhea score.⁸ This suggests that perhaps a significant component of GI symptoms are related to the release of mast cell mediators, such as histamine or prostaglandins, and some studies have implicated GI peptides, such as gastrin, neurotensin, substance P, or vasoactive intestinal peptide, as also playing a role.^{7,20,21} It is not clearly established whether the mediators triggering GI symptoms are derived directly from the mast cells localized to the GI tract mediators derived from mast cells at distant sites away from the GI tract.

GI involvement in mastocytosis is markedly heterogeneous with distinct variations as to the specific symptoms and severity of any given symptom with any given individual. Abdominal pain may be caused in large part by dyspepsia and peptic ulcer disease, which is associated with increased gastric acid secretion in a subset of patients and may respond to H₂ antagonists.⁷ Multiple studies have suggested that patients with mastocytosis are at higher risk for gastroduodenal ulcers.^{7,8,11} The pathogenesis of diarrhea in mastocytosis is also unclear, with contributions from gastric hypersecretion or prostaglandin D₂ overproduction postulated.^{7,20} Malabsorption in systemic mastocytosis is rare and is not associated with pancreatic abnormalities; it may be related to small intestinal dysfunction and, again, possibly gastric hyperacidity.^{6,22} Additional GI findings in systemic mastocytosis are detailed in **Table 2**.^{3,5,6,8,23,24}

Table 1
Gastrointestinal symptoms reported in patients with systemic mastocytosis

Clinical Symptom (% Patients with Reported Symptom)	Demis, ⁹ 1963, n = 113	Mutter et al, ¹⁰ 1963, n = 29	Webb et al, ¹⁴ 1982, n = 26	Yam et al, ¹⁶ 1986, n = 13	Cherner et al, ⁷ 1988, n = 16	Travis et al, ¹² 1988, n = 58	Horan et al, ⁵⁴ 1990, n = 21	Pagano et al, ¹³ 2008, n = 24	Lim et al, ¹⁵ 2009, n = 342	Sokol et al, ⁸ 2013, n = 83	Doyle et al, ²⁸ 2014, n = 24
Any GI symptom	—	—	—	—	—	—	—	—	65	59	—
Abdominal pain	23	48	40	46	80	35	81	17	—	27	33
Nausea and/or vomiting	23	45	28	31	—	21	57	17	—	23	25
Diarrhea	23	28	40	54	63	24	67	8	—	34	75
GI bleeding	23	24	—	8	—	7	5	—	—	19	—
Peptic ulcer disease	4	14	24	31	44	36	24	17	—	11	—
Malabsorption	—	—	—	—	25	5	24	—	—	—	—
Bloating	—	—	—	—	—	—	—	—	—	33	8
Hepatomegaly	12	83	45	77	—	41	38	46	27	—	—
Splenomegaly	11	86	50	62	—	48	19	50	37	—	—

Table 2 Gastrointestinal abnormalities reported in systemic mastocytosis	
Location	Features
Esophagus	Esophagitis Esophageal stricture Esophageal varices Lower esophageal sphincter dysfunction
Stomach	Acid hypersecretion Peptic ulcer disease Gastritis Altered motility "Urticarial" lesions
Small intestine	Dilated small bowel Villous atrophy or blunting Malabsorption Mesenteric thickening Nodular mucosal densities
Large intestine	Nodular densities Polypoid lesions Intestinal telangiectasias Steatorrhea
Liver	Elevated liver function tests Hepatomegaly Portal hypertension Infiltration and liver stiffness Ascites Portal venopathy Budd-Chiari syndrome
Spleen	Splenomegaly Hypersplenism Splenic infarct
Lymph nodes	Lymphadenopathy: retroperitoneal, periportal, mesenteric

Upper and lower endoscopies are often performed with biopsies in the work-up of patients with suspected mastocytosis. Endoscopic findings may include the appearance of mucosal erythema, mucosal nodules, pigmented areas, thickened folds, and ulcerations, or may appear visually normal.^{19,25,26} There remains an urgent need for additional rigorous and quantitative diagnostic criteria in the evaluation of all mast cell activation disorders, but even in the histologic evaluation of GI biopsies in systemic mastocytosis the findings are not necessarily straightforward, because mucosal mast cell quantitation in pathologic studies has reported increased, normal, or even decreased numbers of mast cells in patients with mastocytosis compared with control subjects.^{8,18,27–32} Indeed, two of the more recent comprehensive pathologic studies of GI involvement in systemic mastocytosis vary significantly with regards to GI mast cell expansion in mastocytosis (Table 3).^{8,27} The most commonly involved sites in the GI tract are the colon and ileum, with the stomach less commonly involved and the esophagus rarely involved.²⁸ Histologic features that can suggest a diagnosis of systemic mastocytosis in comparison with other disorders where there may a local GI mast cell tissue expansion, such as with eosinophilic GI disease, parasitic disease, and inflammatory bowel disease, include spindle-shaped mast cells in large aggregates or sheets; coexpression of CD25 on mast cells; diffuse membranous staining of KIT; and a mast cell/inflammatory cell ratio that favors mast cells (Table 4).^{3,5,8,28}

Table 3
Recent studies quantitating mast cells in the GI tract

Anatomic Location	Hahn & Hornick, ²⁷ 2007 ^a		Sokol et al, ⁸ 2013 ^b	
	Normal	Mastocytosis	Normal	Mastocytosis
Stomach	12 (5–21)	57 (24–90)	17.9 ± 1.8	20.5 ± 5.1
Duodenum	27 (4–51)	175 (74–339)	24.1 ± 2.7	40.3 ± 6.1
Ileum	32 (21–40)		28.4 ± 2.7	45.7 ± 3.5
Colon	21 (10–31)	209 (110–301)	14.4 ± 3.1	45.1 ± 8.8

^a Mean/high-power field (range).

^b Mean number of mast cells counted on five fields/high-power field.

GASTROINTESTINAL INVOLVEMENT IN THE MONOCLONAL MAST CELL ACTIVATION SYNDROME (MMCAS)

MMCAS is a term used to describe patients with symptoms suggestive of mast cell activation and who do not have cutaneous findings of mastocytosis (ie, no maculopapular cutaneous mastocytosis or urticarial pigmentosa) but are found to have the KIT D816V mutation or mast cells with an aberrant immunophenotype (ie, CD2/CD25⁺ mast cells) in the bone marrow. These patients generally have baseline serum tryptase levels less than 20 ng/mL, have a low burden of mast cells in the marrow without immunophenotypically abnormal mast cell aggregates, and thus may have one or more World Health Organization criteria for the diagnosis of systemic mastocytosis without meeting the full diagnostic criteria for the diagnosis of systemic mastocytosis.³³ Initial reports of MMCAS included subjects who had unexplained hypotension after hymenoptera stings with negative testing for hymenoptera-specific IgE or syncopal episodes accompanied by one or more symptoms suggestive of mast cell degranulation, including the GI symptoms of abdominal pain and diarrhea.^{33,34} Subsequent case reports of subjects diagnosed with MMCAS have reported multisystem reactions including hypotension plus cutaneous, respiratory, cardiovascular, and GI symptoms,^{35,36} although in one report the criteria used to define MMCAS was not entirely clear.³⁶

Outside of these reports there have not been extensive retrospective series describing the clinical phenotype of patients with MMCAS using uniform diagnostic criteria and no prospective reports of any significant number of patients with MMCAS with respect to natural history and disease progression. There have not been significant numbers of cases reported of MMCAS subjects who experienced multisystem

Table 4
Interpretation of GI biopsies in systemic mastocytosis

Issue	Response
Mast cell infiltrate is focal, heterogeneous, or patchy	Perform multiple biopsies, either systematic and sequential or random
Inflammatory cell infiltrates, especially eosinophils, can mask the mast cell infiltrate	Quantitate the mast cells and inflammatory cells; in mastocytosis, the mast cell/inflammatory cell infiltrate favors mast cells
CD25 coexpression is variable on mast cells	Correlate with KIT D816V status
Tryptase expression by mast cells may be weak or variable	Immunostain for CD117/c-KIT and for CD25

complaints, including GI symptoms, in the *absence* of concomitant syncope/hypotension/anaphylaxis. MMCAS subjects having the clinical presentation of venom anaphylaxis in the absence of venom-specific IgE either were not recognized as having additional mast cell-implicated clinical symptoms or were classified as having absent other mediator-related symptoms.^{37,38} Based on the available clinical data it may be reasonable to find at this point in time that GI symptoms can occur in patients with MMCAS in the context of anaphylaxis with multisystem involvement (concomitant symptoms involving the cardiovascular, respiratory, skin, GI systems) but it is unclear to what extent patients with MMCAS present with GI symptoms in the absence of acute anaphylaxis.

GASTROINTESTINAL INVOLVEMENT IN THE IDIOPATHIC MAST CELL ACTIVATION SYNDROME (MCAS)

GI involvement is considered a key clinical symptom in the idiopathic MCAS. The current working criteria for diagnosing MCAS includes typical clinical symptoms; an increase in serum total tryptase by at least 20% higher than baseline + 2 ng/mL within 4 hours of a symptomatic event; and a documented clinical response of clinical symptoms to a mast cell targeting therapy, such as an H₁ or H₂ receptor blocker or cromolyn sodium. Included in the typical clinical symptoms category for diagnosis are GI symptoms, such as abdominal cramping, vomiting, and diarrhea.³⁹ Although not explicitly articulated in the consensus diagnostic criteria, it is assumed that the appropriate consideration or studies have been performed to exclude the possibility of a clonal disorder, such as systemic mastocytosis or MMCAS. As experience with MCAS has evolved, proposed refinements to the MCAS diagnostic criteria include an understanding of the episodic nature of the clinical symptoms consistent with mast cell activation; use of alternative tests to total serum tryptase, such as the assay of urinary histamine or prostaglandin metabolites during/after symptomatic episodes; and a requirement that there should be at least two independent measurements of elevated mast cell mediators documented with clinical symptoms.^{40,41}

The evolving nature of the idiopathic MCAS diagnostic criteria is an important issue because various investigators have used different criteria to report their respective case series.^{39–43} Given that one diagnostic criteria includes the presence of episodic symptoms consistent with mast cell activation, there should be some consensus as to which symptoms from the GI standpoint should be included to fulfill this criteria. Some authors have included symptoms self-reported at baseline in addition to symptoms reported with acute attacks; the appropriateness of including baseline versus acute symptoms is not resolved.⁴¹ Some authors include GI symptoms that occur specifically during an episode of anaphylaxis, so it is not clear that GI symptoms would be reported in the absence of frank anaphylaxis. Some authors have specifically excluded an irritable bowel syndrome diagnosis or irritable bowel syndrome symptoms as a mast cell activation criterion; other authors include irritable bowel-like symptoms.^{43,44} Regardless, there seems to be a rough consensus among the limited reported case series available that at least abdominal pain and cramping (from 22%–100% of cases), diarrhea (18%–67% of cases), and nausea and vomiting (25%–90%) should be included (Table 5).^{36,43–45} Other symptoms, such as bloating (44%–100%) and reflux (44%–50%), could be considered given that patients with biopsy-proven systemic mastocytosis may also report these symptoms. Such symptoms as constipation, constipation alternating with diarrhea, dysphagia, and other findings such as abnormalities in the liver enzymes, bilirubin, or hepatomegaly and splenomegaly, likely require further investigation and replication. It is unclear that it is appropriate to

Table 5
Gastrointestinal symptoms reported in patients with the idiopathic mast cell activation syndrome

Clinical Symptom (% Patients with Reported Symptom)	Álvarez-Twose et al, ⁴⁵ 2010, In-between Episodes, n = 32	Acute Episodes, n = 32	Molderings et al, ³⁶ 2010, n = 20 ^a	Hamilton et al, ⁴⁴ 2011, n = 18	Ravi et al, ⁶¹ 2014, n = 25	Afrin et al, ⁴³ 2017, n = 413 ^a
Any GI symptom	16	35	—	—	—	—
Abdominal pain/cramping	—	22	100	94	52	48
Diarrhea	—	18	60	67	48	27
Nausea and vomiting	—	25	—	—	—	57
Nausea alone	—	—	90	33	—	—
Bloating	—	—	100	44	—	—
Reflux	—	—	—	44	—	50
Constipation	—	—	20	—	—	14
Diarrhea alternating with constipation	—	—	5	—	—	36
Dysphagia	—	—	—	—	—	35
Hepatic involvement						
Elevated liver enzymes	—	—	20	—	—	—
Elevated bilirubin	—	—	10	—	—	—
Organomegaly						
Hepatomegaly	—	—	5	—	—	—
Splenomegaly	—	—	10	—	—	—

^a These studies use diagnostic criteria for mast cell activation disorders that substantively differs from the other studies listed.

assume that once the diagnosis of MCAS is made then any or all symptoms localized to the GI tract, or any other organ system for that matter, can solely be attributable to mast cell disease.

Endoscopic evaluation with mucosal biopsies is often performed in patients with GI symptoms undergoing evaluation for possible MCAS. In general, MCAS is not associated with any specific visible endoscopic abnormalities. A pathology study comparing mast cell mucosal counts from colonic biopsies of 10 subjects with idiopathic MCAS versus 100 subjects with diarrhea-predominant IBS versus 100 asymptomatic subjects found no increase in mean mast cell counts in the MCAS cohort (28 mast cells/high-power field; range, 14–48) versus the asymptomatic cohort (26 mast cells/high-power field; range, 11–55), although the degree or extent of GI symptoms in this particular MCAS group was not discussed.²⁸ Mast cells normally traffic to the GI tract and this normal broad variation in mast cell density in the colonic mucosa in asymptomatic individuals should be taken into consideration before claiming that GI mucosal mast cells are increased in chronic diarrhea or any other condition.⁴⁶ Regardless, the available evidence suggests that the pathogenesis of GI symptoms in MCAS is presumably caused by the effect of mast cell mediators on the GI tract because there is currently no study demonstrating immunophenotypically abnormal mast cells, abnormal mast cell positioning, or a substantial increase or infiltration of mast cells in the GI tract of patients with MCAS.

TREATMENT OF GASTROINTESTINAL SYMPTOMS IN MAST CELL ACTIVATION DISORDERS

Treatment options for GI symptoms in systemic mastocytosis include medical therapy targeting mast cell mediators to control clinical symptoms and then cytoreductive therapy for aggressive or advanced mastocytosis disease classifications, which by directly targeting mast cells and reducing mast cell load may alleviate clinical symptoms (Table 6).⁴⁷ H₁ and H₂ blocker antihistamines remain the mainstay of therapy and sedating and nonsedating H₁ blockers can be used and their dose titrated based on each individual patient's severity of symptoms. In addition to being an H₁ blocker, ketotifen and desloratadine may also decrease mast cell mediator release, although ketotifen has not been shown to be superior to traditional H₁ antagonists in mastocytosis.^{48–50} It may be the H₂ antagonists that provide the most GI symptom relief in systemic mastocytosis; although some earlier studies have suggested that H₁ antagonists may improve GI symptoms, a more recent double-blind, placebo-controlled study of the second-generation dual H₁ receptor/platelet activating factor antagonist rupatadine in adult mastocytosis subjects found statistically significant improvement in the treatment group for a large number of clinical symptom parameters except for GI symptoms.^{50–53} Abdominal cramping and diarrhea may be responsive to oral cromolyn sodium.⁵⁴ Malabsorption may respond to cromolyn sodium and low doses of oral corticosteroids.⁵⁵ Nonsteroidal anti-inflammatory drugs (NSAIDs) could be considered in the control of GI symptoms and diarrhea, but must be considered with caution because NSAIDs can also provoke anaphylactic reactions in patients with mastocytosis.^{56,57} Individual case reports suggest leukotriene antagonists may improve GI symptoms in mastocytosis.⁵⁸ Several case reports describing the administration of omalizumab in patients with mastocytosis report a reduction in anaphylactic symptoms and possibly an improvement in GI symptoms.^{59,60} It must be noted that most studies suggesting drug efficacy for GI symptoms in systemic mastocytosis are derived from case reports or uncontrolled and mostly retrospective case series and randomized, controlled studies are few.

Table 6
Treatment of gastrointestinal symptoms in mast cell disease—targeting mediators

Symptom	Treatment Options
General: avoidance of triggers	Possible triggers include: Physical stimuli Emotional factors Drugs/medications Venoms and toxins
Peptic ulcer disease	H ₂ antagonist antihistamines Proton pump inhibitors
Nausea, vomiting, abdominal pain, cramping	H ₁ and H ₂ antagonist antihistamines Proton pump inhibitors Leukotriene antagonists Cromolyn sodium Low-dose corticosteroids
Diarrhea	H ₂ antagonist antihistamines Cromolyn sodium Leukotriene antagonists Low-dose corticosteroids Anticholinergic therapy
Malabsorption	Cromolyn sodium Low-dose corticosteroids

Other therapies: nonsteroidal anti-inflammatory drugs may help with abdominal pain and diarrhea; consider with caution because nonsteroidal anti-inflammatory drugs may also provoke anaphylaxis. Omalizumab: case reports suggest improvement in a variety of clinical symptoms, including GI symptoms.

To date there has not been any published randomized, controlled trials for the treatment of any specific clinical aspect of idiopathic MCAS. Because a subjectively defined positive clinical response to anti-mast cell mediator therapy is a diagnostic criterion of idiopathic MCAS, there is a potential impediment to designing clinical trials of MCAS free from bias because a response to therapy is required to make the diagnosis in the first place.^{41,42} Given this caveat, case series describing idiopathic MCAS report marked improvement in abdominal symptoms (82% response, 14/17 patients) with antimediator therapy with responses sustained with continuous medical therapy for up to 4 years.⁴⁴ In patients with idiopathic MCAS diagnosed based on elevated urinary prostaglandin metabolites treated with acetylsalicylic acid at doses from 81 mg to 500 mg daily, a decrease in urinary prostaglandin excretion was noted with improvement in clinical symptoms, although several subjects had GI symptoms caused by chronic NSAID therapy.⁶¹

SUMMARY

GI symptoms are commonly described in patients with systemic mastocytosis and idiopathic MCAS. Although GI biopsy studies have shown that some patients with systemic mastocytosis have increased mast cell numbers and abnormal immunophenotypic or structural abnormalities, the GI pathology specimens of other patients with mastocytosis contain only more subtle findings, thus suggesting that the GI symptoms may be largely caused by the effect of mast cell mediators on the GI tract. The published case series of patients with MMCAS suggest that GI symptoms in patients with MMCAS occur largely in the context of acute anaphylaxis. There remains some controversy as to what GI symptoms should be attributed to MCAS. Further studies

are urgently needed in systemic mastocytosis and idiopathic MCAS to confirm and develop treatment options in mast cell patients.

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