Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

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Background: Diagnostic criteria for mast cell (MC) activation syndrome have been recently proposed, but clinical studies to validate these criteria are lacking.
Objective: We sought to determine the clinical manifestations of this newly recognized syndrome in a cohort of patients.
Methods: We prospectively evaluated 18 patients seen at our institution with MC activation syndrome from 2006 to 2009. Patients enrolled had at least 4 of the signs and symptoms of abdominal pain, diarrhea, flushing, dermatographism, memory and concentration difficulties, or headache. Response to treatment with anti-MC mediator medications was assessed based on established criteria. Laboratory tests indicating MC mediator release and histopathology and immunohistochemical studies on gastrointestinal biopsy samples were performed.
Results: Ninety-four percent of the patients had abdominal pain, 89% had dermatographism, 89% had flushing, and 72% had the constellation of all 3 symptoms. Patients additionally had headache, diarrhea, and memory and concentration difficulties. All patients had at least 1 positive laboratory test result for an increased MC mediator level. On the basis of the response to treatment criteria, 67% of the patients in the cohort had either a complete or major regression in symptoms while taking medications targeting MC mediators. There was no significant difference in the numbers of intestinal mucosal MCs between our patients and healthy control subjects.
Conclusion: MC activation syndrome might be the underlying cause of unexplained symptoms when several organ systems are involved, such as the gastrointestinal tract and the skin. It is especially important to be able to recognize the constellation of clinical features because response to anti-MC mediator medications is often excellent. (J Allergy Clin Immunol 2011;128:147-52.)

Key words: *Diarrhea, mast cell, abdominal pain, histamine, tryptase, flushing, mast cell activation*

Abbreviations used
hpf: High-power field
IA: Idiopathic anaphylaxis
IHC: Immunohistochemistry
MC: Mast cell
MCAS: Mast cell activation syndrome
PGD_2: Prostaglandin D_2

Mast cells (MCs) are immune cells that are important in allergy and anaphylaxis. There is increasing evidence that MCs play a role in a host of inflammatory, infectious, and functional disorders of the lungs, eyes, skin, joints, and gastrointestinal tract. In gastroenterology, for instance, the role of MCs has been studied in irritable bowel syndrome, inflammatory bowel disease, and infectious disorders of the gastrointestinal tract.[1-9]

Patients with the clonal MC disease systemic mastocytosis often present with signs and symptoms that are characteristic of MC mediator release. These include flushing and other cutaneous manifestations and neuropsychiatric symptoms (eg, headache and poor concentration and memory).[10] The majority of these patients have significant gastrointestinal complaints. Of the 16 patients with systemic mastocytosis characterized in a prospective study, 80% had abdominal pain and diarrhea.[11]

A subset of patients have been identified who had a history of anaphylaxis and were subsequently found to have evidence of an MC clonal disorder on bone marrow examination.[12] These patients did not meet the World Health Organization's criteria for systemic mastocytosis,[13] and they have been classified as having monoclonal mast cell activation syndrome (MCAS). Although the clinical manifestations of this disorder have not been fully characterized, many of these patients had symptoms suggestive of MC degranulation (eg, flushing) along with gastrointestinal symptoms, including abdominal pain and diarrhea.

In a recent publication, Alvarez-Twose et al[14] studied a cohort of patients who presented to an allergy clinic with symptoms attributable to MC activation. Clinical data were obtained, and bone marrow MCs were studied to evaluate for clonality. The authors found that 32 (39%) of 83 patients did not have evidence for a clonal MC disorder and were labeled as having nonclonal mast cell activation disorder. The pathogenesis and certain clinical aspects of the similarly termed MCAS were recently reviewed, and diagnostic criteria were proposed.[15] However, there is little published information based on clinical trials of the clinical manifestations and laboratory features of patients with MCAS.

We now describe a cohort of patients who were referred to an allergy or gastroenterology clinic for a question of mastocytosis or unexplained abdominal pain, respectively. These patients were

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found to have a constellation of symptoms and signs that suggested MC mediator release. After ruling out clonal MC disease in the appropriate patients, we further phenotyped this cohort by using laboratory studies indicative of MC activation and response to therapy with anti-MC mediator medications. Based on the clinical manifestations described below, we have classified these patients as having MCAS. We believe this is a unique and underrecognized population of patients who might be encountered in various medical specialty clinics, especially allergy, immunology, and gastroenterology clinics.

METHODS

Patients

Eighteen adult patients who had characteristic signs and symptoms of MC mediator release were prospectively identified from 2006 to 2009 in an allergy clinic (referred to rule out mastocytosis) and a gastroenterology clinic (referred for unexplained abdominal pain) at a tertiary care center (Brigham and Women's Hospital, Boston, Mass). This study was designed and initiated several years before 2010, when the current proposed diagnostic guidelines for MCAS by Akin et al[15] were published. We used similar criteria for a diagnosis of MCAS. Symptoms specifically sought included intermittent abdominal pain, diarrhea, flushing, memory and concentration difficulties, and headache. The characteristic sign checked on physical examination was dermatographism. Data were also collected on whether the patients had a history of rhinitis or conjunctivitis, asthma, anaphylaxis, and/or upper gastrointestinal symptoms. Additional data were obtained by using our hospital's electronic record system and any outside hospital records. The study was approved by the Institutional Review Board at Brigham and Women's Hospital.

Patients were included in the study on the basis of 3 criteria: (1) they had at least 4 of 6 clinical features (abdominal pain, diarrhea, flushing, headache, memory and concentration difficulties, and dermatographism), (2) symptoms responded to anti-MC mediator medications, and (3) they had laboratory evidence of MC mediator release. Patients were excluded if they had another primary medical disorder to explain their symptoms, such as pheochromocytoma, carcinoid syndrome, inflammatory bowel disease, eosinophilic disorders, celiac sprue, or irritable bowel syndrome.[16] In patients with this constellation of symptoms and a history of anaphylaxis, a baseline serum tryptase level of greater than 11.4 ng/mL, and/or urticaria pigmentosa, a bone marrow biopsy and aspirate smear were obtained to exclude systemic mastocytosis, which is in keeping with diagnostic guidelines.[13] Additional immunohistochemistry (IHC) studies specific for mastocytosis were performed on available gastrointestinal biopsy specimens and as described in the IHC methods below to exclude patients with a clonal MC disorder. Patients with cutaneous, indolent, or systemic forms of mastocytosis and idiopathic anaphylaxis (IA) were not included in this study.

Laboratory tests

Results of laboratory tests used in this study were obtained from urine and peripheral blood specimens collected at the Brigham and Women's Hospital outpatient facility and while patients were in their baseline clinical states. Serum total and mature tryptase studies were performed at either the Virginia Commonwealth University Laboratories (Richmond, Va) or Mayo Clinic Laboratories (Rochester, Minn). Twenty-four-hour urine levels of histamine were measured at ARUP Laboratories (Salt Lake City, Utah), and 24-hour urine levels of prostaglandin D_2 (PGD_2) were measured at the Inter Science Institute (Inglewood, Calif). Some patients in the cohort were also tested for the D816V (substitution of aspartic acid at position 816 for valine) mutation in the c-Kit tyrosine kinase receptor from a bone marrow aspirate.

Treatment

Patients with suspected MCAS were treated by means of stepwise application of mediator-targeting drugs, as proposed in the Standards and Standardization in Mastocytosis Working Conference, Vienna, Italy, 2005.[17] Patients were initially prescribed type I and II histamine blockers (ie, diphenhydramine [Benadryl; McNeil, Fort Washington, Pa], cetirizine [Zyrtec, McNeil], short-acting loratidine [Claritin Reditabs; Merck & Co, Inc, Whitehouse Station, NJ], and ranitidine [Zantac; GlaxoSmithKline, Research Triangle Park, NC]). Depending on the response to treatment, additional medications were sequentially added, including MC membrane–stabilizing medications, such as cromolyn sodium (Gastrocrom; Azur Pharma, Inc, Philadelphia, Pa), and leukotriene receptor antagonist medications, such as montelukast (Singulair; Merck & Co, Inc). Response to anti-MC mediator therapy was evaluated by at least 2 treating physicians after the patients had been on a stable medical regimen for at least 12 months. The criteria used were consistent with those proposed for the treatment of systemic mastocytosis in the Vienna Working Conference.[17] The criteria were defined as follows: a complete regression was resolution of all symptoms during the minimum 12 months of therapy, a major regression was an improvement in symptoms by greater than 50%, a partial regression was improvement by 10% to 50%, and no regression was less than 10% improvement in symptoms.

TABLE I. Baseline characteristics of patients with MCAS

Characteristic	No. of patients (%)
Sex	
Male	2 (11)
Female	16 (89)
Age (y)	
20-29	1 (6)
30-39	4 (22)
40-49	8 (44)
50-59	5 (28)
Patients with medication allergy	13 (72)
Patients with food allergy and/or environmental allergy	6 (33)
Endoscopy and abdominal imaging before referral	12 (67)
Mean no. of years symptomatic before referral	4.6
Range of years before referral	1-9

Histopathology and IHC

Biopsy specimens of the 10 patients in our MCAS cohort who had an endoscopic evaluation at our institution were analyzed. Histologic and IHC studies were performed on 4-μm-thick, formalin-fixed, paraffin-embedded tissue sections and stained for c-Kit and MC tryptase, as reported previously.[18] For enumeration of MCs, 10 contiguous high-power fields (hpfs) were counted per biopsy specimen, and the mean was calculated. Only intact MCs with visible nuclei were counted for analysis. Our reference standards were taken from a previously published study from one of the authors (J.L.H.)[18] that documents the numbers of mucosal MCs per hpf from 10 healthy (asymptomatic) patients for each anatomic site. IHC was also used to evaluate for the presence of CD25 expression on MCs, as reported previously.[18]

Statistics

P values were determined by using the Student *t* test. A *P* value of less than .01 was considered statistically significant.

RESULTS

Patients' characteristics

We identified 18 patients in our clinics (Table I) with features consistent with the diagnostic criteria for MCAS used in the current study. All but 2 of these patients were women, and age at the time of diagnosis ranged from 20 to 60 years. The most frequent age group represented was 40 to 49 years (44% of patients).

TABLE II. Signs and symptoms of patients with MCAS

Sign or symptom	Total (%), n = 18
Abdominal pain	17 (94)
Dermatographism	16 (89)
Flushing	16 (89)
Headache	15 (83)
Poor concentration and memory	12 (67)
Diarrhea	12 (67)
Naso-ocular	7 (39)
Asthma	7 (39)
Anaphylaxis	3 (17)

Importantly, patients were symptomatic for a mean of 4.6 years (range, 1-9 years) before being given a diagnosis of MCAS. A high incidence of allergies among the patients in our cohort was noted (6 [33%] patients). Allergy was confirmed with a clear and relevant history of allergic symptoms to a suspected exposure in addition to the diagnostic tests to confirm allergy (specific IgE testing, skin prick testing, or both). Thirteen (72%) patients reported allergies to at least 1 medication. In addition, 3 (17%) patients in our cohort had a history of anaphylaxis.

The most frequent signs and symptoms of MCAS in the patients in our cohort are shown in Table II. As in patients with systemic mastocytosis and monoclonal MCAS, gastrointestinal complaints were prevalent in our cohort. The most common abdominal complaint was pain (17 [94%] patients), and 12 (67%) patients had diarrhea. Some patients also described symptoms of bloating (8 [44%] patients), nausea (6 [33%] patients), and reflux (8 [44%] patients). Overall, patients complained of a myriad of other symptoms in keeping with the systemic nature of MCAS. Patients in our cohort either complained of flushing (16 [89%] patients) or were found to have flushing in a predominately mantle (head and neck) distribution on physical examination. In studies of patients with mastocytosis, heat and alcohol are known to trigger MC mediator release.[10] Interestingly, we found that many patients with flushing also described intense whole-body redness after hot showers or water baths that often resulted in pruritus and avoidance of hot water (9 [50%] patients). Of the patients in our cohort, 12 (67%) described intolerance to alcohol ingestion, which either increased flushing (10 patients) or abdominal pain (2 patients). Overall, only 2 patients in the cohort who admitted to at least occasional alcohol use did not complain of increased flushing or abdominal pain with ingestion. The remaining 4 patients had completely abstained from alcohol.

Headache was a common symptom and was elicited by history in 15 (83%) of our patients. We also found that 12 (67%) of the patients complained of decreased concentration or poor memory. On physical examination, the finding of dermatographism was nearly universal and absent in only 2 patients in our cohort. Although 5% of the general population will have a localized wheal to blunt-object trauma,[19] dermatographism is a common finding in patients with MC disorders.[10] Importantly, a total of 13 (72%) patients in our MCAS cohort were determined to have at least the combination of abdominal pain, flushing, and dermatographism. In addition to the gastrointestinal tract and skin, many patients in our cohort had involvement of other organ systems: 7 (39%) patients had symptoms related to asthma, and 7 (39%) patients had rhinitis, conjunctivitis, or both.

Laboratory testing for MC mediators

Patients suspected of having MCAS based on the defined characteristic signs and symptoms underwent confirmatory laboratory testing. Table III details all of the MC mediator laboratory studies that were performed for each patient in the cohort for the 4-year duration of the study. Plasma total and mature tryptase levels were generally obtained on our patients to exclude systemic mastocytosis. In our cohort 5 (33%) of 15 patients who had a tryptase level measured had a positive result while in a baseline state. It is worth mentioning that none of the 3 patients in our cohort who were tested for the D816V c-Kit mutation from a bone marrow aspirate had a positive result on this test. Patients with suspected MCAS also had 24-hour urine studies for PGD_2 and histamine. In our cohort 10 (56%) of 18 tested patients had increased urine levels of histamine, and the mean increase was approximately 2-fold the upper limit of normal (700 $\pm$ 98 vs 386 nmol/g creatinine). Seven (44%) of the 16 tested patients in our cohort had increased PGD_2 levels (476 $\pm$ 111 vs 280 mg/24 h [upper limit of normal]). Only 2 patients had increases in levels of both of these mediators.

Response to anti-MC mediator medications

Patients with characteristic signs and symptoms of MCAS and positive laboratory study results for MC mediators were started on anti-MC mediator medications. Overall, patients with MCAS had an impressive treatment response with regard to symptoms. As depicted in Fig 1, 6 (33%) patients had a complete regression in symptoms, 6 (33%) had a major regression, and 6 (33%) had a partial regression.

It is important to mention that no defining characteristics (eg, presence of allergies or history of anaphylaxis) could be identified that distinguished those who had a complete regression in symptoms versus those who did not. The most impressive treatment responses (see Table E1 in this article's Online Repository at www.jacionline.org) were for abdominal pain (14/17 of the patients who initially had the symptom responded), headache (12/15), poor concentration and memory (7/12), and diarrhea (9/12); there was a more modest response to flushing (6/16). We also found that all but 1 of our patients with MCAS had a sustained response to anti-MC mediator medications. Patients in our cohort were followed for an average of 2.8 years (range, 1-4 years).

Quantification of intestinal mucosal MCs by means of IHC

Histologic and immunohistochemical analysis was performed on the biopsy specimens available from the patients who had undergone endoscopic procedures at our institution. All biopsy specimens evaluated were histologically normal (see Fig E1, *A* and *B*, in this article's Online Repository at www.jacionline.org). Using IHC with c-Kit and tryptase stains, we did not detect any significant differences in the numbers of intestinal mucosal MCs between the study patients with MCAS and our reference standard (Table IV).[18] These MCs were normal in appearance and were individually distributed throughout the lamina propria (see Fig E1, *C* and *D*). There were no CD25-expressing MCs in any of the biopsy specimens evaluated to suggest a clonal MC disorder.

DISCUSSION

We have identified a group of patients at our tertiary care center with MCAS based on the characteristic symptoms, laboratory

TABLE III. Patients' laboratory studies for MC mediators

Patient no.	Total tryptase (ng/mL); normal, 1-15 ng/mL	Mature tryptase (ng/mL); normal, <1 ng/mL	Histamine (nmol/g creatinine); normal, 0-386 nmol/g creatinine	PGD_2 (ng/24 h); normal, 100-280 ng/24 h
1	5.4	<1	380	**511**
2	6.6	<1	—	—
	5.4	<1	**403**	**291**
3	3.1	<1	**1197**	—
4	—	—	**674**	57
	—	—	327	75
5	3.8	<1	236	105
	4.6	<1	**423**	—
	4.2	<1	195	—
	5.6	<1	**486**	—
	4.0	<1	**453**	—
6	4.4	<1	280	**446**
7	15	<1	—	—
	14.4	—	—	—
	12	<1	280	92
	19	—	—	—
8	3.1	<1	76	45
	—	—	**563**	—
9	1.9	**1.9**	60	**297**
10	3.2	<1	—	—
	—	—	46	262
	3.4	<1	—	—
	3.5	**1.4**	—	—
	3.5	**1.2**	—	—
	3.6	**2.8**	66	—
11	2.4	<1	—	—
	3.4	<1	—	—
	2.7	<1	74	**294**
12	—	—	**491**	134
13	3.3	<1	—	—
	—	—	74	**1114**
	5.9	<1	—	—
	6.4	<1	—	—
	7.1	<1	—	—
	6.8	<1	—	—
14	—	—	—	190
	—	—	**1100**	
15	8.2	<1	102	155
	—	—	**500**	—
16	—	—	**500**	—
	—	—	64	**376**
	3.2	<1	70	—
	3.4	<1	47	—
	6.8	**3.0**	—	—
	3.6	<1	—	—
17	2.7	<1	**1115**	81
18	—	—	280	—
	19	—	—	—
	21	—	—	—
Mean for increased values	**10.7 ± 3.7**		**700 ± 98**	**476 ± 111**

evidence of the presence of MC mediators, and response to anti-MC mediator medication. These patients met our inclusion criteria for MCAS, as well as the criteria established by Akin et al.[15] Final criteria for this syndrome will have to be established after prospective studies are performed on larger cohorts of patients. Most of our patients had frequent gastrointestinal and systemic symptoms for many years (average, 4.6 years [range, 1-9 years]) before the institution of appropriate treatment. These patients were seen by multiple physicians in the ambulatory and emergency department setting, and many had been referred by other allergists and gastroenterologists. We found that patients with MCAS had undergone many laboratory, radiology, and invasive tests, such as endoscopy, before diagnosis. Although we believe that it is important to exclude other more common disorders that can present in a similar manner, a high index of suspicion for MCAS in select patients could possibly eliminate many costly and unnecessary tests.

An active area of research is the discovery of objective measures to identify MC activation. Although all of our patients with MCAS had a positive test result for at least 1 MC mediator, only 33%, 56%, and 44% of the patients had positive test results for tryptase, histamine, and PGD_2, respectively. It is worth mentioning that 1 patient in our cohort had a random tryptase level of greater than 20 ng/mL, and 2 patients had levels of greater than 11.4 ng/mL. These patients have had negative evaluation results for systemic mastocytosis, and the remainder of the tryptase-positive patients in our cohort have had random tryptase levels of less than 11.4 ng/mL. Although it is likely that these patients have MCAS, it is also possible that they have a yet undiagnosed clonal MC disorder. Although MC membrane stabilizers and antihistamines do not appear to affect urine histamine levels,[20] a limitation of the PGD_2 assay is that patients ideally should be off aspirin and nonsteroidal anti-inflammatory drugs during the 24-hour urine collection and are symptomatic at the time of the test. We found that many of our patients with MCAS were reluctant to discontinue their anti-MC mediator medications out of fear of recurrence of symptoms. Therefore the number of patients with increased PGD_2 levels reported in this study might be an underestimate. In this initial study of patients with MCAS, we believed that it would be important to include patients who had at least 1 positive test result for an MC mediator. We have collected several additional patients who met our criteria for MCAS based on symptoms, signs, and response to treatment but who did not have a positive test result for MC mediators while at baseline. These patients are candidates for anti-MC mediator medications despite normal laboratory study results, but repeated laboratory measurements of MC mediators should be done at the time of active symptoms to establish a definitive diagnosis in keeping with the currently proposed diagnostic criteria.[15]

Most patients with MCAS in our cohort who were treated with anti-MC mediator medications responded dramatically. After an average of 4.6 years of MC-related symptoms, 66% of the patients with MCAS achieved a complete or major regression in symptoms to MCAS treatment. In the last 2 years of our trial and because of a small study that showed benefit to treating patients with MCAS with increased PGD_2 metabolite levels with aspirin,[21] we added this to the medical regimen of our patients with MCAS with increased baseline 24-hour urine PGD_2 levels (dose range, 81-650 mg/d). These patients were already improved with regard to their symptoms before starting aspirin, and therefore it was difficult to discern any additional benefit from the medication.

A limitation of this study is the nonblinded design with regard to assessment of treatment response and the lack of a placebo control group. Patients were included in the cohort if they had signs and symptoms compatible with MCAS and the clinical diagnosis was confirmed after assessing response to anti-MC

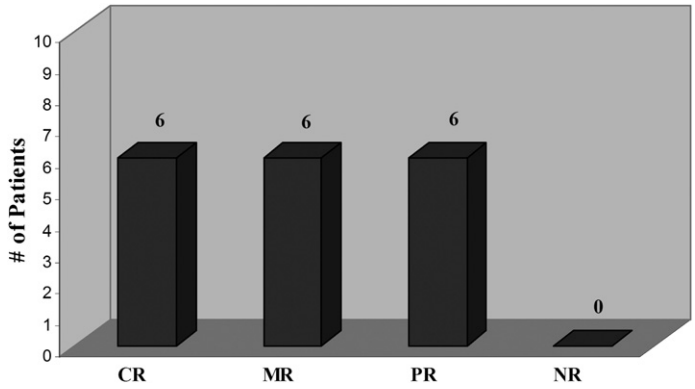

FIG 1. Assessment of treatment response. The total number of patients in each response-to-treatment category is shown by using the criteria established for mastocytosis. Complete regression *(CR)* was resolution of all symptoms, major regression *(MR)* was improvement in symptoms by greater than 50%, partial regression *(PR)* was improvement in symptoms by 10% to 50%, and no regression *(NR)* was less than 10% improvement in symptoms.

TABLE IV. Mean number of MCs at each site

Site of biopsy	No. of patients	Mean/hpf (normal)*	Range (normal)*
Stomach	7	17 (13)	14-28 (5-21)
Duodenum	7	23 (27)	18-26 (4-51)
Left colon	5	20 (21)	15-27 (10-31)
Right colon	4	17 (21)	12-18 (10-31)

*Data from Hahn and Hornick.[18]

mediator treatment and MC mediator laboratory studies. Patients were seen by at least 1 other provider with expertise in MC disorders, and the symptoms, signs, and responses to medical treatment were verified to enhance objectivity. We identified approximately 5 patients who had at least 4 of the characteristic signs and symptoms of MCAS but importantly did not respond to anti-MC mediator medications and had negative laboratory study results for MC mediators. These patients were excluded from our cohort because they did not meet the inclusion criteria. These patients might have a type of MCAS characterized by the release of mediators that we are not able to detect currently and for which we do not have medications to antagonize their systemic effects.

This study was conducted at a tertiary referral center with clinical and research expertise in MC disorders, and therefore it is not possible to estimate the prevalence of this disorder in a community allergy, gastroenterology, or internal medicine practice. Over the 4 years of the study, we estimate that 300 patients were initially seen at our allergy clinic by 1 provider (M.C.) for a question of mastocytosis. Of these, 50% were believed to have a clonal MC disorder, such as mastocytosis or monoclonal MCAS, and 9 met the inclusion criteria in this study for a diagnosis of MCAS. Thus the estimated prevalence of MCAS in our allergy clinic referred to 1 provider for a question of mastocytosis was 3%. In our gastroenterology clinic we estimate that 400 patients were initially seen for unexplained abdominal pain by 1 provider (N.G.). Of the 400 patients, 30 were screened for MCAS, and 9 were ultimately given a diagnosis of MCAS. Thus the prevalence in our gastroenterology clinic in patients referred to 1 provider for unexplained abdominal pain was 2.3%.

In our cohort 3 patients had a history of anaphylaxis. These patients were included in our cohort because they had primary symptoms characteristic of MCAS that responded to medications and had other laboratory evidence of MC mediator release. We excluded 2 patients who had a primary diagnosis of IA despite having mild, intermittent, treatable MCAS symptoms in between episodes of anaphylaxis and baseline increased test results for a MC mediator. There likely exists a spectrum of disease for MCAS in which the more severe form includes anaphylaxis and a spectrum of IA in which a form includes MCAS symptoms.

Our immunohistochemical analysis led us to the conclusion that there was no significant difference between the numbers of intestinal mucosal MCs in our patients with MCAS and our reference standard. We recognize that there is currently no consensus for what constitutes a normal number of MCs in the various intestinal tissues. We therefore chose data from a recently published study by one of the authors[18] to be the reference standard. In this study normal numbers of MCs were tabulated for each tissue site. Although we did not find appreciably increased numbers of MCs or abnormal morphology, it is possible that patients with MCAS have a different threshold for MC activation and differentially release MC mediators on activation or that peripheral tissues have an abnormal response to these mediators. We also recognize that a population of patients with chronic diarrhea has been described and labeled as having mastocytic enterocolitis. These patients had a greater number of MCs per hpf in duodenal and colon biopsy specimens compared with the control population (>20 vs 13 MCs/hpf).[22] We were not able to verify this observation in our cohort because many of our control population biopsy specimens had more than 20 MCs/hpf.

Finally, a limitation of our study was the focus on gastrointestinal and skin organ symptoms. We hope that this study will spur other research groups to analyze other patient populations, perhaps from other specialty groups (eg, pulmonary), so that we can have more clinical data to support the evolving diagnostic criteria for MCAS. The true frequency of gastrointestinal and skin symptoms in patients with MCAS will not be known until multiple populations of patients have been analyzed with finalized diagnostic criteria.

We emphasize that although unique criteria were used in the recruitment of patients in this cohort, our criteria overlap with the recently proposed criteria by Akin et al,[15] and all of our patients met the proposed symptom criteria for MCAS. In this regard

many of our patients had other organ systems involved, including the pulmonary (wheezing) and naso-ocular (rhinitis and conjunctivitis) systems.

In conclusion, our study underscores the importance of increased awareness for MC mediator–related symptoms because a population of patients who fit the clinical profile for MCAS has an excellent and sustained response to anti-MC mediator treatment.

Clinical implications: This is a prospective cohort study to describe the clinical features of MCAS. Response to treatment in patients with MCAS might be excellent.

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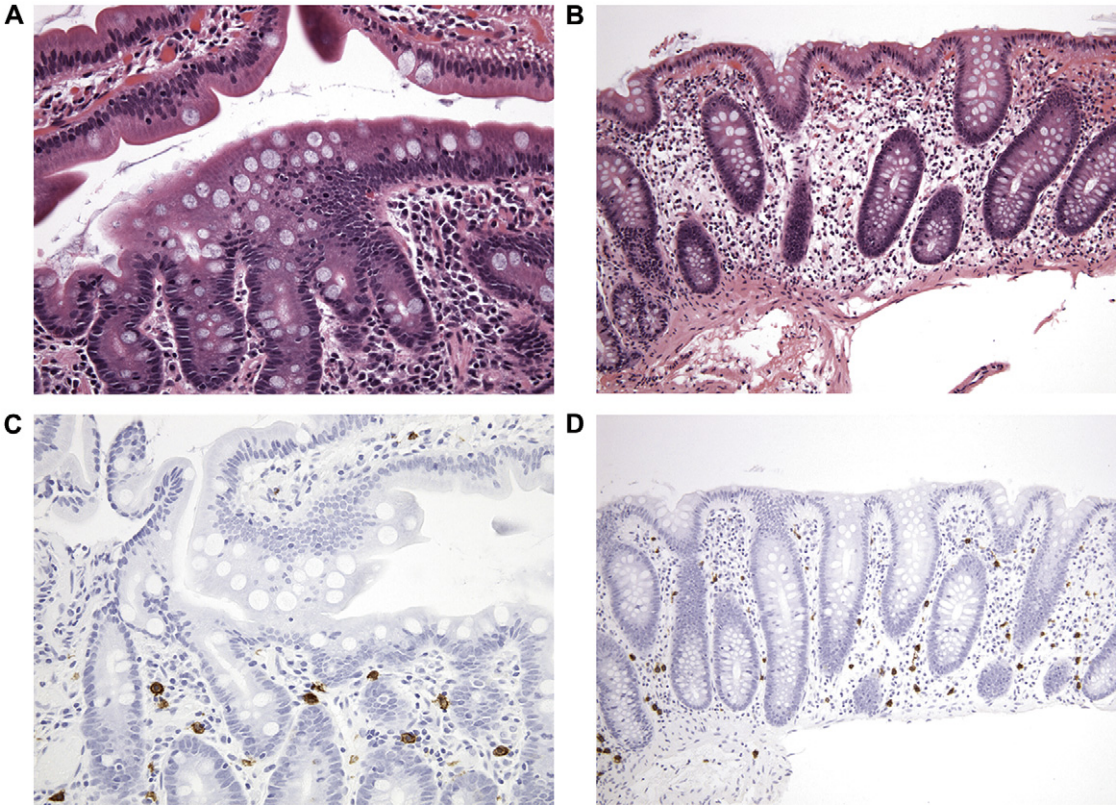

FIG E1. MCAS gastrointestinal histology and IHC. Hematoxylin and eosin–stained sections of the duodenum **(A)** and colon **(B)** of a representative patient with MCAS demonstrate no histologic abnormalities. The corresponding sections stained with an antibody to c-Kit (**C** and **D**) highlight the brown-staining MCs. These cells are individually dispersed throughout the lamina propria.

TABLE E1. Symptoms of MCAS before and during treatment

	Abdominal pain		Flushing		Headache		Poor memory and concentration		Diarrhea	
Patient no.	Before	During	Before	During	Before	During	Before	During	Before	During
1	+	−	+	+	+	−	+	−	+	−
2	+	+	+	+	+	−	+	−	+	−
3	+	−	+	+	+	−	−	−	+	+
4	+	−	+	−	+	−	+	−	−	−
5	+	−	−	−	−	−	+	−	+	−
6	+	−	+	−	+	−	−	−	+	−
7	−	−	+	+	−	−	+	−	+	−
8	+	−	+	+	−	−	+	+	+	+
9	+	−	+	+	+	−	−	−	−	−
10	+	−	+	−	+	−	−	−	−	−
11	+	−	+	+	+	+	+	+	+	−
12	+	−	+	−	+	−	+	+	−	−
13	+	−	+	+	+	−	−	−	+	−
14	+	+	+	−	+	−	−	−	+	+
15	+	−	+	+	+	+	+	−	−	−
16	+	+	+	+	+	−	+	+	+	−
17	+	−	−	−	+	−	+	−	−	−
18	+	−	+	−	+	+	+	+	+	−

For each patient in the MCAS cohort, the presence *(+)* or absence *(−)* of the most prevalent symptoms of MCAS is listed before and during treatment with anti-MC mediator medications.